Guidelines to Prevent Malevolent Use of Biomedical Research

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In February 1975, a group of leading scientists, physicians, and policymakers convened at Asilomar, California, to consider the safety of proceeding with recombinant DNA research. The excitement generated by the promise of this new technology was counterbalanced by concerns regarding dangers that might arise from it, including the potential for accidental release of genetically modified organisms into the environment. Guidelines developed at the conference to direct future research endeavors had several consequences. They permitted research to resume, bringing to an end the voluntary moratorium that the National Academy of Sciences (NAS) had instituted several months earlier. They also served to illustrate that the scientific community was capable of self-governance, thereby securing public trust and persuading Congress not to institute legislative restrictions.[1] Finally, they underscored the importance of weighing unforeseen risks inherent in some research against potential benefits that may arise from these same endeavors.

In February 2000, a second meeting was held at Asilomar, bringing together members from the same groups, including some of the original attendees.[2] This meeting was held in honor of the historic event's 25th anniversary and in recognition of the scientific community's increasing attention to the potentially harmful applications of biotechnology in general—for example, to facilitate the use of pathogens as deadly weapons.[3] Risk of this latter sort that arises not from research per se but from its intentional misapplication for nefarious purposes constitutes the focus of this report.

The possibility that scientific research may generate knowledge with the potential for harmful as well as beneficial applications is not new. In recent years, however, it has become imperative to develop parameters within which to address such research, as heightened concerns have arisen from the threat of biochemical terrorism and warfare.

Background

Physicians' involvement in biomedical research, whether clinical or preclinical, traditionally has been guided by a desire to help alleviate patient morbidity and

The Council on Ethical and Judicial Affairs of the American Medical Association (AMA) formulates ethical policies for the medical profession through its interpretations of the AMA's *Principles of Medical Ethics*. The Council at the time this report was adopted consisted of Michael S. Goldrich, M.D. (Chair); Priscilla Ray, M.D. (Vice-Chair); Regina M. Benjamin, M.D., M.B.A.; Daniel Higginson (student member); Mark A. Levine, M.D.; John M. O'Bannon III, M.D.; Robert M. Sade, M.D.; Monique A. Spillman, M.D., Ph.D. (resident member); and Dudley M. Stewart, Jr., M.D.

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mortality. In the AMA's *Principles of Medical Ethics*, research activities are grounded in obligations to advance scientific knowledge and to contribute to the betterment of public health (Principles V and VII).[4] The Association's more recent Declaration of Professional Responsibility, which has been supported by numerous state and specialty medical societies, further encourages physicians to "work freely with colleagues to discover, develop, and promote advances in medicine."[5]

Although the fundamental goals of biomedical research may be morally sound, it remains that researchers sometimes make discoveries that can be put to harmful, as well as beneficial, use. Despite providing considerable guidance to ensure the ethical conduct of physicians engaged in human subjects research,[6] the *Code of Medical Ethics* does not currently address the importance of physicians playing a proactive role in trying to assess foreseeable consequences of their biomedical research endeavors, nor does it offer a framework to assist them in doing so.

In this, the *Code*'s research guidelines may reflect the uneven impact of the Nuremberg Code, which was drafted in response to wartime atrocities that Nazi physicians committed against captive human subjects under the guise of biomedical research. To prevent the recurrence of such blatantly unethical "research," the Nuremberg Code set out ethical principles intended to guide all future medical research involving human subjects. It focused largely on the requirement for informed consent from all research subjects, rather than on possible ramifications of the research; these were addressed only briefly in a statement that "experiment[s] should be such as to yield fruitful results for the good of society."[7] The requirement for consent has remained integral to modern clinical research in the United States. With regard to the latter provision, however, research has been vetted only to ensure that it produces beneficial results, while neglecting to consider the harmful ways in which the results could be misapplied. Arguably, this constituted a missed opportunity to develop normative guidance for the assessment of the goals and potential impact(s) of biomedical research in general.

Classes of Research with Potential for Malignant Application

The development, production, stockpiling, or use of biological weapons (BW) by any nation is banned under the 1972 Biological and Toxin Weapons Convention (BTWC),[8] which has been signed by 167 nations and ratified by 151.[9] Still, the World Medical Association (WMA) contends that there remains "a need for the creation of and adherence to a globally accepted ethos that rejects the development and use of biological weapons."[10] Moreover, according to the WMA, physicians are morally obligated to play prominent roles in establishing such an ethos because biological and toxin weapons (BTW) are intended to incapacitate or kill individuals, outcomes that are antithetical to the professed duties of physicians. Moreover, as professionals entrusted by society to advance human welfare, physician–researchers should actively speak out in condemnation of the creation and use of BTW. As to participation in defensive weapons development, physicians should consider the potential for offensive application of their research and carefully weigh the risk of misapplication against the risks associated with forgoing all weapons research.

Additionally, researchers have begun to contend with the possibility that countless areas of biomedical research can lead to nefarious applications and inadvertently may aid in the creation of BW. A recent report from the U.S.

National Research Council (NRC), *Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma*,[11] listed seven classes of "experiments of concern" considered to be especially problematic due to their potential implications for the creation and use of BW. Specifically, the NRC called attention to experiments 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 nonpathogen 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
7. Would enable the weaponization of a biological agent or toxin.

This list excludes many other areas of research that are less easily distinguished but equally dangerous if misapplied. For example, researchers have been able to construct functional polio virus particles de novo using relatively standard laboratory techniques and equipment and freely available genetic information.[12] Although the potential danger of such an experiment has not been overlooked,[13] many of the prerequisite experiments that allowed for it, such as the sequencing of the polio virus genome, certainly could be considered innocuous. Similarly, genome sequencing of many other pathogens, including those responsible for anthrax, Ebola hemorrhagic fever, and bubonic plague, would not fall within the NRC's categorization; however, the publication of these sequences in the open scientific literature,[14] although undeniably important to further understanding of pathogenicity, could unintentionally facilitate the illegitimate creation and subsequent misuse of these pathogens.

Categorical classifications run the risk of being either over- or underinclusive, as a broad range of important and seemingly innocuous biomedical research could be used malevolently. This inherent ambiguity necessitates that *all* biomedical research be ethically assessed.

Professional Obligations of Physician–Researchers

It has been argued that pure scientific research is morally neutral and thus only its subsequent application should be subject to ethical scrutiny.[15] Many of the scientists whose discoveries in atomic energy gave birth to nuclear weapons initially held this position. However, in the wake of the bombings of Hiroshima and Nagasaki at the end of World War II, some of these same scientists openly grappled with the possibility that they were ethically responsible in part for the destructive applications of their findings. As their experience suggests, researchers may be morally accountable for harms that do not result from their research per se, but are born of its applications.

Indeed, there is growing acceptance in the scientific community that scientists are obligated to pursue knowledge both as an end in itself and as a means of improving the world for humankind. For instance, the preface of the American Society for Biochemistry and Molecular Biology's (ASBMB's) Code of Ethics states:

> Members of the ASBMB are engaged in the quest for knowledge in biochemical and molecular biological sciences with the ultimate goal of advancing human welfare. Underlying this quest is the fundamental principle of trust. The ASBMB encourages its members to engage in the responsible practice of research required for such trust by fulfilling the following obligations: . . . [including that] investigators [should] promote and follow practices that enhance public interest or well-being.[16]

Similarly, in its Code of Ethics, the American Society for Microbiology (ASM) states that its members should "aspire to use their knowledge and skills for the advancement of human welfare."[17] With respect to the potential for malign use of research findings, the Society's Code recently was revised to include the following language:

> ASM members are obligated to discourage any use of microbiology contrary to the welfare of humankind, including the use of microbes as biological weapons. Bioterrorism violates the fundamental principles upon which the Society was founded and is abhorrent to the ASM and its members. ASM members will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology.[18]

Unlike the ASBMB and the ASM, however, most scientific societies have not codified this notion of social responsibility. Nonetheless, the obligation to preserve public trust extends to all scientists, as a critical element of their collective professional responsibility.

Physician–researchers share in this obligation not only by virtue of their membership in the scientific community, but also because the preservation of public trust is a fundamental aspect of medical professionalism, the moral duties of which bear upon the whole of their professional conduct. The WMA has articulated this requirement in its Declaration of Washington on Biological Weapons, which states that "physicians who participate in biomedical research have a moral and ethical obligation to consider the implications of possible malicious use of their findings."[19] Although this is an undeniably complicated undertaking, physician–researchers, who possess profound knowledge of their research and of human health and disease, are arguably in the best position to assess the potential for and the ramifications of misapplications of their research.

Self-regulation

The *Code* states that "[t]he ultimate responsibility for the ethical conduct of science resides within the institution (academic, industrial, public, or private) which conducts scientific research *and with the individual scientist* [emphasis added]."[20] In science as in medicine, individual responsibility is a fundamental aspect of professionalism. To that end, physician–researchers need to understand research ethics norms, such as scientific responsibility and integrity. Research ethics education, beginning at the trainee level and extending throughout a career, can sensitize physician–researchers to the possibility for misapplications of scientific knowledge and empower them to make responsible assessments of the research used to generate it. Still, differences in opinion will continue to arise. It is precisely because no one physician's ethical judgment is infallible that human subjects research protocols are vetted by Institutional

Review Boards. Similarly, physician–researchers engaged in preclinical biomedical research should peer-review each other's work.

Some experiments present such a degree of potential risk of harmful application that more rigorous oversight may be warranted. The aforementioned NRC report firmly echoes this notion in its proposal for a regulatory system that relies on both voluntary self-governance and scientific review committees to provide oversight for "experiments of concern."[21] Other proposals have included establishing registries, perhaps within the Centers for Disease Control and Prevention (CDC), of researchers who are working with certain pathogens and toxins and requiring that potentially dangerous results, including inadvertent discoveries, be reported.[22]

To date, the U.S. Department of Health and Human Services has created the National Science Advisory Board for Biosecurity (NSABB) that, as part of its mandate, will develop guidelines regarding appropriate oversight by local Institutional Biosafety Committees or federal officials of potentially harmful research.[23] Final authority over whether to accept these guidelines, however, will reside with the federal departments and agencies that support the research. Already, classified research, presumably for biodefense purposes, has been exempted from any guidelines developed by the NSABB.

With the exception of research involving select agents or toxins identified by the CDC as posing a severe health threat,[24] formal oversight currently is mandatory only for studies and/or institutions that receive NIH funding for recombinant DNA research.[25] Although some privately funded research organizations voluntarily comply with current NIH research guidelines, and may elect to comply with NSABB guidelines, they are not required to do so. The NSABB can seek to close the significant gap in the current regulatory framework by extending the scope of federally regulated research and encouraging the private sector to adopt the Board's system of oversight. Cooperation between different countries' research bodies also should be promoted, because research increasingly is becoming a global enterprise. Physician–researchers will be able to play a leading role in calling for the creation of and adherence to such global standards for research governance.

Transparency

In some cases, the dangers presented by research either cannot be fully appreciated before it is conducted or are the inevitable consequence of research of such importance that it must be allowed to proceed nevertheless. Such dangers could be addressed by restricting the dissemination of especially hazardous information. However, such restrictions may be undesirable for a number of reasons. The *Code*, for example, emphasizes that timely publication of research is an essential element in the foundation of good medical care.[26] The elimination of openness in biomedical research would not only create an aura of secrecy likely to compromise public trust in science, but also would impede progress and innovation—notably within biodefense research,[27] the development of vaccines and therapeutics necessary to effectively counter any use of BW.

Under exceptional circumstances, it may be appropriate to limit accessibility to the results of particular experiments. For example, the unexpected discovery of a means by which to engineer a virus capable of infecting even immunized animals recently prompted a reexamination of openness in biomedical re-

search,[28] on account of the potential to misuse the research's findings toward the design of uniquely effective bioweapons. A group including scientist–authors, government officials, and editors of major scientific journals was convened by the NAS to discuss these concerns and issued a statement conceding 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."[29] The screening mechanism employed by the NAS was again tested by a May 2005 paper posted on the *Proceedings of the National Academy of Sciences* Web site that described in detail how a terrorist might contaminate a milk truck with botulinum toxin. The Department of Health and Human Services promptly requested that the paper be withdrawn from the Web site and future print versions.[30]

Publication restrictions alone would likely prove ineffective, because scientific information is disseminated not only through mainstream scientific literature, but also through presentations at scientific meetings and increasingly on the Internet. Hence, it will be essential for members of the scientific community, including physician–researchers, to consider the implications of presenting their data in any form. As an additional part of its mandate, the NSABB will be working with stakeholders, including researchers and editors, to develop guidelines for the communication, in any form, of potentially harmful research. In the absence of such guidelines, if there is any doubt as to the propriety of open presentation, researchers would be wise to consult with colleagues in deciding how to proceed.

Conclusion

Biomedical research is essential for providing means by which medicine can continue to advance human welfare. For it to proceed responsibly, an overall ethical framework must be established that seeks to balance the ability of biomedical research to generate medical innovations against harms that may be incurred through its corruption, notably including its application to the development of biological weapons. As scientists and medical professionals, physician–researchers should seek to play a major role in the creation of such a framework and in the execution of any steps that must be taken to fulfill the obligations it imposes. Chief among these steps is for physician–researchers to appreciate and advocate the need for diligence and moral fortitude in assessing the ethical implications and foreseeable consequences of their research and the dissemination of its findings.

Recommendations

Physicians who engage in biomedical research are bound by the ethical obligations of the medical profession and also are required to meet responsibilities of the scientific community. Beyond their commitment to the advancement of scientific knowledge and the betterment of public health, physician–researchers must strive to maintain public trust in the profession through their commitment to public welfare and safety, as demonstrated through individual responsibility, commitment to peer review, and transparency in the design, execution, and reporting of research.

Biomedical research may generate knowledge with potential for both beneficial and harmful application. Before participating in research, physician–

researchers should assess foreseeable ramifications of their research in an effort to balance the promise of benefit from biomedical innovation against potential harms from corrupt application of the findings.

In exceptional cases, assessment of the balance of future harms and benefits of research may preclude participation in the research, for instance, when the goals of research are antithetical to the foundations of the medical profession, as with the development of biological or chemical weapons. Properly designed biomedical research to develop defenses against such weapons is ethical.

The potential harms associated with some research may warrant regulatory oversight. Physician–researchers have a responsibility not only to adhere to standards for research, but also to lend their expertise to the development of safeguards and oversight mechanisms, both nationally and internationally. Oversight mechanisms should balance the need to advance science with the risk of malevolent application.

After research has been conducted, consideration should be given to the risk of unrestricted dissemination of the results. Only under rare circumstances should findings be withheld, and then only to the extent required to reasonably protect against dangerous misuse.

These ethical principles should be part of the education and training of all physicians involved in biomedical research.

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Commentary: The Application of Medical Ethics in Biomedical Research

Michael E. Frisina

The question of how to prevent the malevolent use of biomedical research is not new. It has its genesis in how to prevent any new technology, invention, or scientific discovery created for the benefit and advancement of human welfare being used for the expressed purpose of harming the human community. There is the ethical component, the social responsibility component, and the intent to preserve the beneficent characteristic of biomedical research (that it not be used for malevolent purposes) at stake in this issue.

The moral legitimacy of biomedical research is grounded in a prima facie

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duty; namely, one ought to do good when one is able to do it even if there is the potential for harm. The ethical tension comes from the *reality* of the good one can produce from biomedical research balanced against the *potential* harm that may result from the nefarious use of that same research. The proposed policy raises this risk/benefit ratio of whether one should abstain from doing the good for the sake of avoiding the risk of harm. Consequently the question becomes which *good* serves the needs of the human community better? Is it more ethical to avoid conducting research, with the benefit of reducing death and disease, to prevent the potential misuse of that research or conduct the research and risk experiencing the harmful effects of its misuse by evil people? If the principle of "do no harm" is to drive policymaking, then the practical problem is choosing those actions that do less harm versus actions causing greater harm. Hence the true nature of what constitutes a moral dilemma. We are left with a bad taste from either choice. Abstaining from research or to limit the findings of research at the risk of having the results used for nefarious purposes is to do a greater harm.

This is the similar dilemma faced by Albert Einstein and the other scientists involved with the atomic energy project. There are those who believe the atomic bombing of Hiroshima and Nagasaki was wrong from its destructive nature. Given the monetary cost and the human sacrifice of a conventional invasion against mainland Japan, the use of the bomb may well have prevented a far worse human tragedy and moral harm. My father was a United States Marine fighting in the South Pacific so I admit to a bias regarding his life being spared the misery of participating in such a planned invasion. Contrary to the view that this research and its destructive use caused harm, Einstein recognized that the basis for this work prevented a far worse evil. He stated during a speech delivered in New York in December 1945, "We helped create this new weapon in order to prevent the enemies of mankind from achieving it first; given the mentality of the Nazis, this could have brought about untold destruction as well as the enslavement of the peoples of the world."[1] The practical problem of the proposed guidelines is that they only apply to those committed to the good of mankind—the total global community. German and Japanese biomedical researchers were already evil. Are we to suppose that their modern day successors will give any heed to such limitations, moral accountability, or compliance with global standards for research governance?

There are fundamental flaws in the human character, and finding ways of killing one another is one of those fundamental flaws. General Omar Bradley commented that "we know more about killing than we do about living . . . more about the atom than we do the Sermon on the Mount."[2] Establishing ethical policy to govern the conduct of unethical people lacks practical merit. The threat of biochemical terrorism and warfare is not a new phenomenon. Policy to govern the ethical conduct of biomedical research is not new either. What continues to make conducting ethical research problematic is the real danger of its exploitation for evil purposes. Hence the practical question, not so much an ethical one, is how to prevent the use of beneficent research for nefarious purposes.

Military biomedical research has always been inherently problematic with regards to how to prevent the "militarization" of its research, militarization in the sense of using defensive research (vaccine development, antidote development, and other prophylaxis

modalities) for offensive biochemical weapons development. Recently the military biological research program has jointly ventured with the National Institutes of Health. The purpose of this partnership has always been driven by the openness of the research, establishing trust with civilian partnership and accountability, so as to demonstrate the commitment of the United States to maintaining the beneficent nature of biomedical research. By maintaining a policy of "openness," the intent is one of deterrence. If we reveal to our enemies our own understanding of the potential offensive application of our research, doing so indicates our knowledge of how to counteract that offensive application, thereby limiting the practical use of a biochemical weapon as a viable threat.

Open programs also carry the connotation of global cooperation in biomedical research programs. Eliminating the element of secrecy serves as a deterrent from other countries investigating the use of this research for offensive purposes. If they are welcomed into the research at the front end as partners in the beneficent application of research, they are less likely to see the need to develop offensive capabilities. Patents, profits, and scientific notoriety aside, there is tremendous waste of effort and money in massive duplication of research efforts.

An overall ethical framework to govern the conduct of biomedical research has been in effect for some time. The effort by the Council on Ethical and Judicial Affairs to expand its scope and application is a noble one. The problem is how to establish and apply consequences to those who will be noncompliant to its fundamental tenet, namely, "do no harm." The very nature of evil use by evil people presumes their intentional disregard for ethical conduct, properly designed research, and a resolute defiance of inspections and regulatory oversight of their biomedical research programs. In that same New York speech delivered in 1945, Albert Einstein stated, "we dare not slacken our efforts to make the peoples of the world, and especially their governments, aware of the unspeakable disaster they are certain to provoke unless they change their attitude toward one another and recognize their responsibility in shaping a safe future."[3] Our resolve must always be to seek to do good when we can and to restrict evil when we have the ability and power to do so. The conjoining of these two principles will allow for the continued advancement and proper application of science with the will to seek out and bring to bear the full weight of consequences and judgment to those who would do us harm. We cannot have one without the other.

Notes

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Commentary: Physicians and the Risk of Malevolent Use of Research

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Although research findings have always been subject to abuse, scientific

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advances and recent events have increased concern about the perils of some biomedical knowledge. The Council on Ethical and Judicial Affairs (CEJA) addresses this potential in its guidelines[1] for physician–researchers (PRs). The guidelines do not advance many novel ideas or provide substantive guidance for PRs. Advocacy for professionalism, weighing costs and benefits, and balanced oversight are uncontroversial and have been proposed before.[2] The difficult task is to define what they require, and here the guidelines are vague. We discuss critically two issues that deserve careful attention.

Guidance for Regulators

CEJA deems inadequate the National Research Council's categorization of "dual use" research because there is no obvious way to delineate the scope of risky research. This is like saying that the Department of Homeland Security should not single out any potential terrorist targets for heightened attention because terrorists could strike anywhere. CEJA also contends that all biomedical research should undergo security review, analogous to IRB review. Such extensive review would be extremely expensive and time-consuming, and could impede research progress. Considering that most biomedical research poses minimal risks of abuse, reviewing all of it does not seem cost beneficial. Although no list of high-risk categories of research can be exhaustive, limiting automatic oversight to research that falls under an adaptive, expert-derived high-risk classification scheme balances risk reduction with budgetary constraints and research efficiency.

As a further precaution, CEJA proposes ethics training for all PRs. Ethics training may impress upon PRs their obligation to consider the effects of unintended uses of their research. But the cornerstone of ethical assessments of sensitive research is weighing potential risks and benefits, and normative training will not better equip PRs to make the necessary empirical assessments. "More responsible assessments" might be achieved with instruction in biosecurity,[3] but it would be more practical to provide access to biosecurity experts than try to hone the risk assessment skills of every PR. A committee of scientists and security experts, possibly organized by the National Science Advisory Board for Biosecurity (NSABB),[4] should be available for researchers, journal editors, and others to anonymously query regarding concerning research not subject to mandatory review.

Guidance for PRs

Concern about the abuse of research has typically been framed as an ethical issue affecting all scientists, regardless of discipline. But CEJA implies that different ethical issues arise when the scientists are physicians. When performing research with the potential for malevolent misuse, or "dual use" research, PRs must both "meet responsibilities of the scientific community" and the "ethical obligations of the medical profession." Why might PRs have different duties than nonphysicians when conducting the same research? And what are the implications of the difference?

Following the World Medical Association, CEJA suggests that PRs have a special duty not to conduct offensive CBTW research because it is "antithetical to the professed duties of physicians" and to "the foundations of the medical profession." Most offensive CBTW research is impermissible because of international weapons conventions and concern for public welfare. CEJA contends that PRs are further

constrained by the Hippocratic duty of nonmaleficence—the medical injunction against inflicting harm. Just as physicians cannot justify imposing harms or risks on patients by appealing to the public welfare, PRs may not justify harms or risks that their research imposes on individual members of the public by appealing to the aggregate public good.

Such a duty would have implications beyond PRs' participation in offensive CBTW research. Most obviously, PRs could not participate in some potentially ethical but intentionally offensively biomedical research, possibly including research on nonlethal chemical calmatives for use in hostage rescues,[5] nociception for the development of microwave-based crowd control,[6] or neuroscience-based methods to improve remote control of military robots.[7] Although a duty of nonmaleficence would limit PRs' participation in *intentionally* offensive research, it is a contentious matter whether or not nonmaleficence might also preclude some actions that impose risks that are *foreseeable* but unintended.[8] All researchers have duties to the public welfare and to weight risks and benefits. However, if medical nonmaleficence bears upon the foreseeable risks of research, PRs could not justify unintended security risks to some by weighing them against expected benefits for others—and CEJA contends that *all* biomedical research is subject to foreseeable but unintended abuse by malevolent third parties. For this reason, the significance of unintended but foreseeable risks will have a profound impact on the scope of biomedical research that PRs may ethically conduct, assuming PRs' laboratory work is constrained by a duty of nonmaleficence.

However, the basis of a medical duty of nonmaleficence that extends to physicians' work in the laboratory is unclear. One explanation might be that the duty arises from PRs' use of medical skills and knowledge. But the knowledge that physicians use in conducting biomedical research is not different than that used by their nonphysician colleagues, who are presumably not bound by Hippocratic duties. Traditionally, the medical duty of nonmaleficence arises from the nature and goals of the relationship between physicians and their patients: Patients make themselves voluntarily vulnerable to physicians, and physicians rely on patients' trust. There is no such relationship between physicians in the laboratory and the unidentified individuals that their research might harm. Debate lingers over whether physicians have a duty of nonmaleficence to their human research subjects,[9] let alone to strangers.

PR's use of medical knowledge does invoke special obligations, but not of nonmaleficence. As CEJA notes, physicians must act to preserve trust in the medical profession, and physicians' activities reflect most strongly upon the medical profession when they involve the use of medical training, equipment, or procedures. CEJA is wrong to imply that a duty of nonmaleficence prevents PRs from conducting potentially harmful biomedical research,[10] but a duty to preserve trust in medicine might preclude involvement in research likely to appear medically improper. On the other hand, CEJA agrees that nonphysician scientists also have an obligation to preserve public trust. In the conduct of dual use laboratory research, any difference between the duties of researchers with M.D.s and those with Ph.D.s is likely to be negligible and stem only from differences in public perception of medicine and general science. This suggests that if a sensitive research project is ethical for nonphysician scientists to conduct, it is ethical for PRs, too.

Conclusion

CEJA is laudable for acknowledging that the prospect of misuse makes some research too risky to conduct or disseminate, that PRs who fail to exercise due care can be blameworthy for harms resulting from misuse of their findings, and that some regulation of research is warranted. But to have practical significance, elaborations on risk management proposals and the particular requirements of medical professionalism are essential.

Notes

1. Green SK, Taub S, Morin K, Higginson D. Guidelines to Prevent Malevolent Use of Biomedical Research. *Cambridge Quarterly of Healthcare Ethics*, this issue, 432–447.
2. Starting in 1972 with the Biological and Toxin Weapons Convention (BTWC), later in 1993 with the Chemical Weapons Convention (CWC), and most recently in 2004 with the National Research Council's *Biotechnology Research in an Age of Terrorism*, there have been mounting efforts to codify legal norms and ethical guidelines.
3. The World Medical Association makes a related recommendation in E.16(c) of The WMA Declaration of Washington on Biological Weapons. See http://www.wma.net/e/policy/b1.htm (accessed Jun 27, 2005).
4. The NSABB addressed related issues in its first meeting, archived at http://www.biosecurityboard.gov/meetings_archive_062005.asp (accessed Sep 10, 2005).
5. The Chemical Weapons Convention has an exception for nonlethal agents used in "law enforcement." Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction, (CWC), Jan 13, 1993, Article II, Paragraph 9d.
6. The future of crowd control. *The Economist* 2004 Dec 2. Available at: http://economist.com/science/tq/displayStory.cfm?story_id=3423036 (accessed Jun 27, 2005).
7. Ling G. Human-assisted neural devices. Available at: http://www.darpa.mil/dso/thrust/biosci/hand.htm (accessed Jun 27, 2005).
8. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*, 5th ed. New York: Oxford University Press; 2001.
9. For example, there is no consensus over whether it can be ethical for physicians to intentionally infect research subjects with an illness. See Miller FG, Grady C. The ethical challenge of infection-inducing challenge experiments. *Clinical Infectious Diseases* 2001;33:1028–33.
10. Although, in rare cases a duty of nonmaleficence may constrain an individual PR when research poses disproportionate risks to his or her own patients. For instance, nonmaleficence might preclude a doctor serving prisoners of war from conducting otherwise ethical research on interrogation strategies.

Commentary: The Ethics of Dangerous Discovery

Michael J. Selgelid

The American Medical Association's (AMA's) Council on Ethical and Judicial Affairs' (CEJA's) new "Guidelines to Prevent the Malevolent Use of Biomedical Research" are both timely and appropriate. These guidelines are a product of the increasing realization of the "dual use" potential of life science discoveries. Although biomedical research usually aims at the development of new medicines, vaccines, diagnostics, and so on, the very same discoveries that could benefit humankind in these ways also often have implications for the development of biological weapons.[1] The CEJA Guidelines draw attention to this fact and hold that physician–researchers have responsibilities regarding the uses to which their discoveries are put. Medical researchers should assess the likely social benefits and harms of their work and avoid projects where the latter outweigh the former. Knowledge and the advancement of science should not be the only aims of scientists; "commitment to public welfare and safety" are also essential.[2] Toward the aim of preventing the malevolent use of research discoveries, the CEJA states that

"regulatory oversight" of research (with an eye to potential harmful uses of potential discoveries), increased ethics education of physician researchers, and sometimes perhaps even censorship of research findings, are warranted.[3]

This CEJA should be praised for broadening the focus of research ethics guidelines, which have traditionally been primarily concerned with the protection of human participants in human experimentation,[4] and for (implicitly) expanding dialogue on ethical implications of the new genetics. Whereas initial discussion of ethical, legal, and social implications of advances in genetics focused on the worry that dangerous material might result from recombinant research and escape into the environment, more recent bioethics discussion has focused on issues of genetic testing, discrimination, eugenics, cloning, stem cell research, and (to a lesser extent) DNA fingerprinting and the patenting of genetic sequences. Though comparatively neglected by ethics discourse, in the meanwhile, biological weapons development may turn out to be the most serious consequence of the genetic revolution.[5] According to the CIA, for example,

> A panel of life sciences experts convened for the Strategic Assessments Group by the National Academy of Sciences concluded that advances in biotechnology . . . have the potential to create a much more dangerous biological warfare (BW) threat. The panel noted [that t]he effects of some of these engineered biological agents could be worse than any disease known to man.[6]

The kind of danger that the CEJA and CIA are concerned about is illustrated by the recent publication of two controversial studies (alluded to in the CEJA Guidelines). In one case, Australian researchers aiming to find a way to reduce mouse fertility as a means of pest control accidentally discovered that insertion of the IL-4 gene into the mousepox virus genome resulted in a superstrain of mousepox that killed mice that were naturally resistant to, and also mice that had been vaccinated against, the disease. The scientists proceeded to publish their findings—along with a description of their materials and methods—in 2001.[7] In a second case, American researchers sponsored by the U.S. Department of Defense synthesized a "live" polio virus from scratch by stringing together commercially available strands of DNA (purchased over the Internet) in accordance with the map of the polio virus (RNA) genome (published on the Internet). The addition of protein resulted in a live virus that paralyzed mice. In 2002 they too published their findings, materials, and methods.[8]

Both of these studies have implications for smallpox—a disease that commonly tops lists of feared biological weapons agents. The polio study, for example, reveals that it might be possible to produce the smallpox virus through similar procedures. Although the smallpox virus is much larger than polio, the technical feasibility of artificially synthesizing smallpox is perhaps dubious. More fearsome is the possibility that the straightforward technique used on mousepox could allow the genetic engineering of vaccine-resistant smallpox. As there is no treatment for smallpox, vaccine is our only defense against this disease, which is believed to have killed more humans than any other infectious disease in history. Because routine vaccination ended more than 20 years ago, the world population now largely lacks immunity to smallpox, and modeling has shown that a smallpox attack could cause the devastation of nuclear attack(s).

Critics claim that neither of these discoveries should have been published.

Their complaint is that publication of such studies both alerts would-be bioterrorists of possibilities and provides them with explicit instructions for producing potential weapons of mass destruction. The scientists and editors involved, however, claim that publication was warranted given the importance of alerting the scientific community to the kind of things we may need to prepare to defend ourselves against. These are clear examples of "dual use" discoveries: the same knowledge that may be harmfully used in weapons production has benefits with regard to biodefense.

Whether or not the mousepox and polio studies should have been conducted and/or published, the CEJA is right to draw the medical community's conscience to the potential dangers of both research and publication. It would be wrong to think that scientists should only be concerned with the generation of knowledge—which is often assumed to be inherently valuable for its own sake or, at worst, neutral. Because the misuse of knowledge would not be possible without its generation and dissemination in the first place, those who generate and disseminate potentially dangerous knowledge are ethically implicated in any misuse that occurs, especially when the harmful application of the knowledge in question is foreseeable.

This raises a difficult question left unanswered by the CEJA Guidelines. What should the process of censorship be? Given the importance of openness for scientific progress and the importance of transparency for public trust in science, the CEJA sounds generally (though not entirely) resistant to even self-censorship. For similar reasons, the U.S. National Research Council has explicitly argued against governmental censorship of "sensitive" information resulting from life science research, advocating "voluntary self-governance" of the scientific community as the preferred alternative.[9]

Though scientists should be encouraged to refrain from research with implications for weapons development and to voluntarily limit dissemination of research findings in cases where likely harms outweigh benefits, it is doubtful that the scientific community should be relied upon to regulate itself in such matters. This is simply because scientists will not always, contrary to what is said by the CEJA, be "in the best position to assess the potential for and the ramifications of misapplication of their research."[10] In the case of the mousepox study, for example, the danger of publication is largely a function of the likelihood that there has been proliferation of the smallpox virus from the Soviet biological weapons program (or other secret sources), insofar as aspiring bioterrorists would need to have access to the smallpox virus in order to apply the mousepox technique to it. The true danger of publishing the mousepox study, therefore, depends on information that the scientific community (like the general public) is systematically denied access to. Details about the likelihood of smallpox proliferation are classified.[11] Assuming they lacked security clearance, the editors and authors of the mousepox study would not have been able to accurately assess the danger of publication. Given that the government will sometimes be in the best position to judge the danger of publication, censorship by government may sometimes be justified.

Notes

1. U.S. National Research Council. *Biotechnology Research in an Age of Terrorism*. Washington, D.C.: The National Academies Press; 2004.
2. Green SK, Taub S, Morin K, Higginson D. Guidelines to Prevent Malevolent Use of

Biomedical Research. *Cambridge Quarterly of Healthcare Ethics*, this issue, 432–447.
3. See note 2, Green et al. 2006.
4. See note 2, Green et al. 2006.
5. Selgelid MJ. Smallpox revisited? *American Journal of Bioethics* 2003;3:W5–W11. Available at: http://www.bioethics.net/journal/j_articles.php?aid=91 (accessed Jul 19, 2005).
6. Central Intelligence Agency. The darker bioweapons future. November 2003. Available at: http://www.fas.org/irp/cia/product/bw1103.pdf (accessed Jul 19, 2005).
7. Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *Journal of Virology* 2001;75:1205–10.
8. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template. *Science* 2002;297:1016–18. Available at: http://www.sciencemag.org/cgi/content/full/297/5583/1016 (accessed Jul 19, 2005).
9. See note 1, U.S. National Research Council, 2004.
10. See note 2, Green et al. 2006.
11. Annas G. *American Bioethics*. New York: Oxford University Press; 2005:15.