Article

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Combating Bioterrorism and the Potential Misuse of Biotechnology

Ronald M. Atlas

University of Louisville, Louisville, Kentucky

Abstract

The anthrax attacks that followed September 11, 2001 and the fear that bioterrorism could inflict mass casualties have fostered a multifaceted approach for biodefense. New laws and regulations have been instituted to limit access to dangerous pathogens in an attempt to enhance biosafety and biosecurity. New research is being instituted to enhance preparedness and to deter future acts of bioterrorism. Greater attention is being paid to information as well as pathogens and toxins, particularly with regard to the potential misuse of biotechnology to create more deadly pathogens or to use recombinant DNA technology to alter human genomes. Government and the scientific community are struggling with how to achieve a balance between the openness of scientific communication, which is essential for the advancement of the biomedical research effort aimed at biodefense, and secrecy for protecting national security information. Classification remains the principal means of protecting information, but additional means are being considered to protect sensitive homeland security information that is not classified.

Introduction

Since September 11, 2001 and the ensuing anthrax attacks, there have been heightened fear of bioterrorism and demands that we enhance our protection against such future attacks. The bioterrorism attacks challenged our medical preparedness and scientific understanding of the epidemiology of biothreat agents. We have yet to determine how to best safeguard the mail, how to decontaminate buildings, and how clean is safe; thus some mail is delayed and damaged as it is irradiated and a number of contaminated buildings remain closed. Fear remains high and there is a sense that we are inadequately prepared for future acts of bioterrorism that are seen as likely in today's era of terrorism. Vaccines and medicinals are being added to the national stockpile and new immunization policies are being fostered. The public health infrastructure is being strengthened. Research is desperately needed to develop diagnostic methods and improved medical treatments to protect against potentially devastating attacks with anthrax, smallpox, plague, tularemia, botulism, or hemorrhagic fever viruses.

As the investigation into last year's anthrax attacks progresses and focuses on the possibility that it was carried out by someone with access to U.S. bioweapons materials and information, many have raised concerns that terrorists can subvert the normal scientific enterprise. Hence there has been increasing public discussion about restricting access to materials and information that could be used by bioterrorists. Science holds enormous promise for improving health and protecting the public; yet, it also represents opportunity for deliberate harm. Hence there is a need for responsible action by the scientific community. Expanded biodefense research on the most dangerous agents and toxins–select agents–has intensified questions about the secure conduct of scientific inquiry in areas related to biodefense and about the publication of research results

in the life sciences. The biosafety community faces the challenge of heightened scrutiny over the misuse of science by terrorists.

Crucial research related to prevention of bioterrorism or the cure of infectious diseases will require the utilization of pathogenic material and the consequent placement of signs warning of a biosafety risk to protect persons working in the area. However, placement of warning signs may also alert would-be terrorists to the presence of materials that may potentially be used in bioterrorist attacks. Thus, there is a dual aspect to placing warning signs with increasing exposure to misuse of information. Expanded research also means that opportunities for subversion of legitimate research will be increased. The scientific community must confront issues of improving security in research and in the publication of research results. This must be done without compromising vital public health interests by unwarranted or unwise limitations of scientific inquiries or by the publication of research results.

Biomedical Research Challenge

The National Institutes of Health have developed a strategy for research funding aimed at finding effective preventative measures and cures so that infectious diseases are minimized as a threat to humanity. This strategy includes both basic research into microbes with bioterrorism potential, and the specific and non-specific host defense mechanisms against these agents, and applied/translational research with predetermined milestones and the ultimate production of new/improved diagnostics, vaccines, and therapies. The National Institute for Allergies and Infectious Disease has identified six research priorities: (1) microbial biology; (2) host factors; (3) genomics; (4) therapeutics; (5) vaccines; and (6) diagnostics. They have also identified the need for expanded research resources (BL3 and BL4 laboratories). The current administration has proposed a budget that is slated to grow from $25 million in fiscal year 2001 to $1.748 billion in fiscal year 2003. Of the funding for bioterrorism in 2003, $440.6 million will go to basic research and development, $591.9 million to drug/vaccine discovery and development, $194.3 million to clinical research, $371.1 million for intramural research facilities, and $150.0 million to extramural research facilities. This extensive research agenda represents a paradigm shift at the NIH, which must move basic research through translational research to real world application. The success of the research will be measured by the number of licensed drugs and vaccines that are added to the national stockpile in the short-midterm, rather than the traditional long-term scientific advances from basic research. This is a great challenge, especially since there are numerous possible biothreats and since licensing of vaccines and drugs for diseases that have low rates of occurrence will need to depend on surrogate animal testing.

One of the emerging controversies is whether to prevaccinate the first responder community against biothreat diseases and whether to extend that vaccination to the broader population. There is no question that when a population is immune to a specific disease, the threat of bioterrorism with the agent causing that disease is reduced or eliminated. But there are also risks associated with vaccination. Given that smallpox is viewed as the greatest biothreat agent, the current debate is focusing on the development of an appropriate vaccination policy for smallpox. The historical rate of adverse reactions from smallpox vaccination is 1 in 18,000 and the estimated deaths that could occur from mass vaccination in the United States due to complications from these reactions are estimated to be 400-1,400. This is high rate and may be even greater given the increased population of immunocompromised individuals. The Advisory Committee on Immunization Practices (ACIP) has recommended relying on a postoutbreak strategy that could quickly vaccinate individuals in areas where cases of smallpox occur. The ACIP also recommended vaccinating about 15,000 health care workers and developing local response plans for large-scale rapid vaccination to ensure an adequate health care response capability in the event of an attack. These recommendations were based upon the assessment that the risk of a bioterrorist attack with smallpox was low.

The conflict with Iraq has led some in the Bush Administration to press for a response plan based upon the assumption that the risk of attack is higher. Plans are now being developed for vaccinat-

ing 500,000 in the military and 20 million first responders. There also is a plan for providing vaccine to the general public by early 2004. Although this plan is for voluntary vaccination, even voluntary vaccination represents a significant risk, including to those not receiving the vaccine since the vaccination involves a live vaccinia virus and, thus, possible spread of infection. Historical data indicate that 1 in 5 deaths from smallpox vaccination occur among the unvaccinated. Thus, the risk of an attack with smallpox must be high enough to justify the risk to the general public, even for voluntary vaccination; and the research effort must be aimed at lowering the risks of vaccination.

Controlling Access to Select Agents

Several new legislative and regulatory actions are aimed at reducing the threat that microorganisms and toxins can be acquired by terrorists. The USA Patriot Act, signed into law on October 26, 2001, expanded law enforcement's surveillance and investigative powers and established new conditions for the possession of biological agents. Universities can be required to provide records on the activities of students, staff, and faculty. Under a provision of the USA Patriot Act, such requests by law enforcement must be kept confidential so as not to alert would-be terrorists.

The USA Patriot Act also imposes restrictions on the possession of select agents. It restricts aliens from countries designated as supporting terrorism from possessing select agents within the United States. It also restricts select agent possession by individuals who are not permitted to purchase handguns (e.g., some individuals with a history of mental illness or a criminal record). There are no provisions for exemptions under any circumstances. According to the USA Patriot Act, a Restricted Person is defined as someone who: is under indictment for a crime punishable by imprisonment for a term exceeding one year; has been convicted in any court of a crime punishable by imprisonment for a term exceeding 1 year; is a fugitive from justice; is an unlawful user of any controlled substance; is an alien illegally or unlawfully in the U.S.; has been adjudicated as a mental defective or has been committed to any mental institution; is an alien who is a national of a country which the Secretary of State has currently determined to be repeatedly providing support for acts of international terrorism; or has been discharged from the Armed Services of the United States under dishonorable conditions.

The USA Patriot Act also makes 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. Senator Patrick Leahy warned during passage of the Patriot Act that this provision could have unanticipated ramifications depending upon how one defined "bona fide" or "reasonably justified." A troubling case developed at the University of Connecticut when a graduate student placed a culture of anthrax-causing bacteria in a freezer instead of killing the bacteria as instructed by a professor. The U.S. Attorney charged the student and the student accepted a plea bargain to do community service work in return for a clean criminal record. Additional cases are likely and the scientific community must be on guard. Many investigators and institutions have destroyed collections of select agents.

The Public Health Security and Bioterrorism Preparedness Act of 2002 (Public Law 107-188), signed into law on June 12, 2002, added requirements to the USA Patriot Act and extended the 1997 regulations governing the shipping and handling requirements on laboratory facilities that transfer or receive select agents capable of causing substantial harm to human health. This Act requires that facilities that possess, use, or transfer select agents register with the Secretary of Heath and Human Services (HHS). Such facilities are subject to reasonable safety and security requirements, including access controls, screening of personnel determined by the facility to have a legitimate need to handle or use select agents, and inspections to ensure compliance with the requirements.

The Public Health Security and Bioterrorism Preparedness Act of 2002 provides comparable regulatory authorities to the U.S. Department of Agriculture (USDA) as to the HHS for the possession, use, or transfer of listed biological agents and toxins that

present a severe threat to plant or animal health or animal or plant products. Whoever knowingly possesses an unregistered select agent or who transfers a select agent to any person one knows or has reasonable cause to believe has not registered could be fined or imprisoned up to 5 years or both.

The Public Health Security and Bioterrorism Preparedness Act of 2002 requires registered facilities to provide access to select agents only to those determined by the registered facility to have a legitimate need to handle or use select agents. Facilities must promptly submit the names of such individuals to the HHS and the Attorney General who shall promptly use criminal, immigration, national security, and other electronic databases available to the federal government to check if the individual is a restricted person as defined in section 175b of title 18 of the U.S. Code or is reasonably suspected by any federal law enforcement or intelligence agency of committing a crime, of being involved with domestic or international terrorism or crime, or of being an agent of a foreign power. This Act establishes a national database of the names and locations of registered facilities and the select agents they possess, use, or transfer. It aims to collect information about the characteristics of select agents to assist public health and law enforcement officials to identify the origin or source of a select agent used to cause harm to the public.

The Bush Administration has proposed transfer of the select agent possession registration from the Department of Human Health Services and the Department of Agriculture to a new Department of Homeland Security (DHS). While such transfer is being considered, the CDC has issued Federal Register Notices in Response to Public Health Security and Bioterrorism Preparedness Act of 2002. Institutions were required to notify the Secretary of Health and Human Services whether or not they were in possession of a select agent by September 10, 2002. A responsible facility officer was required to inventory each facility and consult with others (e.g., principal investigators) as necessary to obtain the information required for this notification. Facilities that lacked a listed biological agent or toxin were required to complete a declaration of nonpossession and submit the form. Thus, many research and diagnostic facilities had significant new reporting requirements. There was a fair amount of confusion with regard to the reporting process. One area of particular concern arose from a lack of exemptions. Investigational products (e.g., off-label medical uses of botox) were not exempt and had to be reported as possession.

The CDC is in the process of issuing final regulations for reporting of possession. These regulations will include a revised list of select agents. Although the legislation specifically exempts medical uses of licensed products, it is unclear what additional exemptions will be incorporated into the final regulations. There is extensive debate as to how to handle recombinant elements and avirulent organisms. Currently, avirulent strains of select agents are considered to be select agents unless they are licensed vaccines or otherwise specifically exempted, as are virulence genes from select agents. The new regulations will need to establish the procedure for notifying the Attorney General of those with access to select agents as part of the clearance process. The registration will require, if available to the person registering, information regarding the characterization of the select agent to facilitate its identification, including its source.

There also will be requirements for security, which may involve personnel screening, surveillance systems, and guards to ensure restricted access. It is likely that each institution will be required to submit a security plan that addresses the concern that biothreat agents could fall into the wrong hands. Each institution will become responsible for safeguarding the dangerous pathogens and toxins that could be used by bioterrorists.

Controlling Sensitive Homeland Security Information

Besides concerns over the security of select agents, there is a high level of concern that information can be misused. The scientific community must confront issues of improving security in research and in the publication of research results. This must be done without compromising vital public health interests that are posed by unwarranted or unwise limi-

tations of scientific inquiries or of the publication of research results.

Some contend that restrictions should be imposed on the conduct and publication of "contentious research" (i.e., fundamental biological or biomedical investigations that produce organisms or knowledge that could have immediate weapons implications). For example, Arthur Caplan, a bioethicist at the University of Pennsylvania, has said, "We have to get away from the ethos that knowledge is good, [that] knowledge should be publicly available, [and] that information will liberate us.... Information will kill us in the techno-terrorist age, and I think it's nuts to put that stuff on web sites." In contrast, William Wulf, President of the National Academy of Engineering, has said, "...the concept [of sensitive but unclassified information] is so squishy [ill defined] and fraught with danger that the only sensible thing for the research community to do is to demand [classification]." A committee of the National Academies of Science is considering standards and practices that can help meet these conflicting views.

The conflict between openness and secrecy in science is centuries old. Sir Francis Bacon in the 1600s said, "And this we do also: we have consultations, which of the inventions and experiences which we have discovered shall be published, and which not; and take all an oath of secrecy for the concealing of those which we think fit to keep secret; though some of those we do reveal sometime to the State, and some not." And in 1995, President Clinton said, "...our Nation's progress depends on the free flow of information. Nevertheless, throughout our history, the national interest has required that certain information be maintained in confidence in order to protect our citizens, our democratic institutions, and our participation within the community of nations."

During the Reagan Administration this was made clear by National Security Directive 189, issued in 1985, that stated: "It is the policy of this Administration that, to the maximum extent possible, the products of fundamental research remain unrestricted. It is also the policy of this Administration that, where the national security requires control, the mechanism for control of information generated during federally-funded fundamental research in science, technology and engineering at colleges, universities and laboratories is classification." This view was reiterated post-9/11 by Condoleezza Rice, assistant to President Bush for National Security Affairs, who said, "The key to maintaining U.S. technological preeminence is to encourage open and collaborative basic research. The linkage between the free exchange of ideas and scientific innovation, prosperity, and U.S. national security is undeniable...the policy on the transfer of scientific, technical, and engineering information set forth in NSDD-189 shall remain in effect, and we will ensure that this policy is followed."

These views on classification grew out of a 1982 report by the National Academy of Sciences ("the Corson Report") that held that greater security can be achieved by the open pursuit of scientific knowledge than by attempts to curtail the free exchange of scientific information and by increased secrecy. It was echoed by Neal Lane, science advisor during the Clinton Administration, who said, "National security requires scientific excellence. Scientific excellence requires openness. Openness is inherently international." Nevertheless, the Bush Administration has taken action to safeguard information regarding weapons of mass destruction and other sensitive documents related to homeland security. Heads of executive departments and agencies were instructed by Chief of Staff Andrew Card to take steps to protect information regarding weapons of mass destruction as well as other information that could be misused to harm the security of our Nation and the safety of our people. The guidance memo that accompanied that order told departments to take steps to protect sensitive but unclassified information that might reasonably be expected to assist in the development or use of weapons of mass destruction. The Office of Management and Budget has also announced that it will be releasing procedures for the protection of "sensitive homeland security information."

Because the American Society for Microbiology (ASM) is committed to the responsible and ethical publication of science, it has adopted specific policies and procedures for its journals to provide a degree of careful scrutiny in the peer review process of submitted manuscripts dealing with select agents.

This review process seeks to determine if an article contains details of methods or materials that might be misused or might pose a threat to public health and safety. ASM reviewers inform editors if a manuscript contains details that in their view may be subject to misuse. If a reviewer brings a manuscript to the attention of an editor, the editor considers whether in his or her view a risk of adverse use may exist. If, in the opinion of the editor, a risk exists or the editor is unsure, that editor brings the matter to the attention of the editor-in-chief of the journal and the chair of the Publications Board of the Society, and they confer about the issues raised. If warranted, the chair brings the manuscript to the Publications Board for further review and disposition. The ASM's Publications Board, in turn, has made it clear that the ASM will not publish papers that violate the ASM Code of Ethics or that violate other widely accepted guidelines for research such as the NIH Recombinant DNA guidelines for research involving recombinant DNA. Thus, the ASM is sensitive to research reports that might impinge on national security or be used for illegitimate purposes.

At the same time, ASM does not support unwarranted restrictions on the free flow of legitimate scientific communications within microbiology that could lead to valuable advances in biomedical science. The ASM view is that the best defense against anthrax or any other infectious disease is information in a form that can be used by scientists and public representatives to guide rational and effective actions to ensure public safety. Placing major barriers in the path of the flow of information ultimately may contribute to terrorism by interfering with our ability to prepare and respond to the threat of the misuse of science by bioterrorists. The free exchange of scientific information has contributed to the saving of human life, to increased quality of life, and to greater promise for yielding future benefits to health and the environment. Public health and safety depend on the advancement of biomedical science that could be harmed by undue restrictions on publication of research.

Thus, while ASM has modified its own procedures for publication of its journals and increased its internal awareness of the need for careful review, ASM continues to require that research articles contain sufficient detail to permit the work to be repeated by others. Authors also must continue to agree to make materials available to the scientific community while, of course, adhering to all laws and regulations governing the shipment, transfer, possession, and use of biological materials. Omission of materials and methods from the scientific literature would compromise the scientific process and could lead to abuses as well as the perpetuation of errors. Independent reproducibility is the heart of the scientific process. Even within the context of heightened scrutiny, research articles must be published intact. If scientists cannot assess and replicate the work of their colleagues, the very foundation of science is eroded. Open research is essential to discovery and building on past scientific discoveries. Indeed the risk to public health and safety may be greater from restricting research than from allowing the publication of research that could be read by a wrongdoer. Restricting research findings may, in fact, have no effect on deterring terrorists.

By adopting its publication policies, the ASM is attempting to protect against misuse of science without undermining the integrity of the scientific process or appropriate communication of research results that is critical to sound science. Review for "sensitive" information is difficult and complicated. There is no common definition of what is dangerous or sensitive information and no individual is empowered to decide what is potentially dangerous knowledge. There is also the issue of dual application of scientific knowledge for beneficial and malicious purposes. Research to make new drugs sometimes might be used to develop bioweapons. Genomic data are valuable for identifying targets for therapeutic drugs and vaccines, but such information can be viewed as potentially valuable for identifying means to increase the virulence of microbial agents and to counter currently available therapies, vaccines, and detection protocols.

This duality is real, and the potential for both good and evil is encoded within genomes. There has been concern that the complete genome sequence of many pathogens, including the smallpox virus, is publicly available, providing weapons designers with information that may enable them to increase pathogenicity. The same information, however, can be

used to help develop new medical treatments or genetic fingerprinting to trace sources of bioweapons. Genome sequences are far more valuable to legitimate researchers and to the health and safety of the public than to bioterrorists. Transparency in science is also important to differentiate whether offensive or defensive research is being conducted in other countries. In addition, law enforcement and the judicial process depend on methods that must be published in the peer-reviewed literature if they are to be used for prosecution of criminal cases.

The heightened concern about publishing "dangerous" research results and the conviction by some that particular lines of research should be banned emanates in part from an earlier response to experiments conducted in Australia in which the interleukin-4 gene from a mouse was inserted into mousepox virus, enhancing its virulence. When the modified virus expresses the IL-4 gene, it effectively overcomes genetic resistance to mousepox virus and suppresses immune responses to the host to a greater extent than anyone had predicted. Virus encoded IL-4 not only suppresses primary antiviral cell mediated immune responses but also can inhibit immune memory responses. Such experiments may indicate that poxviruses can be engineered by widely available techniques and equipped with readily accessible genes to render immunization ineffective. The implications for smallpox virus, were it to be genetically engineered in the same way, are horrific. With hindsight, some critics have asked whether this research should ever have been permitted. They also suggest that we should have known in advance how dangerous these results might be. Others were surprised by the result and argue that this study alerts us to the need for more research on immune responses to such viruses and the need to develop antiviral drugs. In short, this incident provides one example of the difficult issues in confronting the benefits and potential dangers resulting from research related to pathogenic organisms.

Finally, as the scientific community discusses appropriate measures for security in undertaking and publishing research, it will also be important to have discussions with the national security community. Clearly, this community has legitimate objectives, and it may weigh the costs and benefits of proposed policies differently from the scientific community. Both communities must share a common goal of discouraging the development of biological weapons while taking into account the traditional and necessary openness of scientific research. Ultimately, open and collaborative research is key to U.S. technological advances and to the protection of the citizenry against infectious diseases and bioterrorism.

Conclusion

Bioterrorism presents a major threat to national and global security. We need to support increased investment and research efforts aimed at eliminating the threats of bioterrorism and of epidemics worldwide. We need to deal with an increasingly complex and restrictive legal and regulatory framework. The research community must make hard choices about what research is permitted and must develop self-policing mechanisms for balancing national security with research performance and communication.