National Science Advisory Board For Biosecurity (NSABB)
Summary of Inaugural Meeting
June 30-31 2005
Bethesda, Maryland

Committee Members

Dennis L. Kasper, M.D., NSABB Chair
Arturo Casadevall, M.D., Ph.D.
Murray L. Cohen, Ph.D., M.P.H., C.I.H.
Lynn W. Enquist, Ph.D.
Barry J. Erlick, Ph.D.
David R. Franz, D.V.M., Ph.D.
General John A. Gordon (Ret.)
Michael J. Imperiale, Ph.D.
Paul S. Keim, Ph.D.
Stanley M. Lemon, M.D.
Stuart B. Levy, M.D.
John R. Lumpkin, M.D., M.P.H.
Adel A.F. Mahmoud, M.D., Ph.D.
Mark W. Nance, J.D.
Michael T. Osterholm, Ph.D., M.P.H.
David A. Relman, M.D.
James A. Roth, D.V.M, Ph.D.
Harvey Rubin, M.D., Ph.D.
Andrew A. Sorensen, Ph.D.
Anne Vidaver, Ph.D.
Admiral William O. Studeman (Ret.)
Diane W. Wara, M.D.

Ex Officio Agency Representatives

Natalia Comella, Department of State
Brenda A. Cuccherini, Ph.D., M.P.H., Department of Veterans Affairs
Dennis Dixon, Ph.D., NIH/National Institute of Allergy and Infectious Diseases
Anthony S. Fauci, M.D., NIH/National Institute of Allergy and Infectious Diseases
Maryanna Henkhart, Ph.D., National Science Foundation
Peter R. Jutro, Ph.D., Environmental Protection Agency
Rick Kearney, U.S. Geological Survey
Lawrence D. Kerr, Ph.D., Executive Office of the President
Dale E. Klein, Ph.D., P.E., Department of Defense
Terry L. Lomax, Ph.D., National Aeronautics and Space Administration
Boris D. Lushniak, M.D., M.P.H., DHHS/Food and Drug Administration
Janet K.A. Nicholson, Ph.D., DHHS/Centers for Disease Control and Prevention
Stuart L. Nightingale, M.D., Department of Health and Human Services

Gerald Parker, Department of Homeland Security
Caird E. Rexroad, Jr., Ph.D., U.S. Department of Agriculture
Scott Steele, Ph.D., Department of Justice
David G. Thomassen, Ph.D., Department of Energy
John F. Turner, Department of State
Vincent L. Vilker, Ph.D., Department of Commerce
Ronald A. Walters, Ph.D., Intelligence Community

NIH Representatives

Elias Zerhouni, M.D., Director, NIH
Amy Patterson, M.D., Director, NIH Office Of Biotechnology Activities
Thomas Holohan, M.D., Executive Director, NSABB, NIH Office Of Biotechnology Activities

Thursday, June 30, 2005

Welcome and Opening Remarks

Dennis L. Kasper, M.D.
NSABB Chair
Harvard Medical School

Dr. Elias Zerhouni, M.D.
Director, NIH

Dr. Dennis Kasper, Chair of the National Science Advisory Board for Biosecurity (NSABB) welcomed participants to the Board's inaugural meeting and introduced Dr. Elias Zerhouni, Director of NIH. Dr. Zerhouni stated that the U.S. Government created NSABB to provide guidance and leadership on biological research that has the potential for misuse, thus posing a threat to the public health or national security, i.e., "dual use research." He explained that many trans-governmental discussions preceded the government-wide collaboration that established the Board. Dr. Zerhouni said that dual use issues are novel in the field of life sciences because biosecurity concerns must be weighed against concerns about the free dissemination of useful information to the public. He remarked on the tremendous benefits of exchanging scientific discoveries across borders. As an example, he described the rapid identification and sequencing of the SARS pathogen by the international scientific community. Scientists in China, the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and NIH worked together using all the available technologies. He also cited as examples the international efforts that led to control of avian influenza among poultry flocks, the use of the polymerase chain reaction (PCR) to identify fungal infection in soybean crops, and the sequencing of the human genome. Dr. Zerhouni stated that many scientific advances result from the long-term and sustained investment in basic and applied research made by Government agencies and across the world.

He pointed out, however, that progress in fundamental science for the benefit of mankind has also created tools that have the capability for mischief. Advances in recombinant DNA research, molecular biology, genetics, and other life sciences disciplines create an increasing ability to alter biological systems in ways that could terrorize nations and threaten public health. Because of these concerns, the Department of Health and Human Services and the National Institutes of Health were asked to house NSABB. Dr. Zerhouni stated that the Board will bring together a complete engagement of the components of society necessary to identify the subtle borders between good use and misuse of these technologies. He said the Nation's response to threats must be coordinated and measured and enlightened by evidence, and should employ the wisdom of those with the expertise and common sense to provide sound guidance on research practices. An initial priority for the Board will be an identification of the specific research criteria to be considered "dual use."

Dr. Zerhouni stated that NSABB will adopt an open and public process to the extent possible without jeopardizing security. Participating Government departments and agencies are committed to striking a balance between the needs of scientific progress and biosecurity,

reflected by the fact that the Board has been charged with promoting a culture of responsibility. He said that fostering this culture of responsibility will probably be the most difficult task assigned to the Board.

Although existing laws and regulations address critical aspects of biosecurity for a subset of research involving Select Agents, Dr. Zerhouni said they are not sufficient. Protection of the Nation will require an ongoing and dynamic process of new policies and oversight practices. Recommendations resulting from the work of NSABB will complement existing biosecurity initiatives and the current legislative framework. He described the existing laws and regulations, beginning with the U.S. Patriot Act of 2001, which was the first law to address the use of specific highly pathogenic biological agents by lab workers. It also establishes personal liability in certain cases for scientists engaged in Select Agent work. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and the Agricultural Bioterrorism Protection Act of 2002 updated the Select Agent rule by requiring research facilities to register with the CDC or Department of Agriculture (USDA) if they assess, use, or transfer listed Select Agents. In addition, the Select Agent rules require the development and implementation of safety and security plans for institutions.

Dr. Zerhouni remarked that the Recombinant DNA Advisory Committee (RAC) of NIH underwent an ongoing process of adaptation and evolution as new discoveries have been made. He said that a similar evolution will be necessary for NSABB, and he expressed hope that guidelines promoting a new culture of security evolve faster than the efforts of those who wish to misuse dual use research. Dr. Zerhouni advocated for evidence-based, wisdom-based, and aggressive approaches in this process, rather than rigid responses.

Dr. Zerhouni thanked those who participated in the formation of NSABB and commended the expert members and *ex officio* members of the Board for agreeing to serve. He told them they were appointed because of their nationally recognized expertise and analytical problem-solving abilities and asked them to serve both as scientists and as citizens of the U.S. Dr. Zerhouni then asked Board nominees to raise their right hands and he swore them into service. He stated that he looked forward to receiving the Board's reports and recommendations in the future and said he would disseminate the guidelines and information he receives from them as effectively as possible to Government agencies and stakeholders.

Dr. Zerhouni turned the meeting over to NSABB's Chair, Dr. Kasper, so that he could provide an overview of the meeting agenda and further describe the responsibilities of Board members.

Chair's Remarks and Agenda Overview

Dennis L. Kasper, M.D.
NSABB Chair

Dr. Kasper accepted Dr. Zerhouni's charge on behalf of the Board. He stated that he is a professor of medicine and microbiology and molecular genetics at Harvard Medical School, the Director of the Channing Laboratory at Brigham and Women's Hospital in Boston, and the Director of the New England Regional Center for Excellence in Biodefense and Emerging Infectious Diseases. Dr. Kasper said that his research interests are in microbial immunity, with specific expertise in carbohydrates. He has had a longstanding interest in vaccines and

immunomodulation. The organisms he specializes in studying are Group B Streptococcus, anaerobes such as Bacteroides, and the organism Francesella tularensis, one of the agents of potential bioterrorism.

Dr. Kasper welcomed the Board members, *ex officios*, the public, and those watching the proceedings via Webcast, and explained that they would be hearing from speakers representing a broad range of expertise, including academia, the biotechnology industry, the scientific publishing industry, and the Government. Dr. Kasper provided an overview of the agenda and said that his role as Chair was to oversee NSABB and the conduct of its meetings. He also stated that the Board would be forming working groups composed of regular and *ex officio* Board members, using outside experts to focus on specific areas. The first topics to be explored by these groups include: dual use research, communications, codes of conduct, international collaboration, and synthetic genomics. The subcommittees will confer between regularly scheduled Board meetings and will develop draft work products in collaboration with NSABB staff working at NIH. Recommendations will be presented to the entire Board, which will deliberate and reach consensus before advising Secretary Leavitt and his colleagues in other Federal departments and agencies.

The Board members introduced themselves, citing their fields of interest, experience serving on other Federal advisory committees, and providing other relevant information. Board members Anne Vidaver, Professor and Chair, Department of Plant Pathology, University of Nebraska; Dr. Claire Fraser, President and Director of the Institute for Genomic Research; and Dr. Tom Shenk, Professor of Life Sciences, Department of Microbiology at Princeton were not in attendance on Day 1. Dr. Kasper then introduced Dr. Thomas Holohan, Executive Director of NSABB.

National Science Advisory Board for Biosecurity: Purpose, Structure, and Operations

Thomas, Holohan, M.D.
Executive Director, NSABB
NIH Office of Biotechnology Activities

Dr. Holohan stated that NSABB was established as a result of increasing concerns about the risk of malevolent uses of life sciences research and research results. He said that in recent years, the Government has promoted research on the development of countermeasures for biologic threats. In addition, the legislation described by Dr. Zerhouni placed new restrictions on access to certain materials, and in some cases imposed criminal penalties. During the same time frame, the National Research Council (NRC) produced a report on biotechnology research and the potential for malevolent uses. The NRC coined the term "dual use" to describe technologies that serve legitimate scientific purposes, yet could also be used to harm national security or public health. One of the recommendations made in the NRC report was for the creation of a national advisory board. The report also called attention to the issues of education of the scientific community on dual use research; systems for review of dual use research proposals; self-governance in publication review; and communication among life scientists, security officials, and law enforcement. Dr. Holohan noted that the charter of NSABB includes attention to all of these issues. He said the Board was established primarily to advise the Secretary of the Department of Health and Human Services, the Director of NIH, and the heads of all relevant Federal entities on effective strategies for oversight of federally supported

dual use research.

Dr. Holohan listed the 12 charges established for NSABB. The Board is to:

- Develop criteria for identifying dual use research and research results;
- Develop guidelines for oversight of dual use research, including guidelines for risk/benefit analyses;
- Advise on national policies governing local review and approval for dual use research, including guidelines for case-by-case review and approval by Institutional Biosafety Committees (IBCs);
- Advise on criteria and processes for referral of classes of research or specific experiments by IBCs to NSABB;
- Review/provide guidance on specific experiments that exemplify significant or complex permutation or represent a new category of dual use research;
- Respond to research institutions' requests for interpretation and application of guidelines to specific proposals that have been denied by an IBC;
- Provide recommendations regarding the development of a code of conduct for scientists and laboratory workers for adoption by professional societies and institutions engaged in life sciences research;
- Provide recommendations on the development of mandatory programs for education and training in biosecurity for all scientists and laboratory workers at federally funded institutions;
- Advise on national policies for publication, communication, and dissemination of dual use research methodologies and results;
- Provide recommendations regarding strategies for coordinated international oversight of dual use biological research;
- Advise on national policies for conduct of dual use research, including strategies to address national security concerns while fostering rapid progress in life sciences research; and
- Address other issues as directed by the Secretary of HHS.

The Board's charter calls for no more than 25 voting members, appointed by the Secretary after consultation with other Federal agencies. The Board will meet quarterly and as needed, and the meetings will be open to the public unless otherwise determined by the Secretary. NSABB will be managed and administered by the NIH Office of Biotechnology Activities (OBA). Dr. Holohan listed some of the areas of expertise represented by the Board's members, including molecular biology, public health, pharmaceutical production, national security, intelligence, food production, law enforcement, and scientific publishing. He said that in addition to the voting members, 18 *ex officio* members represent Federal agencies. These individuals will serve as resources for unique experience and expertise.

Dr. Holohan explained that OBA's specific assignment is to manage NSABB on behalf of the Department. OBA will plan and execute meetings, develop background materials, provide support for the development of the Board's work products, and maintain the NSABB website as a resource for the public. OBA will also identify and analyze dual use research issues, facilitate coordination in the development of Federal policies on dual use research, participate in

the implementation and interpretation of the Federal guidelines for dual use research, and develop training and education programs for IBCs. Dr. Holohan closed by providing the NSABB website address: http://www.biosecurityboard.gov.

Perspectives on Biosecurity and the Life Sciences

NSABB Members and Ex Officios

Dr. Kasper asked each NSABB member and ex officio member to comment briefly on their observations and concerns related to biosecurity issues in life sciences research. The following common themes emerged:

- A delicate balance must be found that fosters scientific advancement in the global community while protecting U.S. national security. Our safety depends on the open communication of scientists across the globe, as evidenced by the global efforts to contain SARS. This communication includes the freedom to publish.
- Science must serve as the vehicle for international collaboration, because massive regulatory schemes will not work. NSABB must consider how the U.S. can deal safely with sensitive States without "building walls."
- Interaction among domestic and foreign enforcement and intelligence agencies must be maximized, as threats can emerge from both within and outside U.S. borders. However, it will be challenging to change the cultures of these agencies.
- Public health may be more effectively protected through a greater understanding of the spread of disease and through the development of new diagnostic tools.
- Diseases in animals pose serious threats to public health, yet few research efforts focus on the prevention and eradication of these infections.
- Concerns for potential unintended security risks associated with functional synthetic genomes stress the need for clear guidance to investigators working in this area.
- As one means to address concerns associated with dual use research, NSABB is poised to influence professional societies and academia to encourage educational practices that will instill a strong sense of individual responsibility in scientists early in their careers.
- The general public must be educated on the complexity of dual use issues.

Dr. Kasper introduced Dr. Rajeev Venkayya from the White House Homeland Security Council. He stated that Dr. Venkayya was a Director for Biodefense and Health at the White House Homeland Security Council from October 2003 to May 2005. He played a significant role in the development of U.S. policies related to biosecurity, biosurveillance, public health, medical preparedness, and the national biodefense strategy.

Dr. Rajeev Venkayya
Special Assistant to the President
Senior Director for Biologic and Chemical Defense, White House Homeland Security Council

Dr. Venkayya stated that since the summer of 2003, discussions concerning biosecurity and dual use technologies have been of significant interest at all levels of Government, particularly in the White House. The Homeland Security Council, which is a domestic analog of the

National Security Council, convened a group of Federal partners to discuss biosecurity issues in the same time frame that the NRC published its report on dual use technologies and life sciences research. Over the next 2 years, the Homeland Security Council drafted a set of recommendations that were informed by the NRC report. Briefings at HHS and the White House helped to shape the Government's biosecurity policy, which announced by Secretary Thompson in the spring of 2004. This policy was drafted through an interagency process that proceeded rapidly, coordinated by the Office of Science and Technology Policy (OSTP) and the Homeland Security Council under the leadership of General John Gordon. The recommendations were adopted and a Memorandum of Understanding was signed that led to the creation of NSABB.

Dr. Venkayya emphasized three issues in his remarks to the Board. First, although NIH is the executive agent and the Secretary of HHS has ultimate authority over NSABB, the Board will be advising the conduct, funding, and support of life sciences research across the Government, not only the research supported by HHS. Second, Dr. Venkayya advised the Board to be forward thinking in their approach. He said they should have answers ready before questions arise, anticipating the concerns that may appear on the front page of the Washington Post or the New York Times. Third, he stated that regardless of the constructive actions of the U.S. or any Government, of any professional organization, or of any company, these efforts will be irrelevant if individual scientists are not instilled with a core sense of ethics. He stated his opinion that development of a code of conduct is critical, whether through the Board's efforts or in collaboration with others. Dr. Venkayya advocated for a set of principles that can be infused into educational systems around the world, so that every person emerging from training understands the core tenets of the work they're engaged in. He stated that the individual scientist should mentor his or her disciples in these principles, whether postdocs, graduate students, or laboratory technicians.

Dr. Amy Patterson, Director of the NIH Office of Biotechnology Activities, then responded to a request for clarification, stating that the Board will meet publicly in accordance with the Federal Advisory Committee Act (FACA). On the rare occasion that a Board meeting might be closed, it would be in accordance with applicable laws and regulations. Dr. Patterson acknowledged that the public has provided support for much of the research the Board will be examining and will bear the consequences of the Federal policies that emerge as a result of the Board's deliberations. She considers open meetings of the Board critical to safeguarding public trust.

The group recessed for a lunch break, and upon their return, Dr. Paul Keim served as pro temp Chair in Dr. Kasper's absence (due to a scheduling conflict). Dr. Keim stated that the first information session would address the development of criteria for identifying dual use research and research results. He introduced Dr. Arturo Casadevall from the Albert Einstein College of Medicine.

Session I: The Development of Criteria for Identifying Dual Use Research and Research Results

Microbes as Weapons: Is There a Line in the Sand?

Arturo Casadevall, M.D., Ph.D.

Professor of Medicine and Microbiology and Immunology and Chief of Infectious Diseases
Albert Einstein College of Medicine

Dr. Casadevall stated that the dictionary definition of "weapon" describes something used to injure, defeat, or destroy, such as a club, knife, or gun. He said the human race has used many agents as weapons, whether kinetic, radiologic, nuclear, chemical, electronic, or informatic. He stated that a key problem with biological weapons is their enormous variety. The efficacy of these weapons is dependent on both the microbe and the host, and many of these interrelationships are not understood. Dr. Casadevall suggested that microbes used as weapons can be seen in one of two ways. He characterized the first as "tunnel vision" and the second as "tunnel myopic vision." Tunnel vision looks at microbes as either "weapon" or "not weapon." He said this black and white thinking has been used to generate the Select Agents list. Tunnel myopic vision, he explained, includes shades of gray. For example, microbes can be seen as not bad, somewhat bad, or very bad. He clarified that some organisms with low intrinsic potential to be weapons could actually be very harmful, depending on the host. Yeast and yogurt could be considered weapons because they can cause severe disease, again, depending on the host.

Dr. Casadevall said that Government officials generated the current Select Agent list based on historical use (e.g., the military); a history of causing pandemics; and other assessments, such as deliverability and weaponization potential. However, he said the list omits a number of new agents and many microbes. Examples include the influenza virus, which is estimated to have killed 80 million people in 1918, neisseria meningitis, and Group A Streptococcus. The Select Agent list isn't based on microbial pathogenesis and is often species-based, in other words, he believes the net is too broad. As an example, he stated that non-virulent and highly virulent strains are considered in the same way.

Dr. Casadevall and his colleagues are trying to develop a system to determine the weapon potential of a microbe based on the principles of microbial pathogenesis. To start, they made the following assumptions: that each microbe has some weapon potential, that weapon potential is a function of variables that determine microbial pathogenesis, and that weapon potential may be quantifiable. The theory takes into account the interaction of the microbe and the host, which he referred to as a damage-response framework. The damage can be caused by the host, the microbe, or both. Dr. Casadevall showed a slide indicating that the basic relationship for the damage-response framework is a parabola, because for most microbes that cause disease, damage tends to occur at the extremes of host response. He explained that there is more host damage when there is either a very weak immune system or a very strong immune system. The view of bioweapons from the damage-response framework indicates that they cause extensive damage in a short time. Dr. Casadevall noted that this holds true for most of the Select Agents on the list. He said that in developing the weapon potential relationship, he and his colleagues reasoned that it must take into account the technological capacity of the aggressor, as well as human behavior, such as panic. Eventually, they plan to examine amplification factors and the relationship of damage to time.

In 2003, these researchers defined "virulence" as the relative capacity of a microbe to cause damage in a host. However, Dr. Casadevall said this definition didn't help them in ranking microbes. They developed a quantitative definition, which states that the virulence weapon potential is a fraction symptomatic over the inoculum. Organisms that cause disease of very

low inoculum will appear to have a great degree of virulence. He said the weapon potential of a microbe depends on the inherent virulence but is influenced by communicability, stability, and time. By setting all the variables to the maximum, the scale could have a weapon potential maximum of 100. The researchers set out to perform some sample calculations by using data taken from the literature. He said they lacked the basic information to make weapon potential calculations for most Select Agents, even using this simple type of relationship. He stated that the field doesn't really know the inoculum necessary to cause disease. They can only guess at the value of variables. Giving the example of B. Anthracis using numbers from the literature and assuming no communicability, extreme hardiness, and a time to disease of 14.2 days, the result they arrived at was 5.6×10^{-4} out of a possible 100. [Susan, can you clarify his point?]

Describing the weapon potential of other organisms, Dr. Casadevall said that Variola is approximately 100-fold times more dangerous by this scale. Candida albicans is very, very low, although not zero. He noted that HIV is not on the Select Agent list, yet this organism is depopulating certain areas of Africa. He said it is almost the equivalent of a strategic weapon, if time is not taken into account. He also noted that the weapon potential of SARS it very high. Dr. Casadevall pointed out that deliverability and immunity change weapon potential over time, so that none of these cases are fixed. He said that Bacillus anthracis, for example, was not a biological weapon in 1890 because the technology did not exist to weaponize it. Extrapolating into the future, one could also ask whether the agents on the current list will still be biological weapons in 2020. For example, if the population received a highly effective vaccine against Bacillus anthracis, it would lose its weapon potential. He stated that Variola was probably not a major biological weapon from 1945 to 1950 because of universal vaccination, which led him to ask what could happen in the future with organisms such as the polio and measles viruses. When scientists are successful in eradicating them and the public stops being vaccinated against them, these microbes could be used as biological weapons.

In closing, Dr. Casadevall said he believes that all pathogenic microbes have the potential to be converted to weapons. He stated that placing a microbe on a list may itself be an act of dual use, as it can either protect or harm humanity. He believes that regulations that inhibit research make society more vulnerable. Dr. Casadevall commented that the weapon potential of microbes changes with time, as shown by the fact that public health successes, such as eradicating small pox, can also create weapons. Even though great advances have been made and a Select Agent list has been developed, there are still threats that have not yet been addressed. He closed by stating that the Board must walk a balance between anarchy on one end of the spectrum and a police state on the other.

Dr. Keim introduced Dr. Ronald Atlas, Professor of Biology and Co-director of the Center for the Deterrence of Biowarfare and Bioterrorism at the University of Louisville. Dr. Atlas was a member of the NRC's Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology. He was present to provide his perspective on the experiments of concern outlined in that committee's report, titled Biotechnology Research in an Age of Terrorism, also known as the Fink Report.

National Research Council Perspective: Experiments of Concern

Ronald Atlas, Ph.D.

Center for the Deterrence of Biowarfare and Bioterrorism, University of Louisville

Dr. Atlas thanked the Board for the opportunity to present his own views on the work of the Fink Committee, which led to the creation of NSABB. He presented two very different perspectives on dual use. The first dominates many international discussions. It addresses the concept of dual use as activities intended for biowarfare or bioterrorism that are masked as legitimate activities. He gave as an example a vaccine production facility that is actually growing large amounts of anthrax. Dr. Atlas said this is not the concept the Fink Committee dealt with. The Committee addressed legitimate activities carried out by the scientific community every day that have the potential for subversion by those who seek to do harm. It was with this in mind that they proposed a system for NSABB that will help to protect the life sciences against the potential misuse of biological materials and information and maintain the public trust.

The Fink Committee recommended a series of stages to allow for review of experiments and their results. The goal would be to provide reassurance that there is responsible oversight for the advances in biotechnology that have applications for weapons development. Dr. Atlas said this idea is appalling to some of his colleagues, who believe that science is value neutral and there should be no efforts to limit knowledge. He argued that the prohibitions of the Biological Weapons Convention (BWC) which state that one should not develop or stockpile biological weapons is accepted not only by the U.S., but at the international level.

The Fink Committee defined seven classes of experiments of concern. The classes are process-based, not based on Select Agents or on limiting research. They were developed based on the original NIH RAC Guidelines, which assert that there are certain types of experiments that require review and discussion by informed members of the scientific and medical community. This thinking was applied to vaccines and the Committee considered virulence, transmissibility, host range and detection, and weaponization. Dr. Atlas clarified that the Committee did not say that these experiments should not be done. Rather, they recommended a system of oversight for the life sciences that identifies potential dangers. The primary concern was with microbial pathogens. Although there are currently seven classes of experiments identified, Dr. Atlas said he expected that NSABB would be charged with continuously reviewing and updating the list. The seven classes of experiments of concern proposed by the Fink Committee:

- Would demonstrate how to render a vaccine ineffective; or
- Would confer resistance to therapeutically useful antibiotics or antiviral agents; or
- Would enhance the virulence of a pathogen or render a nonpathogen virulent; or
- Would increase transmissibility of a pathogen; or
- Would alter the host range of a pathogen; or
- Would enable the evasion of diagnostic/detection modalities; or
- Would enable the weaponization of a biological agent or toxin.

Dr. Atlas closed by stating that these classes provide an initial filter and that NSABB was being asked to provide additional guidance.

Dr. Keim introduced Dr. David Franz, also a member of the NRC Committee. He is a member of NSABB, Vice President and Chief Biological Scientist of the Midwest Research Institute, Director of the National Agricultural Biosecurity Center at Kansas State University, and Deputy

Director of the Center for Emergency Care and Disaster Preparedness at the University of Alabama at Birmingham.

Dual Use Dilemma: A View From the Ground

David R. Franz, Ph.D, D.V.M.
Chief Biological Scientist, Midwest Research Institute

Dr. Franz began by explaining the differences he sees between biological warfare and bioterrorism. Both employ dual use facilities, equipment, and people, and lack real-time detection capabilities. However, bioterrorism leaves extremely small "footprints" of the facility and weapons used. There is potentially no attribution. He believes biological weapons fall into a special category because almost anyone could make weapons of some kind and hide themselves relatively easily. In addition, the agents are available in nature. Dr. Franz pointed out that the tools needed to make these weapons are becoming better and more widely available. Technical understanding and capabilities are increasing. He emphasized that because biological experiments are initially designed for good, intent is an extremely important part of the overall equation in determining the threat of bioterrorism.

Dr. Franz explained that his frame of reference is one of military medical biological defense, because he trained and worked in this field. He performed infectious disease research for the military and was greatly influenced by his work with the United Nations Special Commission (UNSCOM), the "Triliaterals" threat reduction program, and the U.S.-U.K.-Russia weapons reduction agreement of 1992. In the context of someone who conducted weapons inspections, he briefly described his view of the dual use nature of people, facilities, and equipment. Dr. Franz described his experiences facing criticism at that time from people who didn't understand his intent. He said that both domestically and internationally, some colleagues in the sciences will have similar concerns about future defensive research designed to protect citizens.

Dr. Franz spoke on the value of science as a common language. When attending a meeting with many former Soviet Union Warsaw Pact scientists who had been involved in offensive programs, he said that communication, open discussion, and collaboration on common problems were critical. In the years that followed, he had the opportunity to tour a number of facilities that had the potential for dual use, yet he said it was difficult to determine the intent of those using them. He stated that the enormous facilities he saw in the former Soviet Union could be used for harmless purposes or for malicious intent. Equipment can also be used either for legitimate purposes or to grow weapons agents. He said that equipment such as orbital shakers, freeze dryers, and liotholizers have dual uses and are found in facilities in Iraq, the U.S., Russia, and other countries. A vaccine developed to protect goats and sheep could be weaponized; substances as ordinary as pure water for a vaccine facility could be used for warfare.

Dr. Franz stated that most of the time he and his colleagues spent on these inspections was "like assembling puzzles." The scientists had to speculate on the uses of the facilities and equipment they were seeing. He said these are difficult problems and there are no bright lines drawn with relation to dual use, whether for people, facilities, or equipment. He stated his opinion that the issues in Iraq, in the former Soviet Union, and in the 1990s were probably

easier to address than the security problems the country faces today. The technologies are improving and will continue to improve. He said vast oceans and friendly neighbors can't protect the U.S. as they have in past years. As a result, he said that determining intent has become even more important.

Dr. Franz stated that regulation must make us safer, yet over-regulation will limit progress. He said the U.S. absolutely cannot afford to impede progress because much more good comes from science than ill. He reiterated the importance of intent and said that because perception and communication are very important, the concept of education was a major focus of the Fink Committee. He closed by stating that a balance must be found in all of these areas.

General Discussion and Questions from the Board: Session I Speakers

Dr. Keim opened the floor to questions. Dr. Keim asked Dr. Atlas if he thought the need for background checks creates problems in training foreign students and experts who work with Select Agents. Dr. Atlas said he believes there is minimal effect and said the Select Agent system is aimed at developing a basis for trusting those in the laboratory. He stated that although a clearance process is required, the Select Agent rule does not eliminate foreign students, postdocs, or visiting scholars from participation. The only exclusions he was aware of pertained to aliens from a limited number of countries, which he said has had little or no impact on the scientific endeavor. Dr. Keim countered that his laboratory has had a Select Agent license since the late 1990s and his experience is that the rules do in fact impede progress. He stated that it's often difficult to have a background check conducted on a foreign national because their records are not as readily available and the timeline can be prohibitive.

Dr. Stanley Lemon stated that the various clearances required for American graduate students in his institution's laboratory make it very difficult for them to enter the labs on rotations. This creates a disadvantage for them and a disincentive for faculty to work on those agents. He characterized this as an unintended consequence of a well-intended regulation. Dr. Casadevall stated that because his laboratory develops antibody therapies for Bacillus anthracis, a Select Agent, a select license is required. However, they don't have a license. They're allowed to work with a vaccine strain that has the toxins, but not the capsule. He said there are many other attenuated strains that have the capsule, but they are not on the U.S. vaccine list. His lab can work with those strains even though they're attenuated, because the Select Agent designation is mostly related to species. He stated that as a consequence, there is much work that cannot be done. It can take place only through work with collaborators, or he could apply for a select license and turn his laboratory into a Select Agent lab, with all the issues that would involve. He stated that his work is being severely hindered. At his lab, they've made reagents that they can't easily test because of the regulations.

Dr. Michael Osterholm asked Dr. Franz to clarify what he meant when he stated that a terrorist footprint is small. Dr. Franz clarified that the potential for great harm can exist in a much smaller facility than was possible in previous years. The confusion was one of terminology; Dr. Osterholm was thinking of the "footprint" as the substantial amount of harm that's possible with the efficient weapon delivery systems that exist today.

Dr. Dennis Dixon said that credit should be given to the CDC for implementing the Select Agent process, even though it has limitations. He said there's a monthly panel meeting of

Government experts, called the Interagency Select Agent Technical Advisory Working Group, which deals with issues as they arise. This group helped create excluded strains of Select Agents. The Working Group uses a data-driven process that allows scientists to petition the CDC for an agent to be de-listed if the data shows that it can be modified so that it can't inflict the same damage that it previously could. He said Dr. Mark Hemphill at the CDC is the point of contact for these proposals. This ongoing process adjusts the Select Agent system over time.

Dr. Stuart Levy commented on the focus of the three speakers. He said Dr. Casadevall focused on the fact that any microbe could potentially be turned into a weapon, depending on its pathogenicity traits or amplification and the ability to spread. Dr. Atlas spoke about experiments of concern that could be used for dual purposes. Dr. Franz described intent and focused on balance as the most important factor. Dr. Levy disagreed with the latter point, stating that he believes the primary emphasis should not be on balance, but on education and communication. He said young students must learn to distinguish between what is good for the world and what is bad for the world. He stated that getting this message out is one of the country's best defenses, as well as encouraging societies worldwide to agree that there are specific criteria for good science as opposed to bad science.

Dr. Murray Cohen asked the speakers about their experiences with screening or routinely re-checking scientists for changes in intent. His point was that people change over time and are influenced by various circumstances, so that the initial background check may not be sufficient. He asked Dr. Atlas if the Fink Committee considered this issue. Dr. Franz commented that the dangers in biology are part of a new world. In the past, the chemical and nuclear communities conducted ongoing examinations that looked for psychological factors affecting individuals. He wasn't sure how this is being handled in biology, but stated that he thought surety programs are conducted primarily in Department of Defense research. Dr. Michael Imperiale asked Dr. Franz how he envisions assessing intent. Dr. Franz said the general approach has been to work with people for a long period of time before allowing them access to high-level biohazard facilities, such as Biosafety Level 4 (BSL-4) labs. Sometimes people are not allowed to go into the labs unaccompanied. In nuclear or chemical facilities, he said there are ways to measure whether something is being taken out, but this process is more difficult to implement in biology labs. He again stressed the importance of open communication, education, and awareness, stating that eventually, trust must be established.

Dr. Lemon asked Dr. Atlas to comment on the tenor of the international response to the Fink Report. He asked whether the report has been recognized, and if so, whether the response was favorable. Dr. Atlas said he's been traveling internationally to talk about the Fink Report and he senses a "wait and see" attitude. There is genuine fear of potential U.S. Government actions, particularly a growing fear that the NIAID biodefense programs are a cover for biological weapons programs. Within the United States, there is a fear of bioterrorism and the possibility that the scientific community may cause harm through misuse. However, the NIAID effort is seen in the U.S. as beneficial to the development of vaccines, therapeutics, and diagnostics, which will offer protection against threats. Dr. Atlas said the Fink Committee saw the need for global outreach from Day 1. They used the recombinant DNA debate as a model, which started in Asilomar with conversations in the United States, but led to the development of parallel structures at the Organization for Economic Cooperation and Development (OECD) and at WHO. This was the start of global agreement on the safe conduct of recombinant DNA research. The Fink Committee hoped that NSABB would move forward with a similar

international dialogue. Dr. Atlas said that otherwise, he would not see much value in NSABB's efforts. Dr. Franz added that the Intentional Epidemics Group at WHO, led by Mary Chan, is working on these issues in collaboration with a number of other countries.

Dr. Harvey Rubin asked Dr. Franz to comment on proposed and expanded research in some of the new labs within the Department of Homeland Security and DoD. He wondered how this research might be perceived in the U.S. and abroad. Dr. Franz was not able comment specifically on what is taking place in those labs, but agreed that perception is important. He hears such questions from the media and said they must be taken seriously. He firmly believes that there is no intent in the U.S. Government to contravene the Biological Weapons Convention, but there are people who believe we might. In cases where research must be classified or results can't be provided because they expose vulnerabilities, Dr. Franz acknowledged that there will be a problem convincing some that the U.S. is not contravening the BWC. He said collaboration with allies might be one way to diffuse some of that speculation, both internationally and domestically.

Admiral William Studeman returned the discussion to the issue of security and intent. He stated that in the intelligence community, there are significant processes in place for clearances, training, ethics standards, polygraphs, financial disclosure, reinvestigations, expedited investigations, and paid investigations, and all of these are necessary but not sufficient conditions for security. He noted that the history of espionage demonstrates that at any given time there are probably two or three "bad apples" in the system, if not more, and that most damage takes place because of the insider threat. One could question whether the cost of these efforts in both process and dollar value justifies the gain, but he said there's currently no mechanism to replace them. Those in espionage have learned to cast a wide net. He said focusing on the threat agent and the connection between the threat agent and the insider is critical, presuming that the insider is not operating on his or her own.

Dr. Barry Erlick then commented that the issues before the Board seem more global than the NSABB charter indicates. He asked Dr. Franz if they may be looking at the pesticide industry and other areas that incorporate biologicals, i.e., if NSABB will have a broader scope than was first conceptualized. Dr. Franz agreed that the topics will be very broad and will continue to be a moving target as technology changes. Dr. Erlick added that the Board should probably be concerned with the engineering aspects of weapons and their delivery systems. This would include experimentation for more efficient dissemination processes. Dr. Casadevall agreed, pointing out that the delivery system for anthrax in 2001 was an envelope carried by the U.S. mail.

Dr. Rubin asked Dr. Casadevall if a significant effort is being made to conduct mathematical modeling of outbreaks. He asked if mathematical modeling of such scenarios becomes a Select Agent in and of itself. Dr. Casadevall stated that any work done in this area has the potential for dual use and part of the Board's responsibility is to discuss this. He said he had considered the possibility that work on algorithms could provide knowledge on biological weapons to those with malicious intent. He came to the conclusion that this would not happen because there would not be enough data. He expressed the belief that such exercises offer protection because they show researchers what to do and expose liabilities and vulnerabilities.

Dr. Osterholm stated that this is a critical point because biosecurity and agents are not just

laboratory-based. He compared the development of weapons to cooking a soufflé: one can invent a better egg (the agent), get a better skillet (the method of transmission), or use a better recipe (how to put it all together). He said the Board must worry about all three aspects because informatics today allows scientists to make the whole recipe readily available to someone who otherwise would not have all of the elements. Dr. Rubin stated that at his institution, engineers are working on these kinds of issues. The Wharton School is conducting computational analysis on the vulnerability of networks and they will be applying to the IBC to perform that work.

Dr. Osterholm said he intended his comment to apply to the issue of both the agent and the millions [of ?] who transmit the agent in a more efficient way. He stated that technology is not limited only to growing bugs, it's also the means for delivering them. Aerosol particle technology has improved dramatically in the last two decades. He said he can buy devices at electronic shops that in past years would only have been available to bioweaponeers at the highest levels of Government. He stated that for the last 15 years, food safety has been approached from the standpoint of hazard analysis of critical control points. This means analyzing the food system to figure out where the vulnerable nodes are, i.e., where "Mother Nature" might create a food problem. Today those very plans are blueprints for a food terrorist. By taking those plans and putting them together in the right setting, a terrorist would have step-by-step instructions, and he said that's one of the issues the Board must consider.

Dr. Atlas commented on the question of engineering delivery systems, because these activities could lead to a real roadmap. Concern must be highest there, because of the clear and imminent danger. He stated that as technology evolves, there will be risks, but he doesn't think technology should be constrained because it's the basis for the advancement of science. The important questions to ask are: When does research get close to development? When is it a road map? When does a technology constitute clear and imminent danger?

Dr. David Relman said he liked the concept of looking at vulnerabilities as a metric for understanding where unusual risks may exist. Vulnerabilities reveal points of intense need for further work. He emphasized the importance of a flexible scientific enterprise that understands where the highest-priority needs are for research. He suggested that the group focus their efforts on vulnerabilities and situations in which vulnerabilities are also accompanied by large gaps in time during which no suitable defenses are in place. Dr. Relman said the idea of identifying roadmaps presents difficulties because many fundamentally important papers on the mechanisms behind virulence are, in fact, blueprints for constructing strains or biological agents of potential untoward effect. Again, the focus comes back to intent.

Dr. Levy said he would like reassurance that good science that can be helpful in the area of infectious diseases will not be destroyed because of the fear that it will end up as a roadmap. He stated that more research is needed to understand how infectious disease microbes move. The sooner scientists know how they're transmitted, at what speed and by which route, the faster they can prevent their spread. He strongly recommended increasing research on disease spread. The field knows very little in this area. He asked Dr. Casadevall for his opinion. Dr. Casadevall agreed and also pointed out that the benefits that accrue are often very difficult to rationalize ahead of time. For example, some research efforts are studying anthrax toxins in the treatment of cancer. He said that even defense research in bioscience may have tremendous benefits in non-defense arenas. It's conceivable that money spent on basic research on infectious diseases may result in tremendous benefits that can't be foreseen.

Dr. Erlick also agreed with Dr. Levy and said the discussion reminded him of the arguments in the last decade concerning Variola major. Some said it should be destroyed because it could be a significant threat agent, but it was later determined that scientists didn't know as much about it they thought. Similarly, although scientists today know a great deal about disease mechanisms and causative agents, they may find out later that they don't know enough to justify eliminating a line of research or a particular agent. Dr. Erlick stated that, "once it's gone, it's gone." He advocated taking a cautious approach toward the regulation of research.

Dr. Keim returned to a point made by Dr. Osterholm; that the threat is really a multiple-stage process in which all components must be obtained. He asked if it would be possible to define some key components and designate them as "safety valves," so that work could be done safely up to a certain threshold. Dr. Osterholm said it's not possible to distinguish key components because there is also a psychological impact that must be taken into account. He said, as an example, that several years ago a group of researchers created the polio virus from gene sequences and amino acids from their general supply. If the polio virus had created an epidemic because it was accidentally released, and if the right connotation of terrorism intent had been present, it would have created a panic. Dr. Osterholm also stated that there are so many possible combinations that he would hesitate to define an "absolute combination." For each situation, scientists must constantly assess the agent, the mode of transmission, the host, and the possible psychological impact.

Dr. Osterholm emphasized the need to work on emerging issues, rather than yesterday's issues. He said the Board must anticipate the likely problems of technology changes in informatics, microbiologics, and delivery. He stated that the problems of today will seem relatively mild in the future. He gave as an example the impact that computer hackers had on society 8 years ago, compared with the present day.

Dr. Lemon said he felt that more importance should be placed on the concept of the weaponization of microbes. He compared a vegetative anthrax bacillus with an anthrax spore that's been well milled and ground, and said the latter could be used more effectively as a weapon. He said this distinction is important in the perception of the work that's taking place in various labs. Labs that are working with infectious agents that can be weaponized are called "bioweapons labs," yet they're not actually dealing with bioweapons. They're dealing with microbiological agents that could be weaponized. He asked Dr. Casadevall to comment. Dr. Casadevall said he thought the overwhelming majority of people who work on these agents do not have the capacity to make weapons, even with intent and the availability of the disease. Dr. Franz agreed and noted that the discussion underscored a point made by Dr. Levy about the importance of education and awareness. The public, the media, and Government leaders must understand that even though scientists are working with dangerous viruses, they're not working with weapons.

Mr. Mark Nance asked Dr. Franz for a point of clarification on intent. He stated that lab personnel in this country are already being monitored if they're dealing with dual use agents. He asked if the threat of most concern should be the asymmetric threat, i.e., the small footprint threat. Dr. Franz replied that the dual use threat is a greater part of the Board's mission. NSABB will address the actions and education of research scientists in this country so they're aware of the potential harm that might come from their research even if they don't have intent.

After a break, Dr. Keim introduced Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID). He said Dr. Fauci serves as a key advisor to the White House, to HHS on global AIDS issues, and on initiatives to bolster medical and public health preparedness against possible bioterrorist attacks.

Balancing Biosecurity and Scientific Progress: The Need for a Culture of Responsibility

Anthony S. Fauci, M.D.
Director, NIAID

Dr. Fauci stated that the Government is working to detect, plan for, and ultimately develop countermeasures against potential threats of biological, radiological, and chemical warfare. He said the expansion of countermeasures has been placed in the hands of the scientific community as a fundamentally transparent process. However, this research brings up issues of potential dual use because certain results raise biosecurity concerns that go beyond the immediate concerns of physical containment. He noted that the Fink Report tried to address research in the arena of terrorism while maintaining an open scientific discourse.

Dr. Fauci stated that NSABB was developed according to the fundamental principles used by the RAC. The RAC serves as a public forum for in-depth review and discussion and eliminated the need for Congress to formally legislate oversight of research activities involving recombinant DNA. Dr. Fauci said that Congressional involvement is not bad in and of itself, but could have the potential to interfere with scientific discourse and experimentation. The RAC was directed to provide guidance and leadership, which is what NSABB is also being asked to do.

In early congressional hearings on the development of NSABB, Dr. Fauci was asked what kind of enforcement and security the Board would take responsibility for. He said it took some time to get the message across that NSABB will not be policemen who are up against the "bad guys." The goal is to set up a culture of responsibility and a framework for providing advice and input to the Secretary of HHS, the Director of NIH, and the heads of Federal agencies. He said this culture of responsibility applies only to work that's supported by the Federal Government, because this is the only arena in which the Board can have true enforcement capability. NSABB doesn't have control over researchers who are not receiving Government funding or over international research. The Board can't tell publishers what to publish or not publish.

Dr. Fauci said NSABB must therefore focus on scientists developing a culture of responsibility that will improve security at the level of the individual scientist and laboratory worker. A framework can be developed to provide guidance, eventually leading to guidelines that, hopefully, can be accepted worldwide. He reminded the group that the RAC doesn't have jurisdiction over international issues, yet in the last 30 years, the guidelines set down by the RAC have become internationally accepted. In an indirect way, the RAC has been very effective in establishing a culture. Similarly, Dr. Fauci called upon the research community to actively participate in the deliberations of NSABB in an open and transparent way. He concluded by stating that the Board's success will depend on the talent and scientific input invested in the process.

Dr. Keim introduced the topics for Session II, stating that the presenters would discuss various perspectives related to the communication of dual use research results, methods, and technologies. He stated that Dr. Judith Reppy would begin with a discussion of dual use information issues for NSABB.

Session II: Communication of Dual Use Research Results, Methods, and Technologies

Dual Use Information Issues for NSABB

Judith V. Reppy, Ph.D.
Associate Director, Peace Studies Program
Cornell University

Dr. Reppy emphasized that security threats today come from both state actors and non-state actors, such as terrorists. She said that biotechnology is intrinsically dual use and that virtually all military uses also have a civilian counterpart. Many, if not all of these civilian uses are of potential interest to the military. Dr. Reppy stated that governments have long had an interest in controlling the spread of dual use technology and information. During the Cold War, the Coordinating Committee of Multilateral Export Controls (CoCom), an international group, oversaw a list of dual use items that required approval before export to the Warsaw Treaty Organization and other countries of concern. These controls extended to information. Dr. Reppy said the current VASANAR arrangement that followed CoCom at the end of the Cold War is much weaker than CoCom.

Dr. Reppy pointed out that biotechnology was not included in any of these dual technology control lists until recently. It wasn't a matter of interest during the Cold War period. The Australia Group, founded in 1985, stepped into this vacuum to extend export control to technologies that might be used for chemical or biological weapons. Dr. Reppy said that because these controls are agreements among states, they are of limited use in combating terrorism. Also, their scope is limited by virtue of the fact that technology is changing rapidly and they work from fixed lists.

Dr. Reppy spoke of serious challenges in safeguarding biotechnology information. She said pathogens are everywhere and even a small amount can do harm. Biologists are numerous and diverse, located in various institutions, and there is no tradition in the life sciences of collaboration between the scientific community and the security community, as there has been in nuclear physics. There is therefore no previous base on which to build trust within a regulatory system. Another challenge involves the established culture of circulating information among scientists internationally in more than 10,000 journals, as well as conference papers and research proposals. She said it's questionable whether the information flow in the life sciences could be controlled in the way that nuclear information is being controlled. If it is attempted, the cost to science will be very high.

The Fink Committee considered these issues and tried to balance the strong need to protect the free flow of information because of its importance to the biological sciences and biotechnology, with the need to prevent some of that information from getting into the wrong hands. The

Committee's solution was a system of self-regulation modeled on the Asilomar and RAC processes, with local IBCs reviewing experiments of concern and journal editors reviewing journal articles. This system has the benefit of relying on existing and trusted institutions at the local level and it gives an important role to scientists. The existence of such a system can provide consciousness-raising for the life sciences community and avoid the imposition of blanket regulations. Problem experiments would be dealt with on a case-by-case basis. Dr. Reppy then addressed three issues:

1.What kinds of information need to be restricted? She stated that tacit knowledge, particularly the kind that comes out of laboratories, is an important component of scientific knowledge. Dr. Reppy pointed out that it's not easy for terrorists to replicate scientific experiments that they've only read about. However, over time, tacit knowledge can become codified. Kits can be obtained from scientific supply businesses that do much of the work that previously required trained technicians. Dr. Reppy emphasized that the insider problem is always the most significant and it's the insiders that have the tacit knowledge.

2. What is the current scope of regulatory review and will this system work for biosecurity issues? Not all industry and Government research is covered by IBC review, which is tied to NIH funding. Some is covered voluntarily by organizations that don't have NIH funding, but this is not required. Dr. Reppy asked what monitoring controls should be extended to labs that are not under IBC review. She said the Fink Committee recommended extending IBC security review to all relevant research institutions, but the Committee left this decision for NSABB.

3. The third issue was the need to affirm the importance of the free exchange of information. Dr. Reppy noted, however, that the "sensitive but unclassified" (SBU) category is problematic. She explained that the Government has a policy that fundamental research funded by the Government should be unrestricted to the maximum extent possible, but when restriction is necessary, the proper mechanism is classification. However, Federal agencies have tried to insert SBU clauses into research contracts, and this category of information may become increasingly closed off from public circulation. Dr. Reppy discussed the fact that the practice of classification of information poses its own problems, such as how to identify information that must be classified. If the criteria are too broad, they will cut off important communication in the open literature. If they are too narrow, they will raise to a high degree the expertise required to determine what should be classified, because every piece of knowledge will have to be inspected. She stated that this is an important issue for NSABB because any exclusions from the regulatory system opens loopholes for abuse, particularly the use of classification to restrict activities from public scrutiny.

Dr. Reppy closed by stating that it's very important for NSABB to find the right balance and determine the costs of either too little regulation or too much control. She emphasized that any solution arrived at must be acceptable around the world.

Dr. Keim introduced Dr. Thomas Bowles, stating that he would share lessons learned in the nuclear physics and cryptography communities.

<u>Past as Prologue: Are There Lessons to be Learned From the Nuclear Physics and Cryptography Communities?</u>

Thomas Bowles, Ph.D.
Chief Science Officer, Los Alamos National Laboratory

Dr. Bowles spoke based on his experience in the nuclear physics and cryptography communities at Los Alamos National Laboratory (LANL). He explained that LANL is a multi-purpose national defense laboratory. The primary mission is stewardship of the Nation's nuclear stockpile; responding to threats of weapons of mass destruction; and responding to the Nation's energy and environmental needs. He stated that there is a strong and growing bioscience program at Los Alamos, which focuses on the intersection of bioscience and national security. Some activities at LANL are purely classified, such as the nuclear weapons program. Some research is fundamental and provides the core capabilities that drive LANL's national security abilities. One of the hallmarks of Los Alamos has been the free and open exchange of unclassified information. The laboratory is operated by the University of California and has academic freedom of expression at the core of its ability to excel in carrying out its missions.

Dr. Bowles said the majority of nuclear physics research is unclassified and often involves large collaborations with several countries. A small fraction of this research generates dual use information. LANL is increasingly dealing with security issues and responding to the needs of homeland defense. For example, some technologies are developed to detect the entry of illicit nuclear materials into the United States. LANL's quantum cryptography (QKD) efforts are also relevant to dual use. Originally, quantum cryptography was envisioned as a means for the intelligence community to provide absolutely secure information transmission. This knowledge has applications for people who are trying to protect information of any type. The field of quantum computation (QC) is directly allied, and its applications range from an entirely new evolution in computer science, to the ability to factor large numbers, which is critical in quickly breaking codes.

LANL deals with two types of information. The first is pure data that comes out of experimentation and theory, the second is the techniques and equipment that have dual use applications. In both cases, they're very careful when information goes from single use to dual use; i.e., when data is combined with a dual use application. It then becomes classified information. In homeland defense, Dr. Bowles said the specific sensitivities to detection and capabilities to detect threats are restricted. There are different classification levels imposed on different types of information, particularly in quantum cryptography.

Dr. Bowles stated that as a scientific organization, LANL publishes about 1,800 open-published, peer-reviewed journals a year. He said that handling the flow of information has been a challenge. LANL has two paths for publication and presentation of research. The first path exempts certain areas from classification under a mechanism called designated unclassified research areas (DUSA). Under this system, certain well-defined areas are considered not essential to national security and are therefore not classified. The approval process for DUSA usually takes about 18 months. It's fairly rigorous, but once it is in place, there's a standing exemption for the approved information. The second path involves review of papers and talks by an Authorized Derivative Classifier (ADC). ADCs are specifically trained to look at classified information issues in a publication and every LANL product that is not under DUSA goes through this process.

Dr. Bowles said that one of the greatest challenges is monitoring mail and email communications, because these pose tremendous susceptibility to security risks. Everyone at Los Alamos is trained to recognize classified and unclassified material and the training is renewed every year. If one is unsure whether information is unclassified, an ADC will check it. Dr. Bowles said LANL's failure rate is about one in ten to the seventh power, which is enough to draw scrutiny from Congress. There are three areas in which problems arise: when content was sent that should not have been sent, which is extremely rare; when the classification level was incorrectly determined; and the greatest problem, when a sequence of emails taken together constitutes classified information. Dr. Bowles said the culture of awareness is very important because it's impossible to provide the detailed guidance required for each and every message sent. The estimated cost for this type of monitoring would be $395 million a year, which is not feasible.

Concerning communication within groups of people, some at LANL are cleared and some are uncleared. Some are foreign nationals, including 540 permanent staff members. Dr. Bowles said that normally, nuclear physics work on dual use technologies can be conducted in open, unclassified environments. In some cases, part of a group has offices inside a secure area and part of the group has offices in an open area. For specific experiments, they use special controls for a limited time, such as physically secure areas. Quantum cryptography is more restrictive, because it deals with intelligence information. This work is carried out inside Sensitive Compartmented Information Facilities (SCIF), with stringent access controls. This system automatically limits communication because not all people in the group have access.

Dr. Bowles said that there is a greater level of concern when dealing with people from sensitive countries (defined as those that present particular threats to the United States). There are currently about 25 sensitive countries, such as North Korea and Iran. Most countries that have been placed on this list are there because of concerns about nuclear technologies. Dr. Bowles said one of the questions for the bioscience community to address is whether to single out people from those countries as a particular threat and decide whether they will be dealt with differently than those from non-sensitive countries.

Every time a foreign national comes in to LANL, they must receive approval, whether they're there for an hour or working permanently. This process includes development of a statement of work that indicates who will oversee the person's work and what access to facilities and computer systems the individual will have. This is reviewed on a case-by-case basis every year to verify that there has been no loss of sensitive information or technologies. Dr. Bowles said the restrictions are becoming increasingly stringent. The foreign nationals soon may not be allowed access to administrative information maintained on the lab's computer system, such as how much vacation time they have. The foreign nationals have felt the impact of this increased scrutiny and they feel discriminated against. Dr. Bowles said that is just a fact of life at Los Alamos. He tried to convince the DOE that the restrictions placed on foreign nationals constitute a greater security risk than the presence of the foreign nationals, because the best minds in the world are needed to address national security issues. DOE rejected this idea because they don't want foreign nationals close to classified information, even though in the last 50 years there has never been a documented case in which a foreign national accessed classified information. Every time there has been a security issue, the perpetrator has been a U.S. citizen with access, i.e., an insider.

In terms of lessons learned, Dr. Bowles said the bioscience community must deal with the increasing rigor that's focused on national security issues, which will be much more challenging than in the nuclear arena. He also said dual use technology necessarily requires additional efforts, such as review of publications and presentations, mail, and email; and awareness in discussions with internal and external personnel. He said the culture of awareness is absolutely critical, but it takes time, money, and resources, which will necessarily be diverted from scientific research. Dr. Bowles reiterated that physical access issues must be discussed, particularly with relation to foreign nationals. He recommended the formation of integrated teams between science and compliance personnel to develop solutions. In closing, he offered the services of the laboratory to NSABB in any way that might be useful.

Dr. Keim then asked Dr. Phil Campbell, editor-in-chief of *Nature* and a Director of the Nature Publishing Group, to share perspectives from the scientific publishing community.

Scientific Publication and Security: The Perspective of Scientific Journal Editors and Authors

Phil Campbell, Ph.D.
Editor-in-Chief, Nature

Dr. Campbell stated that he was presenting his viewpoint, although he said that many editors of science journals agree on the issue of regulation. In January 2003, a number of science journal editors and authors met following a meeting of the National Academy of Sciences to discuss many of the same issues that are of concern to NSABB. Dr. Campbell said they largely reached consensus on the minimum amount of regulation they could accept. He said the meeting was also attended by representatives of Government agencies and departments, which he believed was an effort to help the field regulate themselves by adopting a culture of responsibility. He also stated that Congress was concerned about the content of some recent publications, and the editors and authors wanted to anticipate and preempt any over-reaching regulation.

After much soul searching, the group developed a statement that was published in the journals they represented. The statement allowed that there might be papers that should be modified or not published in the interest of national security. This stance created some controversy, such as Dr. Stanley Falkow's call for clarification on what information might be regulated, which appeared in the journal *Science*. The Public Library of Science made a strong statement on their website that any such control was a form of censorship. Others, including Dr. Richard Meyer of the CDC, was concerned that the policy left room for too much openness and recommended that key details not be published.

Nature followed up by establishing an informal group of advisors with representatives from the defense establishment, including national labs in the U.S. and at Porton Down in the U.K. They held informal discussions and established an internal framework for consultation. The policy they developed is very straightforward; *Nature* and its sister publications maintain a network of advisors that they contact specifically to discuss publications on biosecurity issues. Once publication decisions have been reached, the authors under discussion are informed that the biosecurity network has been consulted.

Dr. Campbell said he has been asked why the security advisors' identities and advice is

confidential. He said it would be a cultural leap to announce the identities because the policy of anonymity applies. In addition, these reviewers are often providing technical advice. He has been asked what happens when a paper is rejected on security grounds. Currently, author confidentiality overrides all other needs. He said there is no agreement in place by which Nature tries to prevent a paper from being considered by another journal. Dr. Campbell stated that this is an issue for the Board to consider. He said the consensus statement does not include major foreign language journals, although there are a small number of publishers from outside the U.S. represented. He also said the risk reviewers are not asked prescriptive questions about the publication under consideration. As the journal editors can't anticipate non-obvious risks, they request an open-ended assessment of whether the publication might be undesirable for security reasons.

Nature and Science have sent out several papers for dual use assessment and there have been no decisions not to publish. Dr. Campbell said that to the best of his understanding, none of the papers submitted to the American Society of Microbiology (ASM) have been rejected for purely security reasons. Most papers are now co-authored by an average of five people, and he noted that approximately 60 percent of ASM's submissions include multinational partnerships.

Dr. Campbell stated that the emerging consensus is that open publication is a key to public health. Dissemination of information on the pathogenic mechanisms used by organisms to outwit the immune system is necessary to develop new treatments. He said some experiments with hybrid pathogens against scourges that kill many people worldwide are worth the risk. Properly contained experiments in appropriate facilities are crucial, and public outreach and education are necessary to avoid misunderstandings and inappropriate regulations. He noted that publication of the infectious mechanisms and genomes, such as the SARS genome, demonstrates the fact that immediate health benefits can result from openness. Other benefits include economic health, academic quality, the ability to attract talent, and the fact that openness encourages international collaboration.

Dr. Campbell said science is an international activity and it requires international consensus on what constitutes appropriate action. Overly stringent regulation of publications in only one country will be ineffective. For example, classifying certain research unilaterally would create incentives for scientists to move research programs elsewhere, as has occurred with stem cell research moving from the U.S. to other countries. Dr. Campbell noted that there is a key issue of trust in science. He said there is no question that editors and scientists outside the U.S. will be wary about U.S. motivations if publications are restricted. The visa situation, for example, has led to a chilling of the climate internationally and has affected individuals' decisions to enroll in U.S. institutions and businesses. Some of the key information resources that the field depends on are available through public funding in the U.S., such as the National Library of Medicine's PubMed. If this library were to come under some sort of Government control, there are concerns about what might happen, i.e., would NLM have to excise controversial papers at the request of the Government?

Dr. Campbell referred participants to an article in the Journal of Homeland Security (a free access online journal) published in December of 2002, which he thought anticipated the question of the grounds for not publishing papers. Written by Ray Zilinskas and Jonathan Tucker of the Monterey Institute for International Studies, the article lists six types of work that should raise concerns. Each type involves a Select Agent and aims to achieve one or more of

the following weaponization-related goals:

- Enhance pathogen infectivity, pathogenicity, antibiotic resistance, or resistance to host immunological defenses;
- Improve the ability of a microbial pathogen to remain viable and virulent during prolonged storage and/or after release to the environment;
- Facilitate the dissemination of biological agents as a free-particle aerosol;
- Facilitate the dissemination of a biological agent by contamination of food or water sources;
- Create a novel pathogen or one with characteristics that have been altered to evade current detection methods or host immune defenses; or
- Assemble oligonucleotides to synthesize the genome of a pathogenic organism.

Dr. Campbell also highlighted some points made by George Post at the 2003 NAS meeting (and formerly published), which listed areas of research that scientists and journal editors should be aware of in the future, i.e., "bioweaponry to come:"

- Microbiology just part of the landscape;
- Deliberate engineering of immune escape, stealth viral vectors;
- Overproduction of host inflammatory mediators to produce toxic shock;
- Knocking out genes that regulate key cell processes, such as cell proliferation;
- Small molecules that disrupt molecular circuits, e.g., networks in immune response, blood clotting system, higher brain function; and
- Acoustic disruption: bone pain, airway modulation, ultrasonic skin heating.

He said these areas are at the most exciting end of research and pointed out that there are definitely dual use issues in areas other than microbiology. Dr. Campbell referred also to the recommendations of the Fink Report concerning manuscripts that document experiments of concern.

He reiterated that since the editors' meeting in 2003, many journals have published papers that were assessed by security experts and none were sources of contention. He raised an issue that was in the news concerning a paper that was submitted to the NAS. It documented a theoretical mathematical study about the impact of introducing botulinum toxin in the milk supply in the U.S. It analyzed the range of impacts on health and mortality and the responses to protective measures, highlighting security needs. The author checked with HHS, which advised against publication, but the author denies that he received that response. NAS followed their procedures and all the referees approved publication of the paper. The NAS press released the paper and issued it in embargo form to journalists. One journalist contacted HHS and asked for the agency's reaction, after which HHS contacted NAS to express their concern. NAS decided to delay the paper's publication, had a meeting to discuss the issue, and then published it.

Dr. Campbell stated that this incident raises the issue of the responsibilities of researchers, HHS, and other agencies to pursue such topics in a fairly rigorous way. He asked what process is in place for researchers once they have completed a piece of work that they consider

sensitive. He said it's a straightforward issue for the Board to address whether such a system could be set up and what that alert system should consist of. There is also the question of what constitutes sensitive research and how Government should respond. Dr. Campbell said there's a lack of guidance in these areas and the Board can play a key role in addressing the issues.

Dr. Campbell described synthetic biology and some of the issues it raises for journals and the community. An article written by Oliver Morton in the January 2005 issue of Wired magazine describes a program for assembling a set of parts and making artificial replicating chromosomes that don't follow the geometry of naturally evolved organisms. The work involves engineering as well as science, and focuses on the artificial production of cell components. He said questions are being asked concerning registration of the equipment and whether there's a need for engagement with security communities and stakeholders. Dr. Campbell felt that an Asilomar-type moratorium would not be practical. He said the engineering community conducting this work is small enough to establish a national or international society to develop codes of conduct. He said the problem is not that the materials emerging from this work are spreading around the world, but the information developed can easily be posted on databases.

Dr. Campbell then addressed compliance frameworks. They are well established in universities for safety in research involving humans and animals, but less well established for other codes of practice. He said journals have well-established codes of conduct and compliance frameworks for materials sharing, data deposition, and ethical issues concerning research on humans. However, there are fewer systematic guidelines for ethical boundaries in cases of misconduct, and no inter-journal framework for biosecurity concerns.

On the issue of possible restrictions, Dr. Campbell referred to several publications. A paper in the CBW Convention's Bulletin (March 2005) by Elisa Harris and John Sensenbrenner described a framework that starts at the local and national levels and goes up to the international level. Proposals would be peer reviewed for risks versus benefits, including the need for dissemination restrictions. Security clearance would be required for the national body and there would be non-disclosure agreements with penalties.

Dr. Campbell described an exercise that was undertaken at the University of Maryland involving five scientists proposing biodefense studies and 20 peer reviewers assigned to assess those proposals. The organizers wanted to determine the degree of consensus that could be reached in judging risk. They found that significant consensus could be achieved and there were clear criteria that emerged. Dr. Campbell proposed that the Board consider conducting such an exercise. He listed some of the problems with restrictions on publication, which he said other speakers had touched on. They are:

- No definition or consensus on what needs to be restricted;
- Needs to be international;
- Does not prevent Internet distribution or conferences;
- Who would be allowed access?
- Who would pay to maintain the restricted archives?
- Most journals are not well resourced for extra compliance; and
- University opposition, such as that expressed by MIT.

He concluded with some "key truisms," stating that journal editors and scientists must continue to show responsibility and that the integrity of science must be preserved.

Dr. Keim introduced Ms. Wendy White from NAS, who was there to provide an overview of international discussions concerning dual use research.

Overview of Recent International Discussions on Dual Use

Ms. Wendy White
Director of the Board on International Scientific Organizations, NAS

Ms. White described the international forum on biosecurity that took place in Como, Italy in March 2005. It was co-sponsored by the International Counsel for Science, the InterAcademy Panel (a network of about 100 Academies of Sciences from around the world), the InterAcademy Medical Panel, and NAS. The scientists that attended represented more than 20 countries.

The forum divided itself into three working groups, one to discuss guidelines and principles for professional conduct; one on dissemination and communication of research (which Ms. White participated in); and one on codes of conduct. The forum was a direct response to the Fink Committee Report, and the agenda reflected the growing awareness that there are rapid developments in life sciences and biomedical research. The intention was to broaden the debate and advance awareness of these biomedical research issues in the international community. It also served as a major convening and coordinating mechanism. Some of the participants at the Como Forum participated in or will participate as invited experts at meetings of the State's Parties to the BWC convention in the summer and fall of 2005.

Ms. White stated that it was the first time that many of these scientists had seriously considered the implications of dual use. However, at the end of the meeting, they were all convinced that they as individuals, and the scientific community as a whole, have a major and pressing responsibility in this area. The working group Ms. White participated in looked at the principle of the universality of science, which covers three critical areas: the freedom to pursue science and publish the results; the freedom to communicate among scientists and disseminate scientific information; and freedom of movement of scientific materials. This principle has been stated by the International Council for Science (ICSU), one of the sponsors of the meeting.

Ms. White said that the success of the universality of science depends on cooperation, interaction, and exchange, which often transcends national boundaries. For this reason, scientists must have open access to each other and to scientific data and information. She said the changing political climate and concerns about international terrorism have challenged this principle. For example, she stated that there have been boycotts threatened on scientists from other counties, restrictions on publications and the exchange of materials, and the withholding of travel visas and work permits.

The second issue considered by Ms. White's working group was the changing nature of scientific publishing. Researchers face increasing pressure to publish faster and in more internationally accessible media, and they work in environments dominated by Web-based publishing. There are more than 315,000 biomedical articles published each year, and the group

discussed the vast growth of international science. Ms. White said the number of authors from more than one country has increased 200 percent since 1981. International collaboration accounts for more than one-third of co-authored articles across all of science. This means it's almost guaranteed that every biomedical article written will be published somewhere. Ms. White emphasized that it's not enough to focus on the U.S. environment or on traditional publishing outlets. Information is widely and instantly available on the Internet, textbooks, Web pages, institutional repositories, blogs, theses, and many other non-peer reviewed publications. Controlling this environment would be impossible.

Ms. White stated that one participant in her working group consulted with her South American colleagues after the meeting and asked them to what extent they were aware of these problems. She found that most were not aware of the dual use issue. She also cited a lack of adequate national frameworks to control dual use, biological agents, and related research and pointed out that the rigor in science is less in some countries. There are fewer peer-reviewed publications and less knowledge about the ethical responsibilities of scientists. This woman suggested that the American participants in the group encourage international programs that will help raise awareness of scientists around the world and increase their capacity to deal with these issues.

Ms. White presented the Como Working Group conclusions, which echoed the findings of the January 2003 meeting at the NAS described by Dr. Campbell. Ultimately, all the researchers recognized that efforts to control the dissemination of sensitive information at the publication stage are neither desirable nor practical. Once an article is peer-reviewed or published and online, it is too late to enact controls. They also agreed that the benefits of increasing access to information and openness in science are enormous and that scientific process works only in an open environment in which research results are shared and built upon. However, Ms. White said that researchers must address public confidence issues and Government concerns by taking responsibility for the knowledge they generate. The working group concluded that shared ownership of knowledge is often a better safeguard than restricted access. They agreed that researchers could do a far better job of communicating with the public and policymakers about the importance of the universality of science.

General Discussion and Questions from the Board: Session II Speakers

Dr. Harvey Rubin noted the uniqueness of the activities at Los Alamos and asked Dr. Bowles how such controls would apply in a university setting. Dr. Bowles said the first line of defense against the unintentional release of information is the staff itself, meaning that there must be an education process about these issues for faculty and students at universities. Dr. Rubin asked if, from the perspective of the physics and computing communities, universities have published information that has been considered a threat to security. Dr. Bowles replied that problems sometimes arise when various types of information are published that, in and of themselves, are unclassified or nonsensitive, but when combined, become sensitive. He acknowledged, however, that the large, international infrastructure that monitors nuclear capabilities may not be possible in the biothreat arena. Dr. Andrew Sorensen agreed, adding that trying to organize university scientists around common themes and a common code of conduct could be difficult. He said the culture of autonomy is highly valued in research universities. Dr. Bowles stated that NSABB's recommendations will be much more effective if they take into account the culture of the biosciences institutions.

Dr. David Relman said he was struck by how different, and in many ways non-applicable some of the rules and procedures in the realm of nuclear physics are to biosciences. He said Ms. White's presentation pointed out that it's almost inevitable that biological information, in its diversity, ubiquity, and ease of digitalization will become widely disseminated in an electronic format on the Web. He suggested thinking about ways in which the biological community could self-organize using the Web to determine where the potential for harm and untoward effect exists. He raised the issue of whether publications in electronic formats could be monitored.

Dr. Casadevall commented on the importance of lessons learned from the nuclear experience, but said the differences between that field and bioscience are very great. Nuclear weapons are made by humans, while the agents for biological weapons exist in nature. Nuclear weapons require an industrial infrastructure, while biological weapons do not. Dr. Bowles acknowledged the significant differences in these fields, but said one thing they have in common is the inability to restrict information. Others will figure out how to use the same weapons technologies, so the only effective way to respond is to stay ahead of the curve so that our capabilities exceed those of our adversaries. Dr. Bowles told the Board to expect tremendous pressure from agencies, from Congress, and from the public to put controls on this information and he said NSABB's response to that pressure will be extremely important.

Mr. Mark Nance asked if the compliance requirements under international traffic and arms regulations and the Export Administration for biological and dual use materials have hindered the ability of those present to conduct research or have unduly restricted foreign nationals and their labs. Dr. Lemon stated that this is a major and growing concern, particularly if a shipment to another university in the U.S. is received by a foreign national. This is considered an export. Dr. Fauci added that it is very pervasive in academia that foreign nationals who are postdocs have difficulty going home and then returning to the U.S. He said rather than have such a large blanket of bureaucracy, sensitive areas should be looked at specifically. The foreign nationals who are caught in that net have less enthusiasm about coming to the U.S. to study.

Dr. Lynn Enquist said that society journals, such as the *Journal of Virology* document progress in the field, but also document the work done by individuals, leading to job security, promotions, and tenure. She stated that this aspect of the scientific enterprise should not be changed without thinking through the consequences. She also noted that many journals require information on the reagents used in experiments so that that the work can be repeated and some scientists don't want to provide it because of competition. Her concern was with the effect of tampering with openness in publications and the possible effect on the scientific enterprise. Dr. Campbell agreed that openness is essential to the process of science, but said that there are some who are in favor of restrictions.

Dr. Wara asked why the Fink Report recommended that the institutionally based IBCs serve as the first site to initiate review of science-funded protocols for risk of dual purpose, rather than a centralized group, such as the RAC. Dr. Reppy said that in her view, the intent of the Committee was to establish local portals. It wouldn't be practical to centralize the system and send everything to Washington first. It also didn't seem efficient to create a parallel system and make people run through both of them. The Committee, in her opinion, made their suggestion with the hope that the resources would be available to the IBCs once the

importance of the job was recognized. Dr. Fauci added that it would be logistically impossible to refer everything to a central group. Dr. Wara agreed with that logic and stated that the principles set forth by NSABB must be sufficiently robust to be applied across IBCs at all institutions; those with significant resources, those with none, those who are very experienced with research, and those who have less experience. Dr. Casadevall asked the Board to consider how the stringencies and regulations involved in the IRB process slow down clinical research. He said it is very difficult to translate products into useful services. Dr. Keim pointed out that a great deal of research with recombinant DNA is exempted early on because of the specific guidelines for IRB committees, which he said is true in the clinical arena as well. However, no such guidelines yet exist for dual use research.

Dr. Janet Nicholson observed that the Select Agent rule has led to a very keen awareness by scientists of the seriousness of the materials they have in their possession. She noted that the Board could probably enhance this awareness.

Dr. Levy asked what the Board is doing to proactively make the international scientific community aware of the activities of the Board so that the effort can become more international. Dr. Fauci agreed that this is necessary, but said that NSABB as a group must first come to an understanding of their role and the scope of their activities. He said international societies and academies will be a good place to begin reaching out when that time comes. Ms. White added that there are several levels in the international community, and European colleagues may be better equipped to work with NSABB than some developing countries. Some scientists don't have the infrastructure needed to respond. She stated that the InterAcademy Panel has a reach of 100 Academies of Sciences around the world, and that the International Council for Science is also in a position to help reach the developing world. Dr. Natalia Comella of the State Department agreed that there should be a cohesive plan in place before reaching out to the international community. She noted that other countries are waiting to hear what the U.S. has to say. The NSABB concept was presented at the Biological Weapons Convention Experts Meeting and participants were intrigued by the idea. Dr. Comella stated that NSABB should consider international strategies at an informal level, through connections in the scientific communities, and through more formal avenues, such as the State Department, which can facilitate communication with international colleagues.

Dr. Relman asked Dr. Fauci about winning the hearts and minds of the scientific community, as many may be skeptical about this endeavor. Dr. Fauci responded by suggesting that the Board refrain from making any pronouncements until they have been very carefully vetted in the scientific community. He said there must be substantial discussion in forums such as workshops, so that people have the opportunity to understand what is happening. The scientific community doesn't like to be dictated to from above. He also noted that the academic life sciences community would not accept controls such as having their email checked. Dr. Fauci recommended that the Board be very transparent about their direction so that scientists don't feel threatened in their ability to pursue their own academic endeavors.

Dr. Patterson commented that one of the five NSABB subcommittees will be devoted to promoting strategies for international collaboration. One of their first tasks will be to take a full inventory of global activities that are planned or underway.

Gen. Gordon asked Dr. Campbell if there would be value in increased collaboration between

journals for security purposes. Dr. Campbell stated that a system of registration that would cover every journal in the world would be impractical.

Admiral Studeman listed what he believed were the most important strategic messages to come out of the day so far, based on the presentations and the questions asked. They included staying ahead of the curve and openness. In addition, he had the sense that most people thought "the genie is already out of the bottle," but that perhaps some defense is required to guard against the incompetent and the inadvertent. He said raising sensitivities and slowing down the process to buy time were other strategic factors discussed by the group.

Dr. Keim stated that dual use is always going to be a moving target and at some point a group will be needed to help decide what dual use is on a case-by-case basis.

Dr. Fauci asked Dr. Campbell if he could conceive of any piece of work in the biological sciences that he felt shouldn't be published. Dr. Campbell replied that his answer is "no" in the area of basic research. However, he stated that a genuine debate should take place concerning papers dealing with weaponization. Dr. Fauci and Dr. Casadevall agreed with that assessment.

Dr. James Roth stated that the culture of responsibility must be key and that the IBCs must take that responsibility. However, the IBCs should not be overly zealous and shut down research prematurely.

Dr. Stuart Nightingale asked Dr. Campbell how NSABB could be of assistance in the publication review process. Dr. Campbell said the field would welcome a list of possible sources of advice, and that NSABB might want to consider appointing a publicly acknowledged group of people who are willing to be consulted by the journals.

Dr. Osterholm noted that the biologic agents problems of which they are aware are of domestic origin, not international. He asked the group to consider what they're really trying to accomplish, because that will affect the level of scrutiny or control. He said it will take some time and common sense to sort through the scenarios that pose genuine problems. Dr. Osterholm cautioned the group against coming away from the meeting with a fixed definition of dual use. He stated his opinion that there is no such thing as a weaponized biologic agent because any biologic agent can be weaponized. The combination of both "the bug" and the method for delivering it creates the potential for serious problems.

Dr. Keim then introduced the Public Comments session, asking that the public keep their comments brief and to the point. Each individual was allowed three minutes to speak.

Shenne Kayo, M.D.
Midwest Regional Center of Excellence for Biodefense and Emergent Infectious Disease Research

Dr. Kayo stated that while biosafety and biosecurity share many features, there are significant differences. Biosafety primarily focuses on occupational health and environmental protection. Biosecurity focuses on public health and national security. Thus, the potential impact of failure is much broader than in biosecurity. As a result of these differences, he said that existing strategies of compliance with NIH guidelines, which includes risk assessment by the IBC and

primary investigator documentation and training may be not be sufficient to deal with biosecurity issues. He said that the development of additional strategies is essential and should focus on a culture change in the biological research community. Dr. Kayo said that biosecurity precautions and procedures should become part of daily activities for everyone who works in a laboratory. He stated that the most effective way to accomplish this culture change is through education, as proposed by NSABB. He advocated for a mandatory education program for all scientists, lab workers, and graduate students. Additionally, he said a strong partnership should be developed between science and regulatory communities, including a scientific survey and State analysis, with a feedback system established to monitor progress.

Gerald Epstein, M.D.
Center for Strategic and International Studies

Dr. Epstein stated that there are areas in which the genie is out of the bottle, and areas, such as basic fundamental research, in which not enough is known. He suggested that the Board focus on the area in between, where results may be attainable. He said the Board should try to get at "contentious research," which he defined as fundamental biological or biomedical investigations that produce organisms; or knowledge that could result in immediate weapons and raises questions concerning whether and how the research should be conducted and disseminated. He said his operational definition is not a set of criteria or experiments of concern that tell scientists what is and isn't out of their purview. Dr. Epstein stated that there are two kinds of questions. The first are well founded, such as, Should this work be done? Should it be published? Is there potential for more harm than good? There are also questions that may not be well founded in a technical sense, but must be addressed if they worry people and alarm the political system. He said it is the scientific community's responsibility to work with many stakeholders to answer those questions. The answers may not convince everyone, but open discussion is better than just stating that science is pure and has no good or bad. Dr. Epstein stated that the U.S. Congress will be concerned if the scientific community says that these issues are not under their purview. He closed by stating that the Board's job, along with the scientific community, is to make sure they have answers when questions are raised.

Ed Hammond
The Sunshine Project

Mr. Hammond said it was his understanding that the Board was to have public members, which did not seem to be the case. He said public commenters can work through public members to raise concerns and he asked for clarification on public membership. He stated that his major purpose was to introduce a paper, provided to each member of the Board, called, "The Mandate for Failure of the State of IBCs in an Age of Biological Weapons Research." The paper was covered in *Science* and the *Chronicle of Higher Education*. It describes a survey conducted by the Sunshine Project with almost 90 percent of registered IBCs in the U.S. It was intended to study transparency, assessing how fears about bioterrorism were impacting the disclosure of information by IBCs. However, Mr. Hammond said the investigators discovered that in large measure, although there are many exceptions, the IBC system is something of a fiction. He said he believed the NRC erred in the Fink Report when recommending local review, because the system that performs the reviews is inadequate. Mr. Hammond said the survey revealed widespread noncompliance with the NIH guidelines. For example, 60 percent of government IBCs did not provide their minutes. One institution approved four dozen research protocols,

including work with Select Agents at BSL-3 and recombinant DNA, yet their IBC had never met. He estimated that only 10 percent of the private sector is compliant with the NIH guidelines and has a registered IBC. Mr. Hammond said he has an open mind concerning NSABB and welcomes the effort, but he said the local committee system it relies on is failing at its present mandate and cannot handle a new mandate. He recommended devoting considerable attention to making sure that the IBCs exist, comply with recommendations, and actually review the experiments they are responsible for.

Brian Hanley
BW Education and Forensics

Mr. Hanley stated that most people are extremely naive about biological weapons. He recommended controlling access to highly sophisticated simulations, such as EpiSims. NIH allocated a grant in February 2005 to place the source code for EpiSims in the public domain and he strongly disagreed with that decision. He said it has accurate demographics for American cities, is very sophisticated, and allows the user to war game. He also said that in conducting a simulation exercise, it became clear to him that the primary problem is how to determine that something has happened. The system currently depends for information on peoples' deaths, which is very unsophisticated. He pointed to the Viral Defense Foundation's proposal to use blood serum to continuously survey the viruses in circulation to determine true morbidity and assess what's happening. He closed by stating that the primary focus of the Board should be less on control of what is published and more on determining what research needs to be done.

Dr. Kein noted that Robert Harris from Masimax Resources was not present to comment publicly.

David Silberman
Stanford University

Mr. Silberman said he's the community member on the UCSF Biosafety Panel, an active participant at Stanford's IBC, and he directs the health and safety program at the School of Medicine at Stanford University, which includes compliance-related issues. He said he's observed that in dealing with a guideline or regulatory concept in a large, diverse community, it's a good idea to determine what has worked in the past. He noted the 30th anniversary of the Asilomar conference and he stated that there are performance-based health and safety standards that are also known to work. He urged the Board to look to them as a reference point. Mr. Silberman stated that investigators and principal investigators respond better to reason than to regulation and more to guidance than dictation. He recommended that NSABB consult individuals within institutions who are charged with the responsibility for compliance. Concerning balance, he said it isn't necessary for the fulcrum to stay in the middle. Mr. Silberman said there can still be balance when there is a great deal of research and science and only a modicum of security.

Terence Taylor
International Council for the Life Sciences

Dr. Taylor stated that he is from the International Institute for Strategic Studies, whose

membership includes over 100 countries around the world. He heads the U.S. office of that organization, and with other partners in Washington in the Chemical and Biological Arms Control Institute, they developed the International Council for Life Sciences (ICLS), a charter-based organization. They receive funding support from the Nuclear Threat Initiative. He agreed with the focus on people and knowledge in the life sciences area, as discussed during the meeting. He also agreed with a focus on a culture of responsibility. He said his organization's work around the world with ICLS indicates that the overwhelming majority of scientists want to behave responsibly. Mr. Taylor said it's clear that advances in the life sciences are bringing enormous benefits. In the international realm, ICLS is directly responsive to the harmonization of international research. He stated that their mission statement promotes best practices and codes of conduct, but they believe there might not be one global code of conduct that will operate in every professional area in every region of the world. ICLS has a charter that forms the structure under which a number of codes of conduct could operate against. Mr. Taylor urged NSABB to look at this charter and he said their organization stands ready to support the Board, particularly concerning international outreach.

Dr. Keim brought the day's meeting to a close by thanking Dr. Zerhouni and Dr. Fauci for their comments in support of the Board. He also thanked the audience for being present and expressed gratitude to the speakers for sharing their insights and expertise. The meeting was adjourned and scheduled to reconvene at 8:00 a.m., Friday, July 1, 2005.

Day 2: Thursday, June 30, 2005

Session III: Codes of Conduct in the Life Sciences

Dr. Kasper stated that one of the charges of the Board is to provide recommendations on the development of a code of conduct for scientists and laboratory workers that can be adopted by professional organizations and institutions engaged in the performance of life sciences research. He introduced the first speaker, Dr. Phillip A. Sharp, an Institute Professor at the Center for Cancer Research at MIT and a recipient of the Nobel Prize in Physiology or Medicine.

Promoting and Enhancing Responsible Research in the Life Sciences: The Role of a Code of Conduct

Phillip A. Sharp, Ph.D.
Institute Professor at the Center for Cancer Research, Massachusetts Institute of Technology

Dr. Sharp stated that codes of conduct are essential for the work of active scientists and are widely used in the life sciences community for both ethical and pragmatic reasons. He stated that the biomedical research community has been extensively involved in the development of codes of conduct since World War II because of the expansion of the life sciences and the use of humans and animals as subjects. The discovery of recombinant DNA and the field of genetic engineering brought new codes of conduct into the community, including guidelines for the RAC and for other NIH activities. Dr. Sharp said the culture of responsibility in the life sciences is shared by scientists, institutes, and Federal agencies because they collaborate in advancing and translating research.

He stated that the continued advancement of biomedical research is dependent on public support and Congress, because NIH is the major funder of discovery research and biomedical research in the U.S. This research underwrites the medical care system, the pharmaceutical industry, health care delivery in academic hospitals, and the knowledge base from which physicians interact with patients in every part of the country. Continued development of biomedical research is therefore critical for health care and security in the U.S. This research must be done in a safe and transparent fashion with responsible use of human and animal subjects, which requires codes of conduct.

Dr. Sharp described the values of the culture of responsibility in the biomedical research community.
One of the most fundamental shared values is the belief that new knowledge will ultimately lead to a higher plane of understanding about the world. The scientific community is therefore very resistant to limitations on the exploration of new realms. Other shared values are the commitment to education in developing and transmitting science; open questioning, description, and publication of details concerning the validity of scientific data; and the belief that the scientific enterprise is international in scope. Dr. Sharp said that prior to World War II, every major scientist in the U.S. was trained through experiences in Europe.

Dr. Sharp noted that the recombinant DNA guidelines are one example of codes of conduct, although they are not the first set of guidelines developed by the life sciences community. The Hippocratic Oath ("first, do no harm") is a code of conduct for scientists in biomedical research. Codes of conduct concerning human experimentation followed the Nuremberg trials in 1946 and were further developed through the Helsinki declarations in 1953 and 1964, and by the Belmont report in 1979. Dr. Sharp said the recombinant DNA issue arose in the early 1970s because of the newly discovered ability to synthesize and recombine DNA. Experiments became possible that combined genes from different organisms to learn about genes' functions and activities. Concerns arose among the scientific community and the public about this new technology and its implications for safety in research, both in the laboratory and in terms of creating novel infectious agents. If such work created pathogens that became highly infectious, it was feared that scientists could inflict unanticipated harm and discredit the biomedical research community.

In 1974, the biomedical research community, including NAS, proposed a moratorium on recombinant DNA research. It stated that researchers should not conduct experiments in this area until a meeting took place to discuss the relevant issues and consensus was reached on how these issues should be addressed as a community. There was a 6- to 9-month period during which no experimentation occurred. The Asilomar Conference was held in 1975, which recommended that NIH develop guidelines for research. Another year passed without experimentation. By 1976, the NIH guidelines, the RAC, and the Institutional Biosafety Committees (IBCs) were in place, and research experimentation involving recombinant DNA began again. Dr. Sharp noted that the guidelines in 1976 were highly restrictive and were revised in 1979 based on knowledge gained in the laboratory. It became clear that the original concerns were not as great as originally feared. He said there has not been a single example in the last 30 years of a recombinant DNA organism infecting someone in the laboratory or in the public.

The NIH guidelines have been considered very successful in terms of retaining the confidence of the public. Dr. Sharp said they succeeded because they were led by the scientific community, including the funding agencies, and the various entities worked together as a team to make the guidelines effective. The guidelines involve an international process, with essentially the same moratoriums, guidelines, and rules for science in various countries. The process was made public from the outset. Dr. Sharp stated that compliance was almost universal, with only two noted violations, one of which was bureaucratic. He said the guidelines have a mechanism for change built into their structure and they evolve as more is learned.

Dr. Sharp briefly summarized the codes of conduct material he teaches to all second-year graduate students in the department of biology at MIT. He said that codes of conduct are taught both from a departmental perspective and in an MIT-wide course on the topic for students studying other disciplines. The biology department course is titled, "Responsible Conduct in Research." Session one addresses scientific misconduct, record keeping, reporting of results, and data selection. Session two deals with mentoring, authorship, peer review, and confidential information. Session three includes intellectual property, patents, trade secrets, and responsibility to the public in terms of recombinant DNA issues. Session four addresses the use of humans in biomedical experimentation, including ethical uses of humans as research subjects and compliance issues. Session five covers the use of animals in biomedical experimentation.

Dr. Sharp stated that other support activities are considered essential at MIT for research programs and compliance with NIH and other Federal regulations. The MIT Office of Vice President for Research chairs a committee on the use of humans as experimental subjects and a similar committee oversees animal use. Dr. Sharp described MIT's academic misconduct policy, the Office of Intellectual Property, and an Office of Sponsored Programs, which deals with conflicts of interest. The Environmental Programs Office reports independently to the Vice President of Operations at MIT. This office includes the Committee for the Assessment of Biohazard, which is the equivalent of an IBC; Select Agent Control, which retains and reports on agents that could be used for infection or bioterrorism; and chemical, radiation, and lab safety functions. Dr. Sharp closed by stating that the intent of his presentation was to provide an overview of the driving forces behind codes of conduct and their application in a research university.

Dr. Kasper introduced two experts on codes of conduct from institutions in the United Kingdom.
Dr. Brian Rappert is from the University of Exeter and Dr. Malcolm Dando is from the University of Bradford.

Challenges in Proposing a Code of Conduct with Dual Use Perspectives

Brian Rappert, Ph.D.
Lecturer in Sociology, University of Exeter, U.K.

Malcolm Dando, Ph.D.
Professor of International Security, Bradford University, U.K.

Dr. Rappert stated that he would be examining barriers to the adoption of codes of conduct in

relationship to dual use issues and biological weapons. His reflections were based on several sources, including various international discussions over the last few years, recent experiences at a meeting of experts for the Biological Weapons Convention, and conversations with life scientists in the U.K. about dual use.

Historically, there has a long tradition of discussions about codes of conduct for science and medicine, and more recently, for biological weapons. Dr. Rappert presented several examples, including recommendations of the World Federation of Scientific Workers Conference (WFSW) and the International Council for Scientific Unions (ICSU) in 1968. They proposed the idea of an identity card for scientists. The *New Scientist* wrote a provocative editorial in 1968 stating that, "unless some principles of conduct are established for the men and women who manipulate the materials of nature, anarchy will develop, and with anarchy, disaster." Dr. Rappert stated that this topic has been on the scientific agenda for some time, but has not been widely adopted in relation to biological weapons.

Post-9/11 thinking on codes has considered different kinds of codes for different audiences. In 2002, the Working Group of the United Nations on Terrorism advocated for the development of a code of conduct for defense scientists that would restrict WMD-related knowledge and expertise. The British House of Commons Science and Technology Committee called in 2003 for an ethical code similar to the Hippocratic Oath. In 2001, President George Bush called for a code that would provide a solid framework for bioscientists and be universally recognized. More recently, the thinking in the U.K. has advocated for the development of principles that will inform other scientific organizations, who will then develop their own codes. Dr. Rappert said there has been increasing movement away from the idea of a universal code. He then discussed six specific barriers related to codes of conduct.

Barrier 1: What is the problem to which a code is the solution? NSABB's charter doesn't specify the purpose, audience, or type of code necessary. Some problems in addressing these issues include a lack of awareness about dual use; the relationship of individual and professional responsibilities; the fact that international agreements are written for state parties, not individuals; and questions about existing biosafety and biosecurity provisions.

Dr. Rappert displayed a typology of various types of codes and their aims. "Aspirational" codes, often called codes of ethics, are meant to encourage people to think about issues. The American Society of Microbiology (ASM) has an aspirational code in relationship to dual use issues, which calls on researchers not to engage in activities contrary to the welfare of human kind. A second type of code is meant to be "educational" or advisory, and it provides guidance to individual researchers. He pointed to the World Medical Association's Declaration of Geneva, which addresses educational and advisory issues concerning biological weapons. One of its key statements is that individuals' personal benign intent is not sufficient. Dr. Rappert stated that a third type of code is "enforceable." The code used by the journal *Nature*, as described by Dr. Campbell, was given as an example.

Barrier 2: Fragmentation and organizational constraints. Dr. Rappert agreed with the statements that any code developed must be international, but pointed out barriers to development of a universal, widespread code in the life sciences. He said there is no key organization that could take on this task. The National Academies have been engaged in code development over the last few years. However, the Academies differ internationally in terms of their composition,

mandate, relation to governments, and the type of advice they're charged with providing. This has complicated the development of a single code that all could agree on and find relevant. Therefore, they came out instead with principles to inform codes that might be devised by individual Academies. This experience speaks to the difficulties involved in trying to devise a single international code. Dr. Rappert stated that the International Committee of the Red Cross and the Biological Weapons Convention are also interested in developing codes. However, he predicted that they will also decide on key principles to help other organizations develop individualized codes.

Barrier 3: Whose initiative is it? Dr. Rappert said many governments are reluctant to develop a code of conduct for the life sciences community. However, the community itself has also been reluctant to do so. He said its representatives expect government agencies to take the lead on national security issues related to biological weapons and dual use research. Dr. Rappert characterized the key issue as one of initiative, i.e., who will take up the challenge of devising codes? He stated that NSABB has the ability to influence NIH-funded research and could lead international discussions in this area.

Barrier 4: What is it all supposed to mean? Dr. Rappert explained that the standard critique of aspirational, educational, and enforceable professional codes is that the provisions are open to interpretation and are internally conflicting. He also stated that the Board must consider how a code would address current national and international debates about dual use issues. Would it attempt to resolve or only to set the parameters for discussions on issues such as transparency in biodefense, procedures for assessing dual use potential, and permissibility of mid-spectrum chemical incapacitants? Dr. Rappert said the Center for Arms Control and Nonproliferation has developed a code that is moving toward a statement of agreement about some of these controversial issues. He said the Board might want to take similar steps or examine the issues and set some parameters for discussion.

Barrier 5: What are you talking about? Dr. Rappert and Dr. Dando have conducted approximately 25 seminars with 600 life sciences researchers in biology departments in the U.K. to promote conversations about dual use issues and encourage engagement in the international discussions taking place. Dr. Rappert said that many of these researchers weren't interested in dual use issues and that debates have not been widespread in the U.K. Dr. Rappert and Dr. Dando categorized these scientists into two very simplified types. One was the "security-conscious researcher" who knew about some dual use issues, saw them as a problem, and was willing to discuss them. The second type was the "classic open science researcher" who thought the issues were overblown in relation to biological weapons, that the contribution of the life sciences to this problem are negligible, and that pre-project oversight mechanisms are ill-advised. Most of the people they spoke to were overwhelmingly in the classic open science category. Dr. Rappert said this illustrated the importance of awareness raising and education. However, he said it's important to go beyond raising awareness and determine how researchers' behavior can be changed.

Barrier 6: Implementation issues. Dr. Rappert stated that the conversation about international codes is still in a preliminary stage. He said the current question to consider is how code development will be taken forward. The parties involved must agree on the problems a code should address, the type of code necessary, the intended audience, the entity that should initiate code formation, what the code should state initially, and how it can be made relevant. Dr. Rappert suggested

that the Board be informed by the activities of the AMA and the World Medical Association concerning guidelines and review for dual use issues.

Dr. Rappert concluded by providing a website address for more information about codes: http://www.ex.ac.uk/codesofconduct/

General Discussion and Questions From the Board: Session III Speakers

Dr. Kasper opened the floor for members of the Board and *ex officios* to direct questions to the Session III speakers. Dr. Andrew Sorensen asked Dr. Sharp whether representatives from other universities have expressed interest in replicating the codes of conduct course developed in the Biology Department at MIT. Dr. Sharp pointed out that the NIH guidelines require that all graduate students take part in an educational program covering many of the topics addressed in MIT's training. Therefore, in the last 5 to 10 years, courses of this type have been developed at most universities, whether department-specific or university-wide. He stated that the contents of his course are available and he has sent them to several people who have requested them.

Dr. Enquist asked what steps are taken at MIT to educate senior and junior faculty on codes of conduct issues, so that everyone conducting research in the department is engaged in the same ethos. Dr. Sharp stated that once students are trained, this knowledge spreads throughout the department and an ethos naturally develops in the laboratory settings. He explained that there is no specific formal instruction offered to the faculty.

Concerning the survey discussed in their presentation, Dr. Dando clarified that the life sciences are heavily regulated in the U.K. He said Dr. Sharp's point was that despite knowledge of animal welfare, biosafety, and similar issues, the scientists they interviewed were not aware of many dual use issues in the life sciences. He speculated that the same would hold true for U.S. scientists.

Dr. Murray Cohen asked Dr. Rappert for guidance for the Board as it moves forward in developing a code of conduct. Dr. Rappert replied that there are many interesting codes on the web page he supplied, but there is a lack of initiative. He suggested that the Board consider providing the leadership necessary to move the effort forward.

Dr. Franz noted that he was not involved in the most recent talks in Geneva and asked the panel whether it's easier to reach consensus on codes that foster awareness, versus regulatory or enforceable codes. Dr. Dando said the atmosphere in Geneva was more open than in the previous 2 years, with more presentations and involvement from scientists and scientific organizations. However, he believes that substantial work must be done by experts to translate this information into principles that can be assimilated outside of Geneva. Dr. Rappert stated that there was more common ground than he had anticipated on the importance of various kinds of codes. He noted that the BWC's mandate this year doesn't include negotiations on codes. Dr. Imperiale asked which type of code tends to be most effective in terms of compliance. Dr. Rappert said that a code must have mechanisms of enforcement to change behavior. He said, however, that aspirational codes are useful for increasing knowledge about biological weapons and dual use issues and promoting discussion within organizations, and noted that raising awareness is the primary benefit of

any code.

Dr. Dixon asked Dr. Sharp if he teaches on recombinant DNA and asked how he anticipates addressing dual use, Select Agents, and related topics. Dr. Sharp said they discuss recombinant DNA and provide fundamental grounding in biosecurity issues, as well as the specifics of dual use technology. This enables students to understand these issues in their professional lives.

Dr. Comella said the U.S. is working to increase understanding of dual use and is seeking to develop tools and strategies to promote discussion. She said the U.S. suggested the topic of codes of conduct as the focus of the Biological Weapons Convention Experts Meeting and was active in those discussions. She asked the panel for their opinions on the best starting point for promoting understanding of dual use and sharing this knowledge with the international community.

Dr. Atlas said the starting point is the dialogue that's already taking place by various organizations and internationally. The World Health Organization is holding meetings on the issue with other groups. He said there's unlikely to be one prescription for a code, but there may be development of underlying principles that can be accepted globally. Dr. Atlas noted that the phrase resonating with the group was not "codes of conduct," as much as "culture of responsibility." He said that he and Margo Summerville, a bioethicist from Canada, recently published a code in the journal *Science* for people to comment on. They began with the idea that advances in the life sciences in dual use research have the potential for misuse and harm and asked what should be done to protect the science. Some said restrictions should be set in the law and that the community should be regulated. Dr. Atlas disagreed with this idea and said the field needs a culture of responsibility in which scientists collectively discuss the protection of science.

Dr. Dando said the fundamental goal is to prevent the current revolution in biology from being applied to warfare and terrorism. The simplification and spread of biotechnology must lead to increased concerns about substate groups undertaking hostile acts. The Fink Committee discussed the possibility of general advances in life sciences leading to inadvertent assistance to bioterrorists or state programs. Therefore, he said the code of conduct discussion is part of what the International Committee of the Red Cross calls the "web of prevention," a set of integrated policies that must be in place to stop the militarization of biology.

Dr. Osterholm said he felt the Board would be successful if the next 20 to 30 years are uneventful in terms of biologic events. He noted that for the vast majority of scientists, a code is a guideline to help them when they start to stray and he wondered if codes have an impact on those who plan to do harm. He asked if there is evidence, whether in warfare, human rights, or other areas of science, that indicates that a code or standard has had an impact on rogue individuals, groups, or countries.

Dr. Dando pointed out the lack of interest of the life sciences community during the developments of the 1990s and the Biological Weapons Conventions. He stated that the value of a code could be found in its engagement of scientists, who will be influenced to look at the dual use issue and add their expertise. He said that for those who won't be restrained by a code, other aspects of the web of prevention will address their actions, including sensible biodefense with good intelligence capabilities; an effective export control system; and a strong international

legal system effectively implemented in national legislation. He emphasized that codes are a very useful aspect of the overall web. Dr. Sharp added that unless the biomedical community is vibrant and is engaged in research to enhance biodefense, rogue actions will be very difficult to deal with. If terrorist activity occurs, the community must be prepared for it, recognize it, and control it.

Dr. Casadevall agreed on the potential influence of codes. He stated that in his experience as a physician, the Hippocratic Oath has helped him many times when there was no obvious right or wrong choice.

Dr. Caird Rexroad pointed out that there are many communities within the life sciences and asked about the likelihood that a code coming from one group, such as NSABB, will be successful. Dr. Rappert agreed that there are many different communities within life sciences, and other professions for whom this topic is relevant, such as engineering. He reiterated that he believes no one organization or forum is appropriate to take on the issue alone. He stated that NSABB has the power only to help move the issue of codes into the forefront.

Dr. Dando remarked that the Board has some strong allies in the American Medical Association. He said some of their work on codes for physician researchers has addressed interesting questions that are similar to those confronting the Board.

Session IV: Dual Use Research: International Perspectives

Dr. Kasper introduced the fourth session on international perspectives pertaining to dual use research. He said that Ms. Shana Dale would provide an overview of recent international discussions on the dual use dilemma in which she participated.

Dual Use Research: International Perspectives

Shana Dale, Esq.
Chief of Staff and General Counsel
Office of Science and Technology Policy, Executive Office of the President

Ms. Dale spoke on efforts to balance science and security, historically and in the present day. She stated that a 1947 report from the President's Scientific Research Board emphasized the need to maintain an environment of free inquiry. It also stated that security regulations should be applied to research only when strictly necessary and should not cover up basic principles of fundamental knowledge. Similar statements were made in 1949, in a report from the Advancement of Science Committee on Civil Liberties for Scientists. Ms. Dale stated that the 1950s were marked by McCarthyism and the House Un-American Activities Committee.

In the 1980s, the U.S. faced continued concerns about the Soviet threat. In 1982, the Corson Panel of the National Academy of Sciences issued the report, "Scientific Communication and National Security," which stated that there was no practical way to restrict international scientific communication without also disrupting domestic scientific communication. In 1984, OSTP convened a DoD working group to grapple with a climate that seemed to inhibit the free flow of science. The group laid out principles for a more open scientific environment, including the idea that the benefits of open publication far outweigh the risks. In 1985, National Security

Decision Directive (NSDD) 189 was issued by Ronald Reagan. It stated that products of fundamental research should remain unrestricted to the maximum extent possible. Controls would be handled through classification at varying levels. This policy has been re-affirmed under the present administration. Ms. Dale explained that each Federal Government agency is charged with determining whether classification is appropriate for all research grants, contracts, and cooperative agreements.

Ms. Dale explained that in the post-9/11 world, the policy laid out in NSDD-189 is extremely important. Its goal is to enhance biosecurity while minimizing undue impacts on the free flow of science. Since 9/11 and the anthrax attacks on the United States, many other countries have begun to examine potential threats posed by biological weapons. These discussions have addressed how dual use life sciences research fits into the discussion of international biosecurity. Several organizations have sponsored conferences and symposia to address the policy issues surrounding continual advancements in dual use technology. These meetings have brought to light shared concerns and issues. Ms. Dale said the first is, "What is the threat to my country?" She said that some countries appear to believe that the threat is solely a U.S. problem.

All of these international meetings addressed common themes. For example: 1) The risks associated with the dual use nature of bioscience have been universally acknowledged as conceptually difficult as well as difficult to quantify. 2) In the age of genomics, genetic engineering, and mass informatics resources, the risk profile has become much more difficult to define. Ms. Dale stated that restricted access to biological materials and/or information is one possible solution, but this could create impediments to the advancement of science. 3) Biotechnology presents a new potential for the misuse of bioscience. However, a distinction was made between access to *known* harmful pathogens and access to other biological materials, techniques, and information that have the *potential* to be used for harm. 4) The value of broad representation from the public has been widely agreed upon.

Discussions also characterized the threat from many perspectives in the international community, including the threat to public health, plant and animal life, food security, and economic stability. They acknowledged that societal and geopolitical changes, not just technical advances, have influenced how science is conducted. Meeting participants have acknowledged that the global reach of the scientific community transcends national boundaries, which has greatly diminished controls over the use of technology.

Several key concerns were identified as part of the effort to reconcile an open research environment with the threat of misuse of bioscience research. These included the need to understand the real and perceived threats to each nation and region. There is also a need to establish a common international understanding of terminology. For example, participants reported diverse interpretations and uses of the terms "biosafety" and "biosecurity." Discussions also highlighted the need for increased awareness among researchers to encourage responsible stewardship and foster a security-conscious culture. Other topics included the need for codes of conduct, accreditation of facilities, and registration of personnel. A balanced approach was deemed essential in fostering public and political confidence that risks will be correctly identified.

Ms. Dale described some of the international biosecurity efforts underway. She said that in September of 2004, 55 participants were selected from government, academia, industry, public

research organizations, scientific societies, and the scientific publishing field to meet in Frascati, Italy for 3 days to discuss the promotion of responsible stewardship in the biosciences. To facilitate action, a small-scale biannual working group [Susan: was? might be?] organized by the Organisation for Economic Cooperation and Development (OECD) International Futures Programme composed of key players in different stakeholder communities. The general mandate of the working group would be? to:

- Identify and document common concerns in various stakeholder communities regarding the oversight of biosciences research at different stages;
- Develop a common vocabulary concerning the new security issues facing society, particularly in relation to biosciences research;
- Help broker and integrate the concerns of the constituent stakeholder communities;
- Foster development of codes of conduct and mechanisms to ensure their operability;
- Facilitate the convergence of minimum standards for codes of conduct among the science communities and academia, government, and industry; and
- Help develop criteria and relevant processes to render codes and other oversight tools, particularly in the international context.

Ms. Dale stated that the first step taken by the group would be? to inventory the efforts in both OECD and non-OECD countries in which governments, associations, or industry groups are formulating approaches to biosecurity. The inventory should include policy as well as legal approaches and detail specific tools used to address problems. She said that, ideally, a small working group would be formed to review and assess the effectiveness of the measures that have been implemented. This would provide the basis for a gap analysis of current biosecurity efforts, particularly at the international level, and would provide guidance on further work.

Ms. Dale said that further action can be taken at the international level in the area of scientific codes of conduct. Several codes are being developed independently at different levels within industry, at the scientific association level, in the InterAcademy Panel, and within some governments. These codes have different timeframes for development and address different constituencies. A "Codes Archive" can be found at www.biosecuritycodes.org that lists over 20 guidelines, principles, and codes from 10 countries and international organizations.

Ms. Dale displayed a chart from the OECD website (found at www.oecd.org), that allows users to click on a map to see which countries are working on specific biosecurity issues and are planning conferences and events. The site also allows the user to see the types of biosecurity legislation that have been passed or are pending around the world.

Ms. Dale stated that the InterAcademy Panel on International Issues, the InterAcademy Medical Panel, the International Council for Science, and the National Academy of Sciences hosted an International Forum on Biosecurity in Italy in March of 2005. The event was by invitation only and participants attended as individuals, not in their official capacities. People came from Senegal, Mongolia, U.K., Brazil, Canada, Belgium, Australia, the U.S., and several other countries. The forum grew out of a recommendation in the 2003 report, *Biotechnology Research in the Age of Terrorism* (the Fink Report). Recommendation Seven of this report called for "an international forum on biosecurity to develop and promote harmonized national, regional, and international measures that will provide a counterpart to the system we

recommend for the United States." Ms. Dale said this productive meeting had a small-group format that conducted parallel sessions on three issues. The first was on guidelines for professional conduct, including codes of conduct; the second addressed dissemination and communication research results, including publication; and the third grappled with oversight of research, including formal regulation and self-governance.

Ms. Dale stated that a series of expert meetings are taking place in relation to the BWC, most recently on June 13th through 24th of 2005. They provide an opportunity for international experts to raise awareness about the need for each country to take steps to ensure biosecurity. They also facilitate dialogue on emerging codes of conduct. Participation has included many agencies from the U.S. government, the U.S. nongovernmental organization (NGO) community, and other experts. Participation by other countries has included official representatives, foreign NGOs, and university and pharmaceutical representation. Issues agreed to at the last meeting included:

- Heighten awareness and attention to life sciences research and dual use applications is needed;
- Codes are useful to educate and promote responsible behavior;
- Codes facilitate compliance with the BWC;
- Countries are already developing their own codes through advisory or regulatory bodies;
- There is a need to involve the scientific community in developing and implementing codes; and;
- Transparency must be balanced with security.

Ms. Dale said that controversial issues discussed at the last meeting included the idea of obligatory codes of conduct for all scientists, including government researchers; mandatory and multi-tiered review of all dual use experiments, including international review committees; codes of conduct that would be applicable to industry, registration, or licensing of scientists; and universal codes versus national codes.

Ms. Dale closed by stating that the Experts Meeting of the BWC indicated that significant progress has been made in raising awareness and sharing information on individual countries' activities. However, there is an ongoing need for more dialogue, awareness, and sharing of ideas. She said many countries believe these activities are a waste of money because there is no substantial threat. Some say that since many bioagents are readily available in nature, there is no reason to invest in security at facilities containing bioagents. Many countries have expressed resistance to a code of conduct and/or oversight of scientific publications. For these and other reasons, Ms. Dale stated that the issues before the Board are extremely difficult ones.

Dr. Kasper opened the floor for questions. General Gordon asked if the findings of the meeting in Italy were published and Ms. Dale replied that they were not. However, several attendees, including Ms. Dale, were present in the meeting and could provide details on the discussions that took place.

Dr. Harvey Rubin expressed the opinion that there is a disconnect on some biosecurity issues at high levels of government. He asked how the White House adjudicates contentious issues. He

also asked how the recommendations of the Board will be processed. Ms. Dale said the policymaking process in the White House takes place through policy coordinating committees. For the Office of Science and Technology Policy (OSTP), it's through the National Science and Technology Council (NSTC). This Cabinet-level council is chaired by the President, but Ms. Dale said that historically, meetings are not held at that level. She said the President's Science Advisor manages the day-to-day operations of NSTC through the OSTP. Within the four committees on science, technology, the environment, and homeland and national security, subcommittees grapple with cross-cutting scientific issues throughout the Federal Government. Ms. Dale said the issues that come before the Board will be closely linked with the Homeland Security Council and the National Security Council. She stated that the person at the Assistant Secretary level is usually at the [PCC?, rising up to the Deputy's Committee level, and then to the Principles Committee with the President.? Susan: Huh?] Ms. Dale said the President's Science Advisor attends the meetings with the President that concern science and technology. She emphasized that the White House is very interested in seeing NSABB move out expeditiously with guidance and is very receptive to the work of the Board.

Dr. Stanley Lemon asked Ms. Dale if, in the international meetings, she sensed an increase in awareness of dual use issues overseas. She said she has experienced frustration that progress is not moving as quickly as she would like. Other countries have reservations about the viability of the threat and are concerned that the U.S. is spending too much money and has overblown the importance of the problem. She added, however, that she was heartened by the discussions coming out of the BWC, as she heard they had a very good dialogue and are interested in the development of codes of conduct.

Session V: Chemical Synthesis of Bacterial and Viral Genomes

As Session V began, Dr. Kasper noted that Dr. Anne Vidaver, Professor and Chair of the Department of Plant Pathology at the University of Nebraska and NSABB member, had joined the meeting. He then provided an overview of the topic for Session V, biosecurity issues surrounding chemical synthesis of bacterial and viral genomes. He said this rapidly accelerating technology has tremendous benefits for medicine and industry, but could be used for malevolent purposes. Dr. Kasper introduced Dr. Craig Venter, founder and President of the J. Craig Venter Institute, the J. Craig Venter Science Foundation, and The Institute for Genomic Research (TGIR).

Gene Synthesis Technology: State of the Science

J. Craig Venter, Ph.D.
Founder and President, J. Craig Venter Institute

Dr. Venter spoke on the progress made in reading and writing the genetic code. He stated that 10 years ago, the first genome of a living organism was published on Haemophilus influenzae. The technology has advanced rapidly since then, as hundreds of microbial genomes for plants, animals, insects, and the human have been sequenced.

Dr. Venter described the Sorcerer II expedition conducted by his Institute, which is taking seawater samples every 200 miles around the globe and sequencing the initial data. The microbial world is the largest group of species; each milliliter of seawater has 1 million bacteria

and over 10 million viruses. He said his team published over 1.3 million new genes last April based on this work; including as many as 40,000 microbial species for the bacteria alone. He noted that they haven't yet sequenced the viral populations.

To illustrate that the ability to read the genetic code has changed dramatically over time, Dr. Venter said the first Government-funded genome project, for E. coli, took more than 13 years. However, sequencing of the Haemophilus genome took only 4 months, and now such work takes only about 2 hours. New DNA sequencing technologies continue to reduce the time further. Dr. Venter said that a single machine can sequence up to 200 million base pairs per day. The Institute's Marine Microbe Sequencing Project, funded by the Gordon and Betty Moore Foundation, has a $9 million grant to sequence, assemble, and auto-annotate 130 marine microbes. This will result in a 1000 percent increase in sequenced marine microbes. A grant from the Sloan Foundation has allowed them to start the Air Genome Project, which is sequencing viruses and bacteria captured from the air in New York City and Washington.

Dr. Venter explained that TIGR's project in the Galapagos has uncovered approximately 8.3 million new genes from more than 100,000 new bacterial species, and 10 times as many viral genomes. They're attempting a comprehensive view of the whole earth gene catalog and looking at about 29 million ohrs. Dr. Venter estimated that the number of gene families is between 40,000 and 50,000. His key message was that if new samples are taken regularly from the soil and ocean, the number of new gene families will continue to grow at a linear rate. There is no hint of saturation, confirming that only a small portion of microbial biology is currently known.

Dr. Venter defined "synthetic genomics" as the design and construction of genomes from chemical components. He described it as copying biology, rather than designing new biology. He gave as an example the project that originated from the second genome that was sequenced, Mycoplasma genitalium. Dr. Venter stated that DNA synthesis has grown almost as rapidly as the ability to read the genetic code. His team is exploring whether a species can survive with a smaller number of genes. They conduct transposon mutagenesis insertions and knock genes out one at a time. Dr. Venter said it became clear in 1997 that the only way to understand a minimal genome would be to synthesize one, because they could not do cumulative gene knock-outs. Batch-wise analysis showed that cells with different genes knocked out can survive in populations. He said that when they cloned them out as individual cells with a gene knocked out, they obtained different answers concerning which genes are actually essential for life. Because of the conflicting conclusions, the team decided to go forward and build the genome. They've now either sequenced or accumulated the genomes from 13 different Mycoplasmas and compared them. The results have revealed a core set of approximately 173 genes common to all 13 species. If they eliminate one intercellular parasite, the number of genes goes up to 220. The expanded core set of genes is on the order of 310 because of non-orthologous gene displacements. Of these, based on gene disruption studies, at least 36 are nonessential genes. They don't yet know whether the cell can compensate for each of these gene's functions. The definition of "essential" is circumstantial based on what is in the environment.

Dr. Venter described how the team decided to build genomes the way they believe they were assembled in nature, in a cassette-based fashion. Dr. Venter described an error correction method that enabled the team to rapidly synthesize a 5 kb cassette of the complete infectious genome of bacteriophage Phi X174 from a single pool of chemically synthesized

oligonucleotides. The synthetic DNA that resulted was injected into E. coli, which made viral particles and verified the accuracy of the synthetic genomes. The entire process took place in 14 days.

Dr. Venter said it's clear that any sequenced viral genome, including Select Agents, can be made today. He stated that it would be a grave error to think otherwise. However, he said it's important to keep in mind that the DNA from species such as Ebola and smallpox are not infective on their own. Having the genome is not sufficient. He said that new designer viruses are at least a decade away, if ever, because an understanding of the first principles of viral infectivity is not on the horizon. Massive programs to design and develop new agents are taking place only through state sponsorship in the U.S. and the former Soviet Union. Therefore, he said it's unlikely that this field will develop rapidly.

Dr. Venter explained that TGIR is looking at the fact that large numbers of species are completely resistant to radiation. After being exposed to millions of rads, the chromosomes from these species stitch back together within 24 hours. The team is isolating the components involved and trying to reconstitute them in vitro in a cell-free system so they can be used in assembling genomes. Dr. Venter thinks this will yield a new field, called "combinatorial genomics." By putting the various cassettes together, they believe thousands or millions of cassettes and genomes could potentially be made per day. This would allow for selection by screening, whether for chemical production, cellular viability, or hydrogen production.

The team is starting with genome transplantation, taking cell ghosts and planning to put new synthetic chromosomes in them to determine whether the new operating system will support life. Results are expected within a couple years. Dr. Venter said synthetic cells have the potential to transform the world's industries. He believes they could combine synthetic cells and mix cultures to produce biopolymers, sugars, proteins, or capture fixed CO_2. Dr. Venter described a grant from the Department of Energy that is funding their efforts to try to modify photosynthesis, taking the energy from sunlight and switching it directly into hydrogen production. They hope to make progress within 1 to 2 years. They're also trying to modify cellulases and combine them with fermentation in modified and synthetic genomes that have the potential for ethanol production.

Dr. Venter stated that some of the potential benefits of synthetic genomics could be increased understanding of the first principles of biology and chemistry, as well as energy production, improved human and animal health (e.g., vaccine production), and new materials (e.g., bioplastics). He said that designed and engineered species could replace petrochemicals, generate major sources of food, create a source of energy, and conduct bioremediation. Speaking on the ethics of this research, Dr. Venter stated that in 1998, they postponed their work while an ethical policy review took place at the University of Pennsylvania. The reviewers indicated that it was acceptable to move forward in making the first synthetic species. The results were published in *Science* in 1999, along with the team's first minimal genome paper.

Dr. Venter said it's up to the scientific community to set good standards, rather than a Federal regulatory agency. TIGR is trying to lead the way with good stewardship in the laboratory. They don't take their research to stages that aren't necessary. He explained that they have a B-3 laboratory and they don't believe human pathogens or human genome modifications should be taking place at this stage. Dr. Venter said organisms should be designed so they can't survive

outside the lab. He stated that they know how to engineer out pathogenesis and self-evolution mechanisms based on the work they've done with many genomes. Dr. Venter closed by stating that the Board's work is important in terms of open communication with the scientific and non-scientific communities and that there is a tremendous opportunity for doing good through continued research.

Dr. Kasper then introduced another pioneer in genetic research. He stated that Dr. George Church is professor of Genetics at Harvard Medical School and Director of the Lipper Center for Computational Genetics.

Risks and Rewards of Synthetic Biology

George Church, Ph.D.
Professor of Genetics, Harvard Medical School

Dr. Church stated that a technological view of the risks and rewards of synthetic biology must consider sequencing synthesis in systems. He noted that Federal agencies and private sector companies have worked successfully together to sequence human and other genomes. He explained that his group and many others have been working at the intersection of three exponential technologies: computational, synthetic, and analytic. Dr. Church explained that as research continues in these areas, the possibility of destructive technologies increases. The risks are greater in the areas in which codes of ethics have not had a large impact. He said, however, that various representatives of the synthetic biology community have conferred on ways to minimize these risks.

Dr. Church described several defensive options. He stated that, as a starting point, control of recombinant DNA and Select Agents should be expanded so that there are not only codes of conduct, but surveillance; ideally via computer monitoring. He said it would be economically feasible to conduct surveillance on the bio-supply-chain (e.g., chemicals, instruments, and synthetic oligonucleotides) because of the small number of suppliers. Dr. Church explained the benefits of a bio-weather map, which provides a satellite image for monitoring airborne and medical fluids. He is interested in developing this relatively inexpensive technology. In addition, he stated that licensing and monitoring of the international bio-supply-chain would encourage responsibility and have a minimal impact on research. His team is also working on improving vaccines and biosynthetic drugs. Dr. Church said it may be possible to make cells resistant to most existing viruses via codon changes. He said that a profound change will be occurring in computational systems biology, as information becomes increasingly machine readable.

Dr. Church displayed a slide showing two projects on constructing new genetic codes, the first of which is being implemented. The team is changing the 313 UAG stop codons for amber suppression. This will allow the researchers to delete the RF1 that competes with the good tRNAs that they plan to introduce for new amino acids. To produce this in large quantities, they want to get rid of the competing release factor and stop codon. Then they can remove some of the codons or switch them, which has two positive uses. One is for engineering proteins and the other is for isolating genomes so that no piece of DNA can come in or go out in a functional way. The goal is to be able to engineer these DNA and RNA elements.

Dr. Church said there are numerous other examples. Many of their drugs come from biological systems and could be optimized synthetically. They'd like to have the ability to go in and change codons. He said it can be done gene-by-gene as codons are brought in, moving them between organisms. Dr. Church said there are valid uses for making mouse models that are closer to human so that they can test immune reactions and toxicity, which he said might be of interest to the Board.

Dr. Church reiterated the importance and safety of changing the full genome and discussed the process by which it is done. He said his team can make up to ten megabase pairs of oligonucleotides on a $1,000 oligos chip through a variety of methods. Just as a projector can project onto a screen, a genome can be projected onto this chip and synthetic oligonucleotides can be made. Dr. Church noted that Dr. Joe Jacobson's group and Dr. Paul Modrich's group have worked with his team to improve the DNA synthesis accuracy of these chips, which is a rate of about 1 percent. Sub-accuracies can be obtained that are better than the accuracies of PCR, i.e., error rates of about one in 100,000. The researchers have improved the error rate by orders of magnitude and are continuing to do so.

Describing the assembly process, Dr. Church said it dates back to a paper published by Carrie Mullis in 1986, followed by PCR papers and other projects in 1990 to 1995 for polymerase assembly. Dr. Church's team improved the process by adding a computerized design and some multiplexing. This work was published in Nature. Dr. Church stated that the idea was to extend oligonucleotides on the chips onto each other, eventually extending them up to the 10 to 15 kilobase range in vitro. The ends are then trimmed back and annealed up to the 100 kilobase range. Displaying a slide demonstrating this work, Dr. Church said that researchers put in more than 300 kilobases in the process of the genome project. He displayed the E. coli genome, with five megabase pairs. He stated that the last steps were done in vivo, because of the difficulties inherent in handling large DNA on the five megabase scale without fragmenting it.

Dr. Church displayed another process for genome assembly, which is largely automated. It starts with one pool of about 117,000 oligonucleotides, which is half of a chip. It goes into 480 pools, then drops down to 48 in vivo constructs, then drops down to one. He said this process is in a fairly early development stage and there are three ways that they are pursuing putting the constructs together. They can put the 48 constructs in one at a time, which takes about 1 day per stage, or they can use a hierarchical method, by putting them in two at a time, then four, and so on, dropping the number from 48 strains down to one. There's also a highly multiplex possibility for both of those processes, which could be, involve? as little as one stage. They made a 14 kilobase construct of 21 genes from E. coli. The researchers did them in the original form and also by codon re-mapping, so that they could express at higher levels by changing their codon uses. Dr. Church stated that there is great promise in codon re-mapping. They want to be able make the genomes safe for both [both what?] by changing the codons, but also by metabolic dependency.

Dr. Church displayed an example in which the team made a large variety of metabolic dependencies and then determined in detail how they could cooperate to rescue one another, and how they would then evolve. In one example, they evolved the strains from the initial 7-hour doubling time to a 2-hour doubling time. He described a new sequencing method by which they can evolve the strains that have escaped their selection or resistance. This new sequencing method is intended to be easily distributed using a standard microscope that has

been automated with a computer readout. The process is conducted entirely in vitro to avoid the problems of in vivo cloning. It's also capable of doing single molecule detection.

The team has already seen a 30-fold improvement in cost, which is a greater improvement than in speed. However, cost is the most important consideration. Dr. Church said the accuracies are extremely high. He foresees a 100,000-fold improvement without any real changes in technology, just more effective use. He said sequencing is used not only to determine what was done synthetically, but whether and how [the strain?] evolved. Dr. Church displayed a slide on monitoring the environment for viruses and bacteria, indicating how his research team has been sequencing the strain of E. coli they engineered. They have a very high accuracy, on the order of ten to the minus six. Dr. Church emphasized that this technology is very important for many applications, including sequencing humans.

The last slide summarized work on single molecules. Dr. Church stated that this process is very sensitive, requiring environmental monitoring to ensure that every molecule is included. Each molecule is in its own PCR tube and has no competition with the other molecules. There are no crossovers. Dr. Church said they can sample various points along the molecules, as large as 150 megabase pairs.

Dr. Church closed by summarizing the key points of his presentation concerning defensive options: inexpensive monitoring using a bio-weather map; licensing of the international bio-supply chain; multi-epitope vaccines and biosynthetic drugs such as Artimesinin; and cells that are resistant to most existing viruses via codon changes. He stated that the work his team is doing with codon changes in E. coli is transferable to other species of agricultural significance, which could prevent bioterrorist actions.

Dr. Kasper introduced Dr. John Mulligan, President and CEO of Blue Heron Biotechnology. Dr. Mulligan spoke about his perspective on the potential misuse of synthetic genomics and how it impacts the life sciences industry.

Biosecurity Concerns Involving Genome Services Providers: An Industry Perspective

John Mulligan, Ph.D.
President and CEO, Blue Heron Biotechnology

Dr. Mulligan stated that he wanted to make three main points about the regulation of DNA synthesis:

- DNA manipulations are at the heart of modern biology;
- Current regulations need improvement because they lack clarity and specificity; and
- Good choices in regulation can enhance U.S. ability to respond to new diseases and are more likely to be adopted internationally.

Dr. Mulligan explained that Blue Heron Biotechnology is a gene synthesis company that provides customers with access to a secure website into which they can paste a DNA sequence. Blue Heron then manufactures that sequence from phosphoramadytes, clones it, verifies the sequence, and then ships the clone to the customer within several weeks. Most customers are

conventional biomedical researchers in pharmaceutical and biotechnology companies, universities, and Government labs. They use this technology to substitute for other standard research techniques because it's faster and less expensive. Dr. Mulligan stated that access to gene synthesis technology improves the productivity of the research and development (R&D) process and saves time and money. The cost is continuing to decline due to advancements in technology. Researchers also use this method because it gives them complete control of any DNA sequence they need, which improves experimental design and allows new approaches, such as those emerging in synthetic biology.

Dr. Mulligan believes that regulation of this technology is important because molecular biology and genetics are integral to life sciences research and the techniques are ubiquitous, regardless of the discipline. He said that billions of dollars are spent globally to obtain and modify DNA each year. The direct costs to NIH are in the billion-dollar range. Dr. Mulligan explained that tools that improve the speed of R&D could be critical in responding to new diseases. Pandemics are likely to arise from nature, regardless of any nefarious efforts. Although there is a threat from bioterror, there is an equal and perhaps greater threat from the natural evolution of new diseases in the next few decades.

The technology provided by Blue Heron has a direct impact on infectious disease research. Scientists need the DNA from pathogens to study their basic biology and develop new therapeutics. Some pathogens, including all viral pathogens, can be synthesized with today's technology. One or more bacterial genomes are likely to be synthesized within the next year. Given these facts, nefarious uses of the technology are certainly possible. However, Dr. Mulligan pointed out that direct isolation of pathogens is less expensive and less technologically complex than gene synthesis. Therefore, Blue Heron has been very focused on compliance with the current Select Agent regulations.

Government approval is required to possess or distribute certain pathogens and pathogen genes (i.e., Select Agents). Blue Heron complies with these regulations by screening all orders they receive against a database of genes from Select Agents. They review every sequence that resembles a Select Agent gene. Then they conduct a detailed analysis of any genes that are identical or very close to Select Agent genes to determine whether they're covered by the regulations. Dr. Mulligan stated that the current Select Agent regulations require some interpretation. Many genes from Select Agents are not dangerous and not controlled, and many genes from Select Agents resemble harmless genes. Scientists often use non-functional parts of these genes in their research. This includes viral code proteins for vaccine development, enzymes for testing anti-microbial and anti-viral drugs, and DNA fragments or proteins for development of diagnostics.

Dr. Mulligan gave some recent examples of the kinds of situations they encounter when they analyze these sequences. One order had a 100 percent identity with a part of a toxin protein and matched about 30 percent of that toxin protein. If it matched the whole protein, it would be covered by the Select Agent rules. The company found in the literature that this domain is very useful for vaccine development and they determined this use was consistent with the group that ordered it. Since that domain was not functional on its own, they built the gene for the customer. They find that many common metabolic genes come up as identical to a pathogen gene and many Select Agent viruses are similar to non-Select Agent viruses. In each case, input is required from a Ph.D. biologist to decide whether or not Blue Heron should provide that

gene to the customer. They believe regulatory clarity in the area of Select Agent DNA sequences would be helpful for their business and the industry as a whole. Dr. Mulligan stated that the goal should be to restrain and monitor access to dangerous DNA fragments, while retaining the ability to carry out rapid biomedical research and other life sciences R&D. He stated that no national regulatory scheme can completely block the arrival of new pathogens or control activities in other countries. However, poorly conceived regulation could impede the ability to respond to the emergence of new pathogens, whether they arise from natural or human causes.

Blue Heron's perspective on one aspect of the regulatory scheme is that regulations should define the DNA sequences that are covered, because the current Select Agent rules require interpretation. The regulations should also define the actions to be taken when targeted sequences are requested, describing what needs to be reported and to whom, and what the involvement of the customer should be in the process. Dr. Mulligan said that a database that has a list of select DNA sequences, i.e., DNA sequences that could be used to build pathogens or enhance pathogenicity, could be a solution. These sequences would be defined in terms of a reference sequence and a percentage identity to the reference sequence, so it would be possible to tell whether the sequence violates the law. The database would require active maintenance by an oversight panel and a set of organism-specific experts, with updates made on a regular basis. Dr. Mulligan suggested three classes of sequences:

- The specific genes from Select Agents, which currently require a permit to produce;
- A set of related genes or other pathogenicity genes that would require reporting, but not necessarily any other controls on their possession by scientists; and
- All other genes, which would not have reporting requirements.

These classes would facilitate control of the high-threat sequences and tracking of the sequences that could be incorporated into new pathogens. Currently, the Select Agent rules allow ordering of a fragment of a toxin from different gene synthesis groups, but the rules are not violated until these fragments are assembled into a complete pathogen, so it would be useful to track them.

Blue Heron would support a positive requirement to check orders against the select sequence database.
The current rules make it illegal to provide certain sequences, but do not require providers to check for those sequences. Dr. Mulligan stated that clear procedures are necessary for identifying the organizations and individuals that are authorized to possess molecules encoding select sequences. He suggested that a centralized database collate information on reportable sequences.

Dr. Mulligan made the point that gene synthesis is an international industry. Companies operate all over the world, including one in Germany, one in mainland China, a dozen in Europe, several in Asia, and about a dozen other companies in the U.S. Ad hoc (non-commercial) genes synthesis occurs regularly in labs all over the world. Dr. Mulligan explained that there are tens of thousands of people capable of carrying out gene synthesis in their own laboratories. U.S. regulations can't block nefarious access to this technology. However, regulations impact U.S. ability to respond to new pathogens. Regulations can also impact the

development of the technology, because pharmaceutical researchers would not want to outsource gene synthesis to companies such as Blue Heron if the regulations required disclosure of all sequence orders. This information is often confidential. Such regulations would drive the demand for gene synthesis instruments, i.e., "gene synthesis in a box." Technology would then develop that would allow researchers to assemble the genes themselves. Dr. Mulligan stated that any regulations that push toward dispersing the technology to more people would loosen controls, not tighten them.

Dr. Mulligan stated that rapid, effective R&D is the solution. He said our response to new pathogens depends on decades of basic research and the immediate application of today's best technology. Regulations that restrict access to the best technology would increase the risk from pathogens by placing limits on legitimate researchers but would not restrict nefarious access to technology. Scientists working for the good of society currently have a many-fold advantage in resources over small non-governmental organizations that might use technology in nefarious ways. Dr. Mulligan said he believes that the number of people who are unscrupulous and willing to kill innocent bystanders for political end is very small relative to the vast number of people who want to use this technology in good ways. He believes balanced regulations that discourage nefarious projects without chilling the R&D enterprise will preserve the advantage of the "good guys" over the "bad guys."

Dr. Kasper opened the floor for questions for the Session V speakers. Dr. Rubin asked Dr. Church, based on his work with mathematical models, where he thought dual use actually starts. Dr. Church reiterated the idea that just about anything can be weaponized, but that an important way to determine intent is to look at those who are trying to work surreptitiously.

Dr. Franz asked the panel about the international demographics of capabilities in dual use technology. Dr. Mulligan stated that the vast majority of the capacity is in the west, primarily North America and Europe, but it is expanding rapidly in China, India, and throughout the rest of the world.

Dr. Osterholm asked the panel for advice on determining the line between innocent actions and those that might indicate nefarious intent. Dr. Venter replied that those with nefarious intent would probably not do business with Blue Heron or other reputable companies. He explained that there are probably over 50,000 DNA synthesizers in the world, with blueprints for making them on the Internet. They're for sale on ebay for about $5,000. Therefore, tracking the activities of a few reputable businesses will not help. He advocated tracking airborne samples and water samples, as Dr. Church suggested. He also said the DNA sequence is probably the most telling piece of information, which has largely been ignored. The sequence indicates instantly whether it was an engineered. He also said that concentrating only on defensive countermeasures is missing the big picture. The assumption should be made that any viral agent can be produced and the U.S. should ensure that there are good vaccines and new vaccine development procedures that will work against both naturally occurring and man-made viruses. The key issue is to stay one step ahead, using detection and defense systems. Dr. Mulligan agreed and added that he would like to see efforts made to eventually detect the sequences of newly designed pathogens.

Dr. Erlick asked if pharmaceutical companies and others are pushing back against these ideas. There are inevitable trade secret issues that come with quick recognition of early processes that

might lead to a patented element. Dr. Mulligan said he was sure this will be worrisome to some.

Dr. Relman stated that he shared the skepticism of others concerning the feasibility of controls or regulation because of reasons that he felt had not been adequately explored. He said there is an imprecise and insufficient understanding of the meaning of sequences, and he stated that every journal on the subject brings to light some unintended consequences of knocking out genes. Often the consequences are the opposite of the intended result.

Dr. Church addressed the issue of people who are making oligonucleotides in their basement at a higher cost than by using a reputable company. He said that's an indication of intent to develop a toxin. These individuals will leave a trail of the chemicals and instruments they buy and the transactions on ebay. He said that these things can be monitored, and he didn't believe monitoring would drive Dr. Mulligan's customers away. He stated that if a "black box" checked orders for Select Agents, it would drive away only those who have nefarious intent and he believes the pharmaceutical companies could be convinced that monitoring is not harmful to them.

Dr. Mulligan stated that his customers would be comfortable with Blue Heron conducting screening, but not with Blue Heron shipping information off to someone they don't know for analysis. Dr. Venter asked Dr. Relman what he thinks the state of knowledge of pathogens is that would allow black boxes to be built. Dr. Relman agreed that there are major voids and that currently, it would be very hard to have a sufficiently robust black box data set with which to screen. He said it might be hazardous to venture down that path. Dr. Mulligan added that there are many easier and lower-tech ways to obtain a pathogen than by designing a new one that doesn't match known published sequences. Dr. Church stated that if people don't know what's being checked for in the black box, they won't know how to work around the system. If they work in their basement, they'll be revealing that they're not taking the cheapest price and best quality available. They will self-define nefarious and hazardous activity. He agreed that there is no perfect Select Agent list, but said a list based on best guesses will discourage people who are trying to do bad things from using companies like Blue Heron. Dr. Mulligan disagreed with the contention that people will always use the cheapest and most accurate sequence.

Dr. Paul Keim asked Dr. Venter if and where he thought a line should be drawn on experiments with infectious disease models. Dr. Venter replied that the line would be crossed when someone worked on an infectious agent in an unregulated fashion. He said that meaningful research to understand pathogenicity is critical in developing new vaccines, but there must be review of the approaches before they're undertaken. He stated that unless people are working directly in the area of developing vaccines, he would be uncomfortable with someone randomly conducting such experiments. Dr. Keim asked what the timeline is for concern that a dangerous pathogen can be created. Dr. Venter said it would take a dedicated program, which he believed no reputable nation or government would undertake. He mentioned testimony from the former Soviet Union on some of the programs they had, stating that if someone applied these to a known human pathogen, they could try and select for something with greater pathogenicity. However, it would be a very complex and expensive experiment to undertake. Dr. Mulligan added that it would have to be tested in people, which would allow for detection.

Dr. Klein stated that in the military, their experience has been that it takes about 8 years for a

vaccine to be licensed. He asked Dr. Venter for suggestions on shortening that time frame. Dr. Venter stated that he's on a committee to address some of those issues with the Deputy Secretary of Defense. He stated that one of the promises of synthetic genomics is rapid vaccine production. He acknowledged that the major pharmaceutical companies recently laid off all of their antimicrobial teams because they can't make as much money treating infectious diseases as they can treating chronic diseases. He agreed that this priority needs to change radically.

Next Steps

Dr. Dennis Kasper
NSABB Chair

Dr. Kasper and Dr. Keim outlined action steps for NSABB. They established working groups to maintain the momentum on key issues in which NSABB is engaged, composed of board members, *ex officios*, and invited outside experts. The groups were charged with researching, deliberating, and providing information to the full Board on dual use research, communications, codes of conduct, international collaboration, and synthetic genomes. Dr. Keim noted that the recommendations of these subcommittees will be issued only after the full Board reaches conclusions. Participants then indicated their preferences for serving on one or more of these subcommittees.

The dual use subcommittee was charged with defining criteria for identifying dual use research and research results and with considering the flexibility needed in the criteria because of the potential for harm. The communications group was charged with developing methods and technologies for communicating results. They will advise on policies and practices for communicating findings and technologies from dual use research. They will also facilitate consistent application of well-considered principles and make decisions about communication of information with biosecurity implications. The subcommittee considering codes of conduct for the life sciences is charged with soliciting support and recommendations from the scientific community for a code to address dual use research and to provide recommendations for a code that may be adopted by the life sciences to address dual use research concerns. The subcommittee on international collaboration is charged with recommending strategies for fostering international collaboration in the development of appropriate biosecurity policies. They will gather information, develop outreach networks, promote an exchange of information, and develop strategies for engaging the international community. The group addressing synthetic genomes will evaluate the dual use biosecurity concerns involving advanced DNA synthesis technologies and develop potential strategies by working with scientific and genomes service providers to facilitate best practices.

Dr. Kasper then opened up the floor for public comments.

Public Comments

Ranjan Gupta
AAAS, NIH Science Policy Fellow

Mr. Gupta commented on fostering the culture of responsibility in students in the life sciences.

He suggested a reward system, such as certification through a professional society or an international organization (e.g., UNESCO).

Brian Hanley

Mr. Hanley noted that the undergraduate textbook, "Adenoviral Vectors for Human Genome Therapy," provides cookbook-type information on such techniques as recombining animal viruses to produce new viruses to which human beings have no natural immunity. He pointed out that this information could be used to construct new pathogens.

Alan Pearson
Center for Arms Control and Nonproliferation

Mr. Pearson addressed the group on behalf of the Center for Arms Control and Nonproliferation, specifically its scientists' working group on biological and chemical weapons. He said they have over 25 years of experience dealing with these issues at the national and international levels. They've developed recommendations on a code of practice that they are willing to share with the Board. Mr. Pearson also spoke on the concept of dual use in relation to the activities permitted and prohibited under the Biological Weapons Convention. The BWC prohibits the development, production, stockpiling, and acquisition of biological weapons, biological agents, or toxins in types and quantities that have no justification for prophylactic, protective, or other peaceful purposes. It categorically prohibits work on weapons and delivery systems designed to use biological agents or toxins for hostile purposes or in armed conflict. Mr. Pearson asked if it's possible for guidelines and oversight mechanisms to help keep research projects and programs from crossing, whether inadvertently or deliberately, the thin line between permitted and prohibited activities. He asked if assertions of benign intent are enough to meet our responsibilities to maintain national security.

Mr. Pearson stated that in considering these questions, the Board could consider examples of current dual use research, and he mentioned four. First, research that aims to develop more stable forms of Botulinum toxin, recently funded by NIAID. Second, research that aims to identify new therapies based on the modulation of innate immune responses to infection. Third, research on biochemical and incapacitating agents such as the fentanyl derivative used in Moscow in 2002, which many governments are funding. Fourth, threat assessment research that explores the offensive potential of various agents, genetic and physical modifications, and delivery mechanisms. Mr. Pearson stated that today, governments still set the boundaries of and provide the justification for acceptable conduct by those they fund and employ. He suggested that these points are worthy of the Board's serious consideration.

Venkat Rao
Computer Sciences Corporation (CSC) National Security Program, Alexandria, Virginia

Dr. Rao said that the National Security Program works on CBR and threat reduction counter-proliferation and biological arms control programs and biodefense countermeasures development.
He stated that issues relating to biosecurity addressed by the Board are critical to their current engagements with Federal Government agencies. He said that there now exist only partial

solutions to a very complex problem. In his assessment, biosafety, bioassurance, and biosecurity are the three legs of this challenge and the roles of individual scientists and laboratory workers are critical to success at the institutional level. He said biosecurity requirements must exist within the existing biosafety framework, so that institutions do not have to meet multiple requirements, but one set of internally consistent rules. In his opinion, threat assessment and risk assessment are not the same and risk benefit analysis and dual use are not the same. He said the Board must ensure that these fundamentals are clearly laid out as part of a guidance development process. He advocated "choke points" at the grant application review and award stage if good guidelines are to be developed for a transparent review and decisionmaking process. He also stated that, as part of guidance development, the Board should consider a case study-based investigation for a variety of potential threat scenarios involving academia, private sector, and government-supported major programs that involve biosecurity components. This would allow participation of key stakeholder communities and contribution to the development of necessary biosecurity guidelines.

David Silberman
Stanford University

Dr. Silberman noted that the prime focus of the meeting was directed at the roles of scientists and their host institutions. He said the *ex officio* members of NSABB also play critical roles, because they promulgate the policies and regulations under which researchers work. Dr. Silberman then spoke on the problem on fundamental research exemption and the export control. He gave the example of a post-doctoral fellow who has been accepted from a laboratory overseas after many delays because of bureaucratic red tape, who completes his work and post-doctoral fellowship and publishes papers with the senior author. He is then told that when he leaves the U.S., before he can do any work in his home country, he needs an export license. Dr. Silberman said this is unacceptable. He stated that if we are looking for international cooperation, we must look at our own policies and offer some modifications. He mentioned several illustrious scientists in our history who came to the U.S. from foreign countries. He said that in the past, the U.S. was more accepting, and now we're preventing scientists from coming in. MIT had to reject a $1 million DoD grant because of restrictions on foreign nationals. Dr. Silberman then commented on research discoveries that could not have been foreseen by an IBC or any others reviewing it. He said unexpected findings are wonderful, but can have a potential negative effect. He asked what should be done with that information. Should it be made available in a special journal or restricted website? Should a meeting of scientists in the applicable field be assembled so they can talk to one another? How can this information, which is scientifically important, be shared? Dr. Silberman had no answers to these questions but reminded the Board of their charge to provide advice, guidelines, and leadership. His hope was hope that they will advise both the scientific and policy-setting communities.

Drew Endy
Professor of Biological Engineering, MIT

Dr. Endy commented on the topic of synthetic genomics. He opposed the idea that anyone building a gene in their basement or garage must be "up to no good." He asked the Board to consider why someone might build a radio in their garage or might educate their children at home. He was concerned that the Board presumed that the regulation they should consider for

synthetic genomics is straightforward. He asked for further consideration of the facts on this issue.

Concerning the question of when dual use starts, especially with regard to biological engineering and synthetic biology, he believes it starts in the mind of the individual. He said one of the most important things for the Board to consider is how to foster a constructive culture of responsibility in the next generation of biological technologies. He also said it's not too early to consider how to foster a transition in strategy concerning current and future biological risks. He said that at present, it seems we're developing a strategy for fixed defenses for specific threats, such as emerging infectious diseases or engineered diseases. He recommended considering how to transition from threat-specific based defenses to general capabilities-based defenses, so that we can quickly identify, analyze, and respond to new agents as they arise naturally or are engineered and are released.

Adjournment

Dr. Kasper officially concluded the first meeting of NSABB. On behalf of the Board, he thanked the speakers, panelists, and attendees. He stated that the inaugural meeting of NSABB was productive and marked a significant starting point for the Board. He noted the importance of continued contributions from academia, industry, Government, and the general public to achieve the appropriate balance necessary for effective biosecurity without unduly encumbering research efforts.