

Biosecurity concerns: Changing the face of academic research

The need for biodefense research in the wake of the anthrax attacks that followed 9/11 is changing the nature of research and the manner in which it is conducted on University campuses. A huge federal investment in biodefense is leading to more applied research conducted in high containment laboratories on college campuses. Biosecurity concerns are starting to exceed those of biosafety. Compliance with the many new oversight regulations is challenging to the research and safety communities. A series of legal cases discussed in this paper show that compliance is essential—the government is serious about criminal prosecution. The focus of biosecurity is not only on safeguarding dangerous pathogens and toxins; it also is directed to information and knowledge that may be misused. Systems are being developed that will force the academic safety community to determine what information is dangerous and what knowledge must be constrained.

By Ronald M. Atlas

BIODEFENSE RESEARCH

In the aftermath of the anthrax attacks that followed the horrific events of September 11, 2001, fear of bioterrorism has become a driving force within the United States, bringing about major changes in science policy and activities on the Nation's campuses aimed at enhancing protection against the perceived looming biothreat. Biodefense research has been transformed from countering potential military uses of biological weapons to protecting the entire population against a bioterrorist attack—all infectious disease research has become potentially relevant to bioterrorism and, therefore, virtually the entire life sciences community has become "involved" in the response to the threat of bioterrorism. The National Institutes of Health (NIH) and the Department of Homeland Security (DHS) have been made responsible for funding major biodefense

research programs. With the broadening of the biodefense research agenda, university researchers are engaging in Biodefense Research—raising many biosafety and biosecurity concerns that are changing the nature of research in the life sciences and the relationships among researchers as well as between researchers and campus safety officers. More than ever, there is a need to carry out research that will find the cures, diagnostic tools, and preventative measures that are needed to protect the public against bioterrorism; but, the research must be conducted safely and ethically.

The President of the United States has laid out the division of responsibilities of federal agencies for biodefense research in Homeland Security Presidential Directive 10 (HSPC-10).¹ The Department of Health and Human Services (HHS) has been given responsibility for the development of measures that directly protect human health through the research at the NIH and the public health programs of the Centers for Disease Control and Prevention (CDC). The US Department of Agriculture (USDA) has been charged with conducting the necessary research to protect plants and animals from acts of bioterrorism. The Environmental Protection Agency has been assigned the task of developing specific standards, protocols, and capabilities to address the risks of contamination following a biological weapons attack and developing strategies, guidelines,

and plans for decontamination of persons, equipment, and facilities. The DHS has been given several responsibilities related to biodefense, including developing environmental detection sensors for warning, detection, and recognition of biological weapons attacks to permit timely response, and establishing the National Bioforensic Analysis Center of the National Biodefense Analysis and Countermeasure Center to conduct and facilitate the technical forensic analysis and interpretation of materials recovered following a biological attack. Each of these responsibilities is accompanied by new budget appropriations and outreach to the academic research community.

There is little doubt that the availability of new sources of funds is attracting university researchers to the biodefense arena. Since 2001 funding for biodefense research has greatly increased, e.g., the biodefense budget at NIH has grown from \$25 million in 2001 to over \$1.6 billion annually; that is 300% more than it was at the time of the anthrax attacks (see Table 1).

The National Institute of Allergies and Infectious Diseases research plan calls for basic research into microbes with bioterrorism potential, and the specific and non-specific host defense mechanisms against these agents. It aims to establish animal models and standardized reagents, microarray panels, and other materials for the study of priority pathogens. Effectively,

Ronald M. Atlas, Ph.D., is the Co-director, Center for Deterrence of Bio warfare and Bioterrorism, Graduate Dean and Professor of Biology and Public Health, Houchens Building, Suite 105, University of Louisville, Louisville, KY 40292, USA (Tel.: (502) 852-3957; fax: (502) 852-2365; e-mail: r.atlas@louisville.edu).

Table 1. NIH Biodefense Research Funding

Total 2001	\$25M
Total 2002	\$275M
Total 2003	\$1,500M
Basic research and development	\$441M
Drug/vaccine discovery–development	\$592M
Clinical research	\$194M
Research facilities	\$521M
Total 2004	\$1,600M
Total 2005	\$1,694M

it aims to accelerate the discovery, testing, and implementation of new biodefense therapeutics, vaccines, and diagnostics. The very nature of this focused research involves a paradigm shift from the traditional NIH basic discovery research that has been carried out on university campuses to applied/translational research with predetermined milestones and the ultimate production of new/improved diagnostics, vaccines, and therapies. The need to translate research rapidly into products is forcing quick choices so that vaccines and therapeutics can be incorporated into a national stockpile that would be employed to respond a bioterrorism event. Basic research on biothreat agents and infectious diseases must quickly move to translational research and the actual production of drugs, vaccines, detection devices, and so forth. It remains to be seen how university researchers will be able to sustain the applied research and achievable milestones demanded by biodefense.

There is also a need to expand the horizons of biomedical research to allow breakthrough discoveries, including the development of broad spectrum antivirals that would be useful for treating naturally-occurring and re-emerging infectious diseases, e.g., SARS and West Nile Fever, as well as diseases that might be introduced by a terrorist. So far the NIH appears to be able to work across the continuum of natural infectious diseases, through those that are emerging and re-emerging, to those diseases that might be deliberately introduced by a terrorist.

The Department of Defense (DoD) and DHS are also reaching out to universities to participate in critical

research programs. The Defense Advanced Research Projects Agency (DARPA), the central research and development organization for the DoD, is supporting cutting-edge biodefense research that highlights the threat of bioterrorism and the potential responses. DARPA-sponsored research promises to make key major advances in biodefense through the discovery of novel technologies. Some DARPA research, however, like the *de novo* synthesis of polio virus by a university researcher,⁴ have raised controversies within the academic community and with the public about whether it raises the threat of catastrophic bioterrorism rather than lowering it. The DHS has established University Centers of Excellence and also runs HSARPA (Homeland Security Advanced Research Agency) that parallels the DARPA efforts to make major technological advances which can be applied to biodefense. The DHS biological countermeasures budget for fiscal year 05 was \$407 million; of this \$40 million was appropriated for bioassays, \$67 million for detection, \$17 million to accelerate the development of next generation biological detection systems, \$5 million to initiate the development of detection systems for critical food nodes, and \$15 million for forensics.

BIODEFENSE RESEARCH AND BIOSECURITY

The increase of funding for biodefense research at universities has important consequences for the campus safety community. It means more oversight, more concerns, and more uncertainties as one seeks to balance biosafety and biosecurity with the need to make

rapid progress in developing the vaccines, therapeutics, diagnostics, etc. that are critically needed. Biodefense research will require access to cultures of dangerous pathogens, raising concerns about biosecurity of cultures in laboratories and collections and who may legitimately possess potential biothreat agents. There is an ongoing debate with the public about the safety of biodefense research, a debate that is heightened by plans to construct several new BL-3 and BL-4 laboratories where biodefense research can be conducted. While universities are vying for the funds to construct these laboratories, local communities are worried about having universities place these facilities close to major population areas; concerns range from fears that they will be targets for terrorists to their serving as potential sources for dangerous pathogens that could be introduced into the community.

Even before the anthrax attacks, there was a clear need to control access to dangerous pathogens. In 1995, Larry Wayne Harris, a member of the Radical Aryan Nations, tried to obtain *Yersinia pestis*, the bacterium that causes plague, from the American Type Culture Collection. At that time, there were no laws in the United States controlling possession or domestic acquisition of dangerous pathogens; there were no protective material transfer agreements that could prevent a terrorist from trying to obtain biothreat agents from legitimate culture collections; and, for the most part, there was an openness and unquestioning willingness to share materials. Although Larry Wayne Harris was convicted of wire fraud for supplying false laboratory identification number to obtain cultures of plague-causing bacteria, this case clearly showed that additional laws were needed to prevent individuals with ill intent from possessing dangerous biological agents. As a result, practices for supplying microbial cultures to the research community began to change.

The Antiterrorism and Effective Death Penalty Act of 1996⁵ adjusted the restrictions on possession and use of materials capable of producing catastrophic damage in the hands of terrorists. Sec. 511 of that Act made it a federal crime to threaten to use a

weapon of mass destruction and directed the Secretary of HHS to promulgate regulations identifying biological agents that pose a potential threat to public health and safety, and governing their intentional or inadvertent transfer. This resulted, in 1997, in the CDC Laboratory Registration/Select Agent Transfer Program.^{5,13} These regulations placed shipping and handling requirements on laboratory facilities that transfer or receive “select agents” capable of causing substantial harm to human health. They were designed to ensure that select agents were not shipped to parties who were not equipped to handle them appropriately or who lacked proper authorization for their requests. The Select Agent Transfer Program regulated shipment of 36 select agents and their disease related genes. There also was a mandated requirement to adhere to the CDC Biosafety in Biomedical and Microbiological Laboratories Manual (BMBL).¹⁴

The Biosafety in Biomedical and Microbiological Laboratories Manual provides guidelines from CDC and NIH for laboratories using biological agents or toxins capable of causing serious or fatal illness to humans or animals. It primarily is intended for work conducted under the BSL-3 or -4 conditions. Recognizing that plant and animal pathogens are also of concern for biodefense, the USDA will be involved in the next edition of the BMBL. The plan is to include in the next edition of the BMBL a separate biosecurity chapter (or chapters) that will recognize the conflicts between biosafety and biosecurity, e.g., whether or not to post safety warnings in areas where select agents are present. Currently BMBL Appendix F, which covers the biosecurity guidelines for all microorganisms, recognizes that laboratory security is related to but different than laboratory safety.

The BMBL Appendix F establishes a series of critical measures aimed at ensuring biosecurity of the laboratory. The guidelines provide that each institution should: (1) recognize that laboratory security is related to, but different than, laboratory safety; (2) control access to areas where biologic agents or toxins are used and stored; (3) know who is in the laboratory area;

(4) know what materials are being brought into the laboratory area; (5) know what materials are being removed from the laboratory area; (6) have an emergency plan; and (7) have a protocol for reporting incidents.

In general, biosecurity practices require that access to the laboratory should be controlled so that only authorized individuals can enter the laboratory. The degree of control will vary, but all laboratories should be locked when not in use and only authorized individuals will be able to gain entry. Biological Resource Centers and laboratories housing many different types of microorganisms, including plant, animal, and/or human pathogens, must commit to a high level of security. For research and clinical laboratories, the laboratory supervisor should be responsible for establishing a method for identifying authorized users of the laboratory and establishing effective mechanisms for controlling access to the laboratory and detecting unauthorized individuals. A revision to BMBL Appendix F provides guidance for biosecurity specific to select agents. Clearly today, universities—particularly campus environmental health and safety and biological safety officers—must worry about biosecurity as well as biosafety.

The anthrax attacks of 2001 that resulted in 11 cases of cutaneous (skin) anthrax, 11 cases of inhalational anthrax, 5 deaths, and a nation paralyzed by fear, raised, once again, questions about the security of dangerous biological materials. Many questions remain about the identity of the source of the deadly anthrax bacteria and who carried out the attack. Was the anthrax murderer an American Ph.D. microbiologist as proclaimed by high-ranking US government officials? Did the bacteria come from a US laboratory—perhaps the US Army Infectious Disease Laboratory, Edgewood Arsenal, or Louisiana State University—as suggested in court documents filed by the US Department of Justice (DOJ)? What is known is that the attack involved a highly refined (weaponized) powder of spores of the Ames strain of *Bacillus anthracis* that was sent by mail from New Jersey to several media firms and two US Senators.

Against the concern that terrorists could obtain dangerous pathogens and toxins from US laboratories, provisions were included in the USA Patriot Act of October 26, 2001¹² that placed restrictions on the possession of select agents. Aliens from countries designated as supporting terrorism could no longer possess select agents within the United States; nor could individuals who were not permitted to purchase handguns, e.g., some individuals with a history of mental illness or a criminal record. The USA Patriot Act also made it an offense for a person to knowingly possess any biological agent, toxin, or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by prophylactic, protective, bona fide research or other peaceful purpose. The USA Patriot Act made possession, in violation of these provisions, punishable by up to 10 years in prison and a \$250,000 fine. In testimony before the Congress on behalf of the American Society for Microbiology (ASM), I supported the provisions that restricted who could possess select agents; however, I requested a mechanism for granting exemptions and voiced concern about how bona fide might be interpreted—a concern that Senator Leahy entered into the official record.

This concern was realized in 2002, still at the height of the fear of anthrax that gripped the nation and shortly after the death a 94-year-old woman in Connecticut from inhalational anthrax, when Thomas Foral was formally charged with “unjustified possession of a select agent” under the provisions of the USA Patriot Act. Thomas Foral was a University of Connecticut graduate student who allegedly had saved *B. anthracis* in a freezer after being told to destroy the material by faculty member. There was no contention that Foral intended to do harm with the material. Rather the question was whether his possession was “bona fide”—when a university faculty member instructs a student to do something is it criminal for the student not to do so? In this case, the answer was yes. The federal prosecutor offered a deal to avoid possible jail and fines, involving visits to a probation officer, community service, and the insertion of a letter in Foral’s

ROTC file detailing his “illegal activities.” Foral accepted the plea bargain. The fear of bioterrorism had altered the permitted conduct of students at the nation’s universities – for better or worse – and, without commenting on the actions of Thomas Foral or the merits of the case, it had placed academic research institutions clearly in the sights of federal prosecutors and began to align the concerns of university campus safety officers charged with oversight of laboratory safety with those of law enforcement.

The provisions of the USA Patriot Act subsequently were incorporated into the Public Health Security and Bioterrorism Response Act, known as the Bioterrorism Act of 2002.⁹ The ASM supported this Act, which became law on June 12, 2002. The Bioterrorism Act of 2002 required registration for possession of select agents; required the HHS and USDA to promulgate regulations controlling access to select agents (Federal Register notice on December 9, 2002; regulations took effect February 7, 2003); required clearance by the DOJ for individuals possessing select agents; required additional record keeping to track the acquisition, transfer and possession of certain biological agents and toxins; required safeguards and security regulations to be followed; required collection of information for law enforcement; and, established a process for alerting authorities about unauthorized attempts to acquire select agents.

Thus, in only five years, the regulatory regime for biology had gone from a permissive atmosphere, in which biosafety was the primary concern and the laboratory facility – not the individual scientist – the focus of regulation, to a situation in which individuals face criminal sanctions if they violate any of the restrictions outlined in the USA Patriot Act or the Bioterrorism Act of 2002. Complying with public policies, such as those engendered in the USA Patriot Act and the Biopreparedness Act, both of which contain provisions that restrict access to select biothreat agents, is challenging. But compliance with regulations is critical.

Following passage of the Bioterrorism Act of 2002, the number of select agents was increased to about 80 with

the addition of animal and plant pathogens (see Table 2). It is interesting to note that, upon seeing this list, some university researchers are horrified to find that an organism with which they have worked for years is considered a biothreat agent. They

voice concern that their research will be inhibited by the restrictions imposed by the provisions of the Bioterrorism Act of 2002. Others, however, opine the absence of an organism from the list. They seek inclusion with the belief that it will bring an

Table 2. List of Select Agents Following Passage of the Bioterrorism Act of 2002

HHS non-overlap select agents and toxins agents and toxins

- Crimean-Congo haemorrhagic fever virus
- Coccidioides posadasii*
- Ebola viruses
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- Rickettsia prowazekii
- Rickettsia rickettsii
- South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
- Tick-borne encephalitis complex (flavi) viruses (Central European tick-borne encephalitis, Far Eastern tick-borne encephalitis, Russian spring and summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever)
- Variola major virus (Smallpox virus)
- Variola minor virus (Alastrim)
- Yersinia pestis*
- Abrin
- Conotoxins
- Diacetoxyscirpenol
- Ricin
- Saxitoxin
- Shiga-like ribosome inactivating proteins
- Tetrodotoxin

High consequence livestock pathogens and toxins/select agents (overlap agents)

- Bacillus anthracis*
- Brucella abortus*
- Brucella melitensis*
- Brucella suis*
- Burkholderia mallei* (formerly *Pseudomonas mallei*)
- Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*)
- Botulinum neurotoxin producing species of *Clostridium*
- Coccidioides immitis*
- Coxiella burnetii*
- Eastern equine encephalitis virus
- Hendra virus
- Francisella tularensis
- Nipah virus
- Rift Valley fever virus
- Venezuelan equine encephalitis virus
- Botulinum neurotoxin
- Clostridium perfringens epsilon toxin
- Shigatoxin
- Staphylococcal enterotoxin
- T-2 toxin

Table 2 (Continued)

USDA high consequence livestock pathogens and toxins
(non-overlap and toxins agents and toxins)

Akabane virus
African swine fever virus
African horse sickness virus
Avian influenza virus (highly pathogenic)
Blue tongue virus (Exotic)
Bovine spongiform encephalopathy agent
Camel pox virus
Classical swine fever virus
Cowdria ruminantium (Heartwater)
Foot and mouth disease virus
Goat pox virus
Lumpy skin disease virus
Japanese encephalitis virus
Malignant catarrhal fever virus (Exotic)
Menangle virus
Mycoplasma capricolum/M.F38/M. *mycoides capri*
Mycoplasma mycoides mycoides
Newcastle disease virus (VVND)
Peste Des Petits Ruminants virus
Rinderpest virus
Sheep pox virus
Swine vesicular disease virus
Vesicular stomatitis virus (Exotic)

Listed plant pathogens

Liberobacter africanus
Liberobacter asiaticus
Peronosclerospora philippinensis
Phakopsora pachyrhizi
Plum Pox Potyvirus
Ralstonia solanacearum race 3, biovar 2
Schlerophthora rayssiae var zeae
Synchytrium endobioticum
Xanthomonas oryzae
Xylella fastidiosa (citrus variegated chlorosis strain)

entitlement to research funding. Some have even claimed that organisms not on the list are really the greatest threat to humankind—not only claiming that the organism they study should be on the list, but that it should be at the top of the list and, consequently, should be receiving the greatest research investment. Clearly there are significant new requirements imposed on those choosing to possess and conduct research on select agents. The university community is divided over the significance of these new restrictions. Some have destroyed their cultures and some have transferred cultures to other facilities to avoid having to deal with the oversight mandated by the Bioterrorism

Act of 2002. Biosafety officers and other university officials have no choice but to comply if researchers at the institution possess any of the select agent pathogens or toxins in quantities that are subject to regulation. The government disputes claims that this requirement is having an undue negative impact on academic research, and despite various concerns raised by university officials, the federal government has just issued final rules requiring university researchers to carefully safeguard the microbes and toxins they study that could be converted into biological weapons². The CDC estimates that the total annual costs for all research organizations

covered by its regulations will be \$16 million and that the annual costs for individual facilities will range from \$15,300 to \$170,000. The final select agents rules require that universities submit security plans for governmental approval. Guidance on specific requirements is slated to come later. So universities and responsible officials are still concerned that there are uncertainties about the biosecurity requirements of the select agent rules.

In order to fulfill the DOJ responsibilities under the Bioterrorism Act of 2002 and the final rules for the possession, use, and transfer of select agents and toxins, the Federal Bureau of Investigation (FBI) was assigned responsibility for conducting security risk assessments. Since the rules went into effect, 8,394 researchers and employees have received security background checks. Compared with the CDC's estimate in 2002 that 285 academic institutions would register for possession of select agents, only 105 universities have registered which is 30% of all institutions possessing select agents in the U.S. Each facility, responsible official, and employee with access to select agents must obtain a security clearance from the DOJ. Specific clearances by the DOJ are required for all individuals who may enter laboratories where they may have access to select agents. Such vetting of personnel presents special problems for laboratories at academic institutions, which will likely include students who are admitted and authorized for educational purposes, and for clinical laboratories, which will likely select personnel based upon qualifications and skills—the personnel are needed but getting a security clearance may delay or exclude them. Within the laboratory, dangerous pathogens must be housed in secure incubators, refrigerators, or storage cabinets when not being used. When possible the incubators, refrigerators, or storage cabinets should be locked—however, this may not always be possible, e.g., in clinical laboratories where frequent movement of materials into incubators is necessary and where having to open a locked incubator would add risk and reduce biosafety. In such instances, special attention must be paid to ensur-

ing that only authorized individuals have access to the incubators or other locations where dangerous pathogens are housed.

The responsible university officials also are given the mandated responsibility of reporting to authorities any suspected theft or loss of select agents – the fear being that these could fall into the hands of terrorists. A report that vials of plague-causing bacteria were missing from a laboratory at Texas Tech in 2003 resulted in a case that has divided the research and biosafety communities. Thomas Butler, a researcher at Texas Tech and head of infectious diseases, had reported to the responsible university official that he could not account for 30 vials of cultures of *Y. pestis*; later he claimed that he had inadvertently destroyed the cultures. The initial report submitted by the responsible officer of the university sent FBI agents racing to the campus, and set off panic that terrorists might have acquired the cultures and were about to unleash a terrorist attack with plague. Butler was a leading researcher who had pioneered therapy for treating plague victims that has saved innumerable lives. But he also seemingly saw no need to comply with the provisions of the Bioterrorism Act of 2002, nor with other regulations governing the import and export of pathogenic microorganisms.

Butler had apparently carried the plague-containing material on a commercial airliner from Tanzania to the United States, had sent cultures back to Africa by air transport, and had transported cultures to laboratories within the United States – including government laboratories of the US military and the CDC – all without obtaining the necessary authorization. He was charged with illegally transporting Tanzanian plague samples (involving illegal import, domestic transport, and export) and with defrauding the university in research contracts. A number of prominent scientists, including several Nobel laureates, protested the prosecution of Thomas Butler. The National Academies of Science (NAS) voiced concern that this case could have a chilling impact on critical biodefense research. Nevertheless the prosecution went for-

ward with Butler being paraded before TV cameras in shackles and an orange prisoner suit. The jury found Butler not guilty of the critical charges relating to illegal transfer, perhaps because he had supplied them to government laboratories that should have ensured that the transport was carried out in accord with government regulations and, perhaps, because he clearly intended to do good and no harm; but, he was found guilty of fraud charges. The federal judge sentenced him to two years in jail and ordered him to pay fines and restitution of \$58,375.

The Butler case sent a clear signal to the research community that the US government is very serious about enforcing regulations governing transport and possession of microorganisms. The undeniable message from this case is that scientists are not above the law. Nor, despite the protests of how Butler was treated, should university researchers be above the law. Carrying out research with dangerous pathogens must be conducted in a manner consistent with the public trust. Biosafety regulations must be observed by university researchers as part of the pact with the public that permits the research to be conducted. And, in the age of bioterrorism, biosecurity regulations must be complied with fully as part of that same public pact that is critical for public support of biomedical research.

In 2004, yet another case arose that will define the limits of acquisition and possession of microorganisms on university campuses. The DOJ indicted University of Buffalo art professor, Steven Kurtz, and University of Pittsburgh geneticist, Robert Ferrell, on mail and wire fraud charges. Ferrell provided two kinds of bacteria (*Serratia marcescens* and *Bacillus atrophaeus*) to Kurtz for his performance art projects about biotechnology, but the materials handling agreement that the University of Pittsburgh has with the supplier, American Type Culture Collection (ATCC), specifies that “orderers” will use shipped materials only in their own labs. The ATCC Material Transfer Agreement aims to protect the commercial interests of ATCC and to hold ATCC blameless if cultures cause harm. Both *S. marcescens* and *B. atro-*

phaeus have been used to demonstrate and study the spread of bacteria, including in biological weapons development programs.

According to the indictment, pursuant to the University of Pittsburgh Biosafety Manual,¹¹ the biological organism *S. marcescens* was a biohazardous material to be handled at Biosafety Level One. The same manual provided that the biological organism *B. atrophaeus* was a biohazardous material to be handled at Biosafety Level One. The indictment states that: at all times relevant to this Indictment, defendant Robert Ferrell was the principal investigator for the University of Pittsburgh Human Genetics Laboratory, and Chairman of the University’s Department of Human Genetics. As such, defendant Robert Ferrell was directly and primarily responsible for knowing of, and applying the principles and procedures contained within, the University of Pittsburgh Biosafety Manual. These responsibilities included the registration of all biohazardous materials with the University’s Biosafety Officer, including the biological materials *S. marcescens* and *B. atrophaeus*. At all times material to this Indictment, defendant Steven Kurtz was a faculty member of the art department of the State University of New York at Buffalo. In this capacity, defendant Steven Kurtz was obligated to follow the procedures set forth in that University’s biosafety requirements, including notification to the University’s Biosafety Officer whenever potentially hazardous materials were to be used. On or about May 17, 2004, defendant Robert Ferrell told a person whose identity is known to the Grand Jury that Steven Kurtz asked for assistance in acquiring bacteria to be used in showing the spread of bacteria in the environment. As a result, both defendants were charged with scheming to defraud the ATCC and the University of Pittsburgh. This case means that material transfer agreements aimed at protecting commercial interests and internal university policies and procedures aimed at biosafety can be used as prime instruments for criminal prosecution. University officials had best review and modify those instruments and policies

with a view to how they will be used in court as opposed to the purposes for which they were designed.

CONSTRAINING DANGEROUS INFORMATION

Beyond the issue of material control, i.e., how to prevent the acquisition by terrorists of dangerous pathogens, lies the more daunting issue of how to constrain information in the life sciences which is potentially dual use and could be misused to cause harm. The fear that information from life science research may fall into the wrong hands is causing great anxiety within the scientific community and uncertainties among the public and policy makers as to how to balance national security with the traditional openness of science. Some biomedical research may require classification, or at least provisions in the research agreements, to keep certain information secret. This may fundamentally change the open and free exchange of information among academic researchers. A number of universities are grappling with whether to permit classified research to be conducted on campus; some, like MIT, have rejected this idea but others may find the temptation of federal funding irresistible. Some already have begun to accept contracts that restrict access to the information generated by university research.

Several papers that were published in the open literature raised special concerns about how scientific knowledge could be misused. Ronald J. Jackson and colleagues at Australia's Commonwealth Science and Industrial Research Organization and Australian National University, published an article in *Journal of Virology* in February 2001⁶ that potentially demonstrated how to make a vaccine-resistant strain of a pox virus, including possibly smallpox virus. In trying to develop a mouse contraceptive to control pest populations, these researchers inserted a gene for an immune-system molecule called interleukin-4 into the mousepox virus. Instead of rendering mice infertile, the engineered virus was far more deadly than the natural strain, killing even mice that had been vaccinated against

mousepox. In another controversial paper,⁴ Eckard Wimmer and researchers at the State University of New York at Stony Brook Science, used the genetic sequence of poliovirus to patch pieces of DNA that had been ordered from a company into the complete genome of a poliovirus particle—creating de novo a virus that was capable of paralyzing and killing mice. There are claims from the security community that these papers provide roadmaps for terrorists to create biothreat agents. Many of us in the scientific community see these as legitimate papers that advanced the science. The editors and reviewers of these papers obviously felt that they should be published.

Following the anthrax attacks of 2001, several researchers, though, raised questions about whether they could withhold critical information from papers in the scientific literature so that terrorists could not misuse the information. Several of these inquiries were directed to me as President of ASM. Recognizing that self-censorship could fundamentally change the very definition of science, I sent a letter to Bruce Alberts, president of the National Academy of Sciences (NAS), requesting that NAS convene a forum to examine whether publication policies should change in the face of the threat of terrorism. Dr. Alberts accepted this request and appointed me to chair the effort. At a meeting at NAS that I convened, members of the academic, security, and publishing communities discussed the concerns and the pros and cons of changing the nature of scientific publication. The outcome was a clear sense that we should rely on self-governance by scientists and scientific journals to review publications for their potential national security risks. At a follow up meeting attended by editors of many of the leading life science journals, as well as by representatives of the security community and those seeking to protect freedom of expression, the following statement of principles was drafted by the Journal Editors and Authors Group.¹⁰

“Fundamental is a view, shared by nearly all, that there is information that – although we cannot now capture it with

lists or definitions – presents enough risk of use by terrorists that it should not be published. How and by what processes it might be identified will continue to challenge us because – as all present acknowledged – it is also true that open publication brings benefits not only to public health but also in efforts to combat terrorism.” The group also said that: (1) “the scientific information published in peer-reviewed research journals carries special status, and confers unique responsibilities on editors and authors. We must protect the integrity of the scientific process by publishing manuscripts of high quality, in sufficient detail to permit reproducibility. Without independent verification – a requirement for scientific progress – we can neither advance biomedical research nor provide the knowledge base for building strong biodefense systems.” (2) “We recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published information, but also recognize that research in the very same fields will be critical to society in meeting the challenges of defense. We are committed to dealing responsibly and effectively with safety and security issues that may be raised by papers submitted for publication, and to increasing our capacity to identify such issues as they arise.” (3) “Scientists and their journals should consider the appropriate level and design of processes to accomplish effective review of papers that raise such security issues. Journals in disciplines that have attracted numbers of such papers have already devised procedures that might be employed as models in considering process design. Some of us represent some of those journals; others among us are committed to the timely implementation of such processes, about which we will notify our readers and authors.” And, (4) “we recognize that on occasions an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published. Scientific information is also communicated by other means: seminars, meetings, electronic posting, etc. Journals and scientific societies can play an important role in encouraging investigators to communicate results of research in ways that maximize public benefits and minimize risks of misuse.”

In other words: the integrity of science must be maintained – science is too important to jeopardize the integrity of scientific investigations;

editors and scientists will act responsibly without government intervention; each field is different and needs specific ethical practices to protect against its misuse; and, we will constrain information we consider could do harm. ASM adopted a policy consistent with these principles, with the goal of being responsible stewards of scientific information and communication by carefully balancing national security with the value of advancing science for the benefit of humanity. This ASM policy is one of responsible citizenship – not one of censorship.

The statement from the authors and editors, and the adoption of policies aimed at limiting potential misuse of scientific information, did not fully resolve the issues surrounding the potential dual use of knowledge in the life sciences. How can we define what is dangerous and how can we design a system that contains that danger while allowing legitimate biomedical research to proceed in a manner acceptable to society? This is the critical question addressed by an NAS committee chaired by Gerry Fink of the Massachusetts Institute of Technology. The Fink Committee, in its report: *Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma*,⁸ proposed a system that would establish a number of stages at which scientists would review experiments and their results to provide reassurance that advances in biotechnology, with potential applications for bioterrorism or biological weapons development, receive responsible oversight.

In essence, the Fink Committee proposed the development of an architectural structure to help protect the life sciences community against the potential misuse of biological materials and information; it was a bottom-up approach aimed at helping reduce the threat of misuse of the life sciences by mobilizing the scientific community to police itself. Like the 1982 NAS *Scientific Communication and National Security* report,⁷ known as the Corson report—which had dealt with the physical sciences—the report of the Fink Committee sought to protect scientific enquiry from untoward government interference and to permit open communication to the maximum

extent possible. The fundamental conclusion of the Fink Committee was that some information could be dangerous and that we should rely on self-governance by the scientific community to reduce potential national security risks and the potential misuse of legitimate scientific enquiry and communication.

The Fink Committee identified seven classes of “experiments of concern” that illustrate the types of endeavors or discoveries that might present special dangers and, therefore, should undergo review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail. The experiments of concern that would undergo special scrutiny are those that: (1) would demonstrate how to render a vaccine ineffective; (2) would confer resistance to therapeutically useful antibiotics or antiviral agents; (3) would enhance the virulence of a pathogen or render a non-pathogen virulent; (4) would increase transmissibility of a pathogen; (5) would alter the host range of a pathogen; (6) would enable the evasion of diagnostic/detection modalities; and (7) would enable the weaponization of a biological agent or toxin.

Within the United States, all of the experiments that fall within the seven areas of concern should currently require review by an Institutional Biosafety Committee (IBC), a review committee that already exists in most institutions to monitor experiments involving recombinant DNA. The Fink Committee recommended that IBCs be charged with specific oversight of experiments to judge not only biosafety and biosecurity of the materials involved, but also the safety of the information that would be generated and whether it needed to be classified or otherwise constrained. The Fink Committee further recommended that HHS create a National Science Advisory Board for Biodefense (NSABB) to provide advice, guidance, and leadership for the system of review and oversight proposed in the report. At the most general (strategic) level, the NSABB would serve as a point of continuing dialogue between the scientific community and the national security

community, and as a forum for addressing issues of interest or concern. At the operational (tactical) level, the NSABB would provide case-specific advice on the oversight of research, and the communication and dissemination of life sciences research information that is relevant for national security and biodefense purposes.

The recommendation of the Fink Committee to rely upon self-governance within the scientific community forms the basis for a new US Government Biosecurity Initiative. The NIH has been charged with establishing the NSABB to advise and guide the government and research community. The NSABB is chartered to have up to 25 voting members with a broad range of expertise in molecular biology, microbiology, infectious diseases, biosafety, public health, veterinary medicine, plant health, national security, biodefense, law enforcement, scientific publishing, and related fields. The NSABB also is to include nonvoting ex officio members from 15 federal agencies and departments. The NSABB is to provide advice and guidance regarding biological research that has the potential for misuse and could pose a biologic threat to public health or national security. The NSABB will advise the HHS Secretary, the NIH Director, and the heads of all federal entities that conduct or support life sciences research. It will lead an effort to: (1) develop and promulgate national guidelines for local (e.g., IBCs) and federal oversight of dual use research; (2) develop a code of conduct for scientists and laboratory workers in life sciences research; (3) develop and implement programs for education and training in biosecurity issues for all scientists and laboratory workers at federal, as well as federally-funded, institutions; (4) develop and promulgate guidelines for the appropriate communication of dual use research methodology and research results; and (5) foster the extension of these biosecurity policies to the international arena.

CONCLUDING REMARKS

Concerns about bioterrorism and new biodefense research programs are

changing the face of academic research. As a result of the threat of bioterrorism, a number of federal agencies have instituted critical new biodefense programs. Funding for biodefense provides many opportunities for university researchers. The research must be conducted in a safe and ethical manner. The anthrax attacks that followed the horror of September 11 have made scientists and physicians suspects as well as saviors. We must resolve the dilemma of how to harmonize biosafety (defined as the development and implementation of administrative policies, work practices, facility design, and safety equipment to prevent transmission of biologic agents to workers, other persons, and the environment) with biosecurity (defined as the protection of high-consequence microbial agents and toxins, or critical relevant information, against theft or diversion by those who intend to pursue intentional misuse). The myriad of new oversight regulations presents a real challenge to the research and safety communities. But compliance is essential if the research community is to maintain the public trust that is essential for the continued support of research. The scientific community must help establish a framework to ensure that biothreat agents and critical information is withheld from terrorists while permitting the continued advancement of biomedical research

and the protection of public health. The campus safety community must help integrate biosafety and biosecurity concerns to provide a framework where critical biodefense research can proceed while ensuring protection of the public. The norm must be that scientists should be willing to engage in biodefense efforts that aim at protecting humankind against the threat of bioterrorism, and that in the conduct of biodefense research they will act responsibly to limit the potential misuse of scientific materials and information by would-be bioweaponers.

References

1. Biodefense for the 21st Century, 2004. <http://www.whitehouse.gov/homeland/20040430.html>, accessed 10/25/04.
2. Brainard, J. *Chron. Higher Ed.* <http://chronicle.com/temp/email.php?id=mv8mof31sc1mx9iplp63q3b4u4wjd02m>, accessed 3/24/05.
3. CDC Laboratory Registration/Select Agent Transfer Program. <http://www.cdc.gov/od/sap/> and <http://www.cdc.gov/od/sap/downloads2.htm>, accessed 10/24/04.
4. Cello, J.; Paula, A. V.; Wimmer, E. *Science*, **2002**, 297(5583), 1016–1018.
5. Doyle, C. Antiterrorism and Effective Death Penalty Act of 1996: A Summary, 1996. <http://www.fas.org/irp/crs/96-499.htm>, accessed 10/25/04.
6. Jackson, R. J.; Ramsay, A. J.; Christensen, C. D.; Beaton, S.; Hall, D. F.; Ramshaw, I. A. *J. Virol.* **2001**, 75(3), 1205–1210.
7. NAS *Scientific Communication and National Security* report, 1982. <http://www.nap.edu/openbook/0309033322/html/>, accessed 10/25/04.
8. National Research Council. *Biotechnology Research in an Age of Terrorism*; The National Academies Press; Washington, DC, 2004.
9. Public Health Security and Bioterrorism Response Act, 2002. <http://www.fda.gov/oc/bioterrorism/PL107-188.pdf>, accessed 10/25/04.
10. Uncensored exchange of scientific results, Journal Editors and Authors Group, Proceedings of the National Academies of Sciences of the United States of America, 2003. <http://www.pnas.org/cgi/content/full/100/4/1464>, accessed 10/25/04.
11. University of Pittsburgh Biosafety Manual, 1997. <http://www.ehs.pitt.edu/biosafety/BSM.HTM>, accessed 10/25/04.
12. USA Patriot Act of October 26, 2001. <http://www.epic.org/privacy/terrorism/hr3162.pdf>, accessed 10/25/04.
13. US Department of Health and Human Services, 42 CFR Part 73, Possession, Use and Transfer of Select Agents and Toxins; Interim Final Rule. In: Federal Register December 13, 2002. 240:67:76886-905. <http://www.cdc.gov/od/sap/docs/42cfr73.pdf>.
14. US Department of Health and Human Services Centers for Disease Control and Prevention and National Institutes of Health. *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, 4th ed. US Government Printing Office; Washington DC, 1999