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On the Need for a National Board To Assess Dual Use Research of Concern

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After dispersal of anthrax spores through the U.S. mail in 2001, there was heightened awareness of the potential of biological knowledge to be used for nefarious purposes. Consequently, there was greater scrutiny of published articles for information that, although not intended for this purpose, could nonetheless be used to threaten national security or public health. In that atmosphere of increased anxiety, several papers were identified that raised concerns, including those reporting that insertion of interleukin-4 (IL-4) into ectromelia virus could potentially defeat vaccine immunity (1), identification of vulnerable points in the milk supply for the addition of botulinum toxin (2), mechanisms by which variola virus pathogenicity could be increased (3), and the total synthesis of poliovirus from chemical precursors (4). These papers prompted considerable discussion (5–8). The United States Government responded to these concerns in 2005 by establishing the National Science Advisory Board for Biosecurity (NSABB), which promptly set out to analyze and address many of the issues involved. One of the early problems faced by the NSABB was to identify that subset of biological science research that posed major concerns, while leaving the rest of science undisturbed with the goal of not interfering with important research progress.

In 2007, after 2 years of intensive work, the NSABB produced a document titled "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information" (9). After struggling with the fact that history has repeatedly shown that some scientific research has potential for "dual use," i.e., research that generates information and products that can be used for both beneficial and harmful purposes, the NSABB proposed criteria for identifying that subset for which there was the greatest concern and called this type of work dual use research of concern, or DURC. A major accomplishment of the NSABB was to propose a clear definition for DURC as "research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or materiel" (9; see also the resulting policy document, reference 10). In addition, the NSABB provided a roadmap and tools to identify scientific work that could fall under the category of DURC and suggested mechanisms for disseminating such information, including the writing of accompanying editorials. The NSABB proposed seven categories of experiments that could be used to identify work that was potentially DURC (Table 1) with the wording that research included in any one of these categories "should be especially carefully assessed for meeting the criterion for dual use research of concern" (9). The seven criteria are clear and easily applied to manuscripts to identify potential DURC.

In the past year, ASM journals have considered several manuscripts describing studies of highly pathogenic avian influenza virus in which the virus has been genetically altered, resulting in the acquisition of a new biological property (so-called "gain-of-function" studies). In every case in which the study was judged to be scientifically meritorious, ASM has published this work after an additional level of review in which the NSABB tools were used (11). For the ASM journals, the process for handling papers that include DURC includes a second level of review involving editors familiar with issues relating to DURC in addition to the standard peer review given to all manuscripts.

Other journals are also struggling with the problem of DURC in scientific publications. In 2013, the *Journal of Infectious Diseases* considered and published a manuscript reporting a new botulinum toxin serotype after taking the unprecedented step of redacting sequence data that are normally required for publication (12, 13).

DURC evaluations are currently conducted by journal editors with occasional consultation with individuals who serve on the NSABB providing opinions in their individual capacity, various Federal agencies (11, 14), or some combination of these groups. Because the NSABB is a federal advisory committee, only the U.S. Government can give tasks to the board, which in turn can only advise the U.S. Government. Therefore, outside entities, such as journals, cannot directly refer issues to the Board. Consequently, journal editors are the sole arbiters of whether manuscripts describing DURC are published. On occasion, the U.S. Government has asked the NSABB to review research with DURC implications. For example, in 2012, the U.S. Government asked the NSABB to consider two gain-of-function manuscripts involving H5N1 influenza virus (15). In that case, the board recommended publica-

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TABLE 1 Seven categories of possible DURC defined by the NSABB

(1)	Enhances the harmful consequences of a biological agent or toxin.
(2)	Disrupts immunity or the effectiveness of an immunization without clinical and/or agricultural justification.
(3)	Confers to a biological agent or toxin resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates its ability to evade detection methodologies.
(4)	Increases the stability of, transmissibility of, or ability to disseminate a biological agent or toxin.
(5)	Alters the host range or tropism of a biological agent or toxin.
(6)	Enhances the susceptibility of a host population.
(7)	Generates a novel pathogenic agent or toxin or reconstitutes an eradicated or extinct biological agent.

tion of both manuscripts, one unanimously and the other with a majority vote.

Although the criteria listed in Table 1 are explicit, the determination of whether the research in question meets the NSABB DURC definition also requires a judgment call about whether such research can be directly misapplied to pose a threat to society. This criterion may pose problems for editorial boards or institutional biosafety committees (IBCs), which may not have sufficient knowledge, expertise, or breadth of experience to make such a determination with any degree of confidence. Therefore, journal editors and IBCs may not be able to make meaningful DURC assessments in potentially complex cases. Furthermore, even if the research is assessed to be DURC, the options for a journal are limited. If the paper containing DURC is rejected, then the authors would be free to submit the report elsewhere, and there is no guarantee that the assessment by another journal would come to the same conclusion. This situation places journal editors in the uncomfortable position of knowing that rejecting papers that they judge to contain DURC would likely lead to the resubmission of the same paper to another journal with no guarantee that the information would be handled responsibly. If the journals opt for redacting information, it is not clear whether a redaction on security grounds would result in a requirement for an export control license when those data are eventually made accessible and, if so, who would be responsible for such action (12). In the current environment, the most likely course of action would be full publication of the DURC-related study provided that it met scientific acceptability by peer review, possibly with an accompanying editorial explaining the basis for the decision to publish, as has been the case with several recent papers (11, 13, 14). In fact, editors would find support for the decision to publish in the precedent established after full publication of the gain-of-function H5N1 papers after NSABB review (16, 17).

Four decades ago, the scientific community was concerned about the prospect of recombinant DNA unleashing new pathogenic organisms and adopted a self-imposed moratorium for such research after the Asilomar conference in 1975 (18). The moratorium was lifted with the establishment by the U.S. Government of the Recombinant DNA Advisory Committee (RAC), which was tasked with reviewing experiments and providing advice about research involving recombinant DNA (http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/rac). In the early years, the RAC was cautious with the new technologies. However, as it gained experience, it was able to shepherd the biological community to reap the fruits of the recombinant DNA revolution (19). We have numerous drugs today that are available only because of recombinant DNA technology as well as a thriving biotech industry, and in retrospect, the establishment and maintenance of the RAC must be viewed as an unqualified success. In an echo of the decisions taken at the Asilomar conference, a similar moratorium was imposed in 2012 on gain-of-function experiments involving highly pathogenic avian influenza viruses (20); it was lifted after additional safeguards were required for such work (21). Although we recognize that the circumstances surrounding the Asilomar conference and the recent DURC controversies differ, there are analogies in that both gain-of-function experiments and recombinant DNA have been viewed as dangerous by many scientists, both have involved moratoriums, and both have stimulated discussion of the issues involved in the lay press.

The situation today calls for the establishment of a federal advisory board modeled on the RAC for the assessment of DURC. We think this is a government responsibility, since only the government has the resources necessary to include adequate threat assessment reviews. In fact, it could be argued that the need for a national board with access to security information follows as a necessary outcome of the NSABB definition of DURC, which requires a threat assessment. DURC research is essential to advance knowledge about the biology of many highly pathogenic organisms in order to generate countermeasures, including vaccines and therapeutics. Given that DURC research is critically important for preparedness against new and existing microbial threats, and that such research also poses certain risks in the areas of both biosafety and biosecurity, there should be a more organized approach to managing such research and reporting its results. A great advantage of such a designated advisory board is that it would rapidly gain experience as it considers case-by-case problems, and that experience could translate into better advice to navigate the promise and perils of DURC in the biological sciences. Such a board should be accessible to journal editors, IBCs, and investigators with questions about DURC and would be an invaluable national resource for shepherding the fields working with highly pathogenic organisms.

REFERENCES

1. **Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA.** 2001. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. J. Virol. **75:**1205–1210. http://dx.doi.org/10.1128/JVI.75.3.1205-1210.2001.
2. **Wein LM, Liu Y.** 2005. Analyzing a bioterror attack on the food supply: the case of botulinum toxin in milk. Proc. Natl. Acad. Sci. U. S. A. **102:**9984–9989. http://dx.doi.org/10.1073/pnas.0408526102.
3. **Rosengard AM, Liu Y, Nie Z, Jimenez R.** 2002. Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. Proc. Natl. Acad. Sci. U. S. A. **99:**8808–8813.[pii]. http://dx.doi.org/10.1073/pnas.112220499.
4. **Cello J, Paul AV, Wimmer E.** 2002. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science **297:**1016–1018. http://dx.doi.org/10.1126/science.1072266.
5. **Alberts B.** 2005. Modeling attacks on the food supply. Proc. Natl. Acad. Sci. U. S. A. **102:**9737–9738. http://dx.doi.org/10.1073/pnas.0504944102.
6. **Block SM.** 2002. A not-so-cheap stunt. Science **297:**769–770.
7. **Finkel E.** 2001. Australia: engineered mouse virus spurs bioweapon fears. Science **291:**585. http://dx.doi.org/10.1126/science.291.5504.585.
8. **Miller S, Selgelid MJ.** 2007. Ethical and philosophical consideration of the

dual-use dilemma in the biological sciences. Sci. Eng. Ethics **13:**523–580. http://dx.doi.org/10.1007/s11948-007-9043-4.

9. **National Science Advisory Board for Biosecurity.** June 2007. Proposed framework for the oversight of dual use life science research: strategies for minimizing the potential misuse of research information. National Science Advisory Board for Biosecurity, National Institutes of Health, Bethesda, MD. http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf.
10. **National Institutes of Health.** 2012. United States Government policy for oversight of life sciences dual use research of concern. http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern.
11. **Dermody TS, Sandri-Goldin RM, Shenk T.** 2013. A new determinant of H5N1 influenza virus pathogenesis in mammals. J. Virol. **87:**4795–4796. http://dx.doi.org/10.1128/JVI.00474-13.
12. **Casadevall A, Enquist L, Imperiale MJ, Keim P, Osterholm MT, Relman DA.** 2013. Redaction of sensitive data in the publication of dual use research of concern. mBio **5:**e00991–13. http://dx.doi.org/10.1128/mBio.00991-13.
13. **Hooper DC, Hirsch MS.** 2014. Novel clostridium botulinum toxin and dual use research of concern issues. J. Infect. Dis. **209:**167. http://dx.doi.org/10.1093/infdis/jit528.
14. **Hirsch MS.** 2013. Editorial comment regarding H5N1 influenza article in this issue. J. Infect. Dis. **207:**207. http://dx.doi.org/10.1093/infdis/jis528.
15. **Berns KI, Casadevall A, Cohen ML, Ehrlich SA, Enquist LW, Fitch JP, Franz DR, Fraser-Liggett CM, Grant CM, Imperiale MJ, Kanabrocki J, Keim PS, Lemon SM, Levy SB, Lumpkin JR, Miller JF, Murch R, Nance ME, Osterholm MT, Relman DA, Roth JA, Vidaver AK.** 2012. Public health and biosecurity: adaptations of avian flu virus are a cause for concern. Science **335:**660–661. http://dx.doi.org/10.1126/science.1217994.
16. **Herfst S, Schrauwen EJ, Linster M, Chutinimitkul S, WEde Munster VJ, Sorrell EM, Bestebroer TM, Burke DF, Smith DJ, Rimmelzwaan GF, Osterhaus AD, Fouchier RA.** 2012. Airborne transmission of influenza A/H5N1 virus between ferrets. Science **336:**1534–1541. http://dx.doi.org/10.1126/science.1213362.
17. **Imai M, Watanabe T, Hatta M, Das SC, Ozawa M, Shinya K, Zhong G, Hanson A, Katsura H, Watanabe S, Li C, Kawakami E, Yamada S, Kiso M, Suzuki Y, Maher EA, Neumann G, Kawaoka Y.** 2012. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature **486:**420–428. http://dx.doi.org/10.1038/nature10831.
18. **Berg P, Baltimore D, Brenner S, Roblin RO, Singer MF.** 1975. Summary statement of the Asilomar conference on recombinant DNA molecules. Proc. Natl. Acad. Sci. U. S. A. **72:**1981–1984. http://dx.doi.org/10.1073/pnas.72.6.1981.
19. **Falkow S.** 2012. The lessons of Asilomar and the H5N1 "affair." mBio **3:**e00354–12. http://dx.doi.org/10.1128/mBio.00354-12.
20. **Casadevall A, Shenk T.** 2012. The H5N1 moratorium controversy and debate. mBio **3:**e00379–12. http://dx.doi.org/10.1128/mBio.00379-12.
21. **Patterson AP, Tabak LA, Fauci AS, Collins FS, Howard S.** 2013. Research funding: a framework for decisions about research with HPAI H5N1 viruses. Science **339:**1036–1037. http://dx.doi.org/10.1126/science.1236194.