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Double-Edged Innovations:
Preventing the Misuse of Emerging Biological/Chemical Technologies

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DOUBLE-EDGED INNOVATIONS:
Preventing the Misuse of Emerging Biological/Chemical Technologies

Jonathan B. Tucker, Editor

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Chapter 1: Introduction

Jonathan B. Tucker

Several areas of rapid technical innovation, such as biotechnology, nanotechnology, and neuroscience, offer great promise for human health and welfare but could also be exploited for the development and production of biological or chemical weapons.[1] Such technologies pose a "dual-use dilemma" because it is difficult to prevent misuse without foregoing beneficial applications.[2] Indeed, in many cases the technologies that can do the most good are also capable of the greatest harm. Since the terrorist attacks of September 11, 2001, several developments in the life sciences have raised the political salience and urgency of the dual-use issue. One example is the synthesis from scratch of several pathogenic viruses, including the causative agents of polio, SARS, and the 1918 pandemic strain of influenza.

In addition to exploring the characteristics of emerging dual-use technologies in the biological and chemical fields, this book has a practical purpose: to help policymakers devise the most appropriate and effective governance strategies to minimize the risks of double-edged innovations while preserving their benefits.

Definitional Issues

The term "dual-use" has multiple meanings. In the context of defense procurement, it refers to technologies or items of equipment that have both civilian and military applications.[3] Policymakers often promote the transfer of civilian technologies to the defense sector in order to reduce the cost of conventional weapon systems. In a different context, however, dual-use refers to materials, hardware, and knowledge that have peaceful uses but can be exploited for the production of nuclear, chemical, or biological weapons. Certain dual-use chemicals, for example, have legitimate industrial applications but are also precursors for chemical warfare agents.

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[1]James B. Petro, Theodore R. Plasse, and Jack A. McNulty, "Biotechnology: Impact on Biological Warfare and Biodefense," *Biosecurity and Bioterrorism*, vol. 1, no. 3 (September 2003), pp. 161-168; Eileen R. Choffnes, Stanley M. Lemon, and David A. Relman, "A Brave New World in the Life Sciences," *Bulletin of the Atomic Scientists*, vol. 62, no. 5 (September/October 2006), pp. 28-29; Ronald M. Atlas and Malcolm Dando, "The Dual-Use Dilemma for the Life Sciences: Perspectives, Conundrums, and Global Solutions," *Biosecurity and Bioterrorism*, vol. 4, no. 3 (2006), pp. 276-286.

[2]Parliamentary Office of Science and Technology, "The Dual-Use Dilemma," *Postnote*, No. 340 (July 2009), p. 1.

[3] John A. Alic, Lewis M. Branscomb, Harvey Brooks, Ashton B. Carter, and Gerald Epstein, *Beyond Spinoff: Military and Commercial Technologies in a Changing World* (Boston: Harvard Business School Press, 1992).

Similarly, certain items of production equipment, such as microbial fermenters and chemical batch reactors, have the capacity to biological or chemical agents as well as commercial products.

Almost every technology has some potential for misuse: a hammer, for example, can serve as a tool or a murder weapon. Given the pervasiveness of the dual-use problem, developing a useful definition requires striking a reasonable balance. Defining the term too narrowly would fail to capture some potential threats, while defining it too broadly would restrict some beneficial applications unnecessarily. To limit the scope of the analysis, this book does not cover the entire universe of biological and chemical technologies with a potential for misuse but focuses instead on emerging technologies that are "game-changers" because their exploitation for harmful purposes would result in consequences more serious than those caused by existing technologies. To be of concern, in other words, a dual-use innovation must offer a qualitative or quantitative increase in destructive potential over what is currently available. The rationale for this approach is that standard items of dual-use biological and chemical equipment are already regulated to the extent possible.

When thinking about dual-use risks in the life sciences, it is instructive to consider how biotechnology differs from nuclear technology. Methods for the production of fissile materials, such as enriched uranium and plutonium, are considered dual-use because they can be used either to produce fuel rods for generating electricity or pits for nuclear weapons. Nevertheless, weapon-grade fissile materials have several characteristics that make them amenable to physical protection, control, and accounting: highly enriched uranium and plutonium are man-made substances that do not exist in nature, are difficult and costly to produce, have few civilian applications, and emit radiation that can be detected at a distance. In contrast, pathogenic bacteria and viruses are available from natural sources, are self-replicating and thus cannot be accounted for in a quantitative manner, have numerous legitimate applications in science and medicine, and are impossible to detect at a distance. Because of these differences, the process of acquiring biological weapons entails fewer technical hurdles and a lower chance of discovery than the construction of an improvised nuclear device. Finally, whereas dual-use nuclear technologies are advancing slowly—the basic methods of uranium enrichment and plutonium separation have not changed significantly in several decades—many areas of biotechnology are

progressing at an exponential rate, and the time lag from scientific discovery to technological application is extremely short.

History of Dual-Use Technologies

Since 9/11 and the anthrax letter attacks, the potential misuse of emerging technologies for the development and production of biological and chemical weapons has become a major focus of government concern. The problem of dual-use technologies, however, has a much longer history. In the twentieth century, the two World Wars saw the intensive exploitation of chemistry and physics for military purposes, including the development of high explosives, chemical weapons, radar, ballistic missiles, and the atomic bomb.[4] Although biology played a much smaller role in these conflicts, it did not escape application as an instrument of warfare. During World War I, German saboteurs drew on the bacteriological discoveries of Louis Pasteur and Robert Koch to carry out covert operations in which they used anthrax and glanders bacteria to sicken Allied horses, which were then essential for military logistics.[5] Before and during World War II, the United States, the Soviet Union, Britain, France, Germany, Japan, and other countries harnessed scientific advances in microbiology for the development of offensive biological warfare (BW) capabilities.[6] Imperial Japan was the only country that actually used biological weapons during this period. Between 1932 and 1945, Japanese military scientists developed a variety of BW agents, tested them on human prisoners, and employed them against 11 Chinese cities.[7]

The biotechnology revolution began in the early 1970s, two decades after James Watson and Francis Crick published their seminal 1953 paper describing the double-helical structure of the DNA molecule and suggesting a mechanism for its replication. In 1973, Stanley Cohen of Stanford University and Herbert Boyer of the University of California at San Francisco invented the basic methodology for combining genes from different organisms, known as recombinant

[4] William H. McNeill, *The Pursuit of Power: The Pursuit of Power: Technology, Armed Force, and Society since A.D. 1000* (Chicago: University of Chicago Press, 1982).
[5] Mark Wheelis, "Biological Sabotage in World War I," in Erhard Geissler and John Ellis van Courtland Moon, eds., *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945*, SIPRI Chemical & Biological Warfare Studies No. 18 (Oxford, UK: Oxford University Press for the Stockholm International Peace Research Institute, 1999), pp. 35-62.
[6]Malcolm Dando, "The Impact of the Development of Modern Biology and Medicine on the Evolution of Modern Biological Warfare Programmes in the Twentieth Century," *Defense Analysis*, vol. 15, no. 1 (1999), pp. 51-65.
[7] Sheldon H. Harris, *Factories of Death: Japanese Biological Warfare, 1932-45 and the American Cover-Up*, 2nd ed. (New York: Routledge, 2002).

DNA technology or "genetic engineering." Practical applications of genetic engineering, such as ability to synthesize human insulin in bacteria, gave rise to the modern biotechnology industry. Although the first biotechnology firms were spun off from large research universities in the Boston and San Francisco areas, the industry has since spread globally. Several factors have fueled this international expansion, including economic globalization and the growing use of international subcontracting and cooperation agreements.[8] A number of Asian countries, such as China, India, Malaysia, and Singapore, have also championed biotechnology as a key element of their economic development plans. Genetic engineering also has a dark side, however. During the 1980s, the massive Soviet biological warfare program drew on recombinant DNA technology to develop genetically modified pathogens with greater virulence, stability, and antibiotic resistance.[9]

In recent decades, the convergence of biology and chemistry has increased the capacity of both fields for good or ill. Since the early 2000s, the advent of synthetic genomics—the ability to synthesize gene-length DNA molecules from off-the-shelf chemicals in the laboratory—has made it possible to construct entire microbial genomes from scratch. Instead of isolating individual genes from one species and splicing them into the genome of another, synthetic biologists are free to design any conceivable genetic sequence on a computer and convert it into a physical strand of DNA that codes for a useful product or function. A global industry has also emerged to synthesize customized DNA molecules to order for scientific and pharmaceutical-industry clients. Such DNA synthesis firms are not limited to advanced industrial countries such as the United States, Western Europe, and Japan but have also sprung up in China, South America, and the Middle East.

Today, rapid advances in mapping the human genome (genomics), studying the structure and function of the myriad proteins in living organisms (proteomics), and analyzing the complex biochemical circuits that regulate cellular metabolism (systems biology) are yielding a profound understanding of life at the molecular level. At the same time, technological advances have improved the flexibility, efficiency, and yield of biological and chemical manufacturing processes. Thanks to the convergence of biology and chemistry, it is becoming possible to

[8] Christopher Chyba and Alex Greninger, "Biotechnology and Bioterrorism: An Unprecedented World," *Survival,* vol. 46 (2004), pp. 143-162.
[9]John Hart, "The Soviet Biological Weapons Program," in Mark Wheelis, Lajos Rózsa, and Malcolm Dando, eds., *Deadly Cultures: Biological Weapons since 1945* (Cambridge, Mass.: Harvard University Press, 2006), pp. 132-156.

produce fine chemicals and drugs in bacteria and to synthesize biological macromolecules such as DNA and peptides (chains of amino acids) by chemical means. Finally, the dynamic field of nanobiotechnology has made it possible to engineer nanoparticles that can ferry drugs through the bloodstream to specific tissues, while evading the host immune response. Although all of these innovations promise valuable new medicines and therapies, they could potentially be exploited for biological or chemical warfare purposes.[10] The emerging disciplines of synthetic biology and nanobiotechnology, for example, could lead to a new generation of BW agents that are designed and assembled from scratch.[11]

Dual-use risks may also emerge unexpectedly from basic or applied scientific research in the life sciences. In 2001, for example, a group of Australian researchers developing a contraceptive vaccine to control mouse populations found that inserting a single gene for an immune regulatory protein (interleukin-4) into the mousepox virus rendered this normally mild pathogen highly lethal in mice, even in animals that had been vaccinated against it.[12] This surprising discovery had dual-use implications because the mousepox virus is closely related to the variola (smallpox) virus and the monkeypox virus, both of which can infect humans. It therefore seemed likely that performing the same manipulation on a human poxvirus would increase its virulence and make it resistant to the standard protective vaccine.[13] After debating whether or not to publish their findings, the Australian researchers finally did so in the *Journal of Virology* in early 2001. The security implications of the paper, however, triggered a storm of

[10] Ralf Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," *Arms Control Today*, vol. 38 (March 2008), http://www.armscontrol.org/act/2008_03/Trapp.
[11]Caitríonia McLeish and Paul Nightingale, "Biosecurity, Bioterrorism and the Governance of Science: The Increasing Convergence of Science and Security Policy," *Research Policy*, vol. 36, no. 10 (December 2007), pp. 1635-1654.
[12]R. J. Jackson, A. J. Ramsay, C. D. Christensen, S. Beaton, D. F. Hall, and I. A. Ramshaw, "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cyctolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology*, vol. 75, no. 3 (2001), pp. 1205-1210. In retrospect, the unexpected findings of the mousepox experiment could have been predicted because a paper describing the role of interleukin-4 in poxvirus virulence had been published three years earlier in the same journal: G. Bernbridge, et al., "Recombinant Vaccina Virus Coexpressing the F Protein of Respiratory Syncytial Virus (RSV) and Interleukin-4 (IL-4) Does Not Inhibit the Development of RSV-Specific Memory Cytotoxic Lymphocytes, whereas Priming is Diminished in the Presence of High Levels of IL-2 or Gamma Interferon," *Journal of Virology*, vol. 72, no. 5 (1998), pp. 4080-4087
[13]Michael J. Selgelid and Lorna Weir, "The Mousepox Experience," *EMBO Reports*, vol. 11, no. 1 (2010), pp. 18-24.

controversy about whether certain types of scientific information are simply too sensitive to release into the public domain.[14]

Potential Actors

In parallel with the revolution in biology and chemistry, the nature of military conflict has undergone a sea-change since the end of the Cold War. With the easing of the East-West confrontation, the specter of global war between vast armies equipped with tanks and other heavy weapons has receded into history, at least for the time being. The threat of high-intensity warfare has been replaced in the opening years of the 21st century by a variety of low-intensity conflicts, including ethnic and civil wars, insurgency and counterinsurgency campaigns, and "operations other than war" such as peacekeeping and counterterrorism. This sweeping change in the nature of military conflict could create new incentives and opportunities for the hostile exploitation of emerging biological and chemical technologies.[15] Indeed, one consequence of the renewed focus on urban warfare, counterterrorism, and counterinsurgency operations, in which combatants and noncombatants are often intermingled, has been a growing interest on the part of several states in acquiring "non-lethal" or "less-than-lethal" chemical agents.

Whereas riot-control agents (RCAs) such as tear gas have temporary irritating effects on the eyes and skin that dissipate rapidly after the exposure ends, incapacitating agents (such as the opiate anesthetic fentanyl) have persistent effects on the central nervous system and induce a state of disorientation, unconsciousness, euphoria, or depression that lasts for several hours. Some states have explored the possibility of developing novel incapacitating agents based on natural body substances called bioregulators, many of which are peptides. From 1974 to 1989, the Soviet Union pursued a top-secret program code-named "Bonfire," which involved the development of chemical agents based on peptide bioregulators.[16] The U.S. Department of Defense has also funded research on so-called "calmative" agents, including some bioactive

[14] National Science Advisory Board for Biosecurity, "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information," June 2007, available at: http://oba.od.nih.gov/biosecurity/pdf/Framework%20for%20transmittal%200807_Sept07.pdf

[15] Mark Wheelis, "Will the New Biology Lead to New Weapons?" *Arms Control Today*, vol. 34, July/August 2004, pp. 6-13.

[16] Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999), pp. 154-155, 163-164.

peptides.[17] In addition to Russia and the United States, several other countries have reportedly worked on incapacitating agents.[18]

At least in principle, non-state actors such as terrorist or criminal organizations might seek to misuse emerging dual-use technologies to cause harm. Ever since the 9/11 terrorist attacks and the subsequent anthrax mailings, policymaker concern has focused primarily on biological and chemical terrorism. For reasons of motivation and capability, however, this contingency appears unlikely. Terrorist groups generally lack the financial and technical resources to exploit cutting-edge technologies. In addition, most terrorist groups are conservative in their choice of weapons and tactics, innovating only when forced to do so by the introduction of new countermeasures, such as improved aviation security. Al-Qaeda is an exception to this rule, having openly declared its ambition to acquire unconventional weapons, but the organization's chemical and biological warfare capabilities remain rudimentary.

To date, the only terrorist group that managed to move fairly high up the learning curve was the Aum Shinrikyo cult in Japan. In the early 1990s, Aum recruited biologists and chemists from Japanese universities and amassed vast financial resources from a variety of legitimate and criminal enterprises. Cult leader Shoko Asahara ordered the purchase of costly chemical and biological production equipment and materials, and he put his scientists to work developing and producing anthrax bacteria, botulinum toxin, and sarin nerve agent. Despite these efforts, however, persistent technical problems prevented the cult from achieving its malign objective of staging mass-casualty biological and chemical attacks. Aum inadvertently acquired a harmless vaccine strain of the anthrax bacterium and failed entirely to cultivate botulinum toxin, so that its biological attacks resulted in no injuries or deaths. The cult also was unsuccessful in its attempt to manufacture a multi-ton stockpile of sarin nerve agent. Even so, Aum did manage to stage two attacks involving limited amounts of sarin in Matsumoto in June 1994 and on the Tokyo subway in March 1995, claiming a total of 19 lives and injuring hundreds more.[19]

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[17] Joan M. Lakoski, W. Bosseau Murray, and John M. Kenny, *The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique* (College Park, PA: Pennsylvania State University, College of Medicine and Applied Research Laboratory, October 3, 2000), pp. 39-45.

[18] According to a 2009 study by Michael Crowley of the University of Bradford (UK), research and development in this area has been performed by China, the Czech Republic, France, and the United Kingdom, as well as NATO and the European Defence Agency.

[19] David E. Kaplan, "Aum Shinrikyo (1995)," in Jonathan B. Tucker, ed., *Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons* (Cambridge, MA: MIT Press, 2000), pp. 207-226.

Harm vs. Misuse

When discussing emerging dual-use technologies, it is important to distinguish between "harm" and "misuse." Harm encompasses a broad range of negative consequences, including fatal and non-fatal casualties, permanent disability, psychological trauma, social chaos, economic damage, and the incitement of fear. Whereas the capacity to cause harm is an inherent characteristic of a dual-use technology or material, misuse is a function both of the intent of the individual actor and prevailing social norms. From a legal standpoint, misuse is an action that violates an existing national or international law. Humanitarian law, for example, prohibits certain types of weapons because they are indiscriminate and likely to kill civilians, treacherous or insidious by nature, or have effects on the human body that cause unnecessary suffering.

The legal definition of misuse has changed over the course of history in response to the evolution of international law, which follows and embodies trends in global behavioral norms. Thus, the relationship between harm and misuse is different today than it was in the past.[20] During World War I, for example, the Germans believed that the use of biological weapons against humans was immoral but that biological attacks targeting horses and other draft animals were legitimate. The development, production, and stockpiling of germ weapons by states was legal until the entry into force of the Biological Weapons Convention (BWC) in 1975. Although the United States unilaterally abandoned its offensive biological warfare program in 1969, the Soviet Union and then Russia secretly continued its program into the early 1990s in flagrant violation of the BWC. Similarly, before the Chemical Weapons Convention (CWC) went into effect in 1997, it was legal for states to develop, produce, and stockpile chemical arms, although the first use of such weapons in war was prohibited by the 1925 Geneva Protocol.

Today, certain categories of weapons, such as small arms and conventional explosives, are considered legitimate, while chemical and biological weapons (and more recently landmines) have come to be viewed as morally unacceptable. Additional categories of armament, such as incendiary weapons, exist in a legal gray area in which certain applications (in the vicinity of civilians) have been banned by treaty, while others (against military targets) are still permitted. Although most arms control treaties apply only to states that join them voluntarily, the 1925

[20] Jonathan B. Tucker, "From Arms Race to Abolition: The Evolving Norm Against Chemical and Biological Warfare," in Sidney D. Drell, Abraham D. Sofaer, and George D. Wilson, eds., *The New Terror: Facing the Threat of Biological and Chemical Weapons* (Stanford, CA: Hoover Institution Press, 1999), pp. 159-226.

Geneva Protocol has acquired the status of customary international law, making it binding on all states whether or not they have signed and ratified it.

Three Misuse Scenarios

Three scenarios for the misuse of emerging biological and chemical technologies can be envisioned. First, dual-use technologies may *facilitate or accelerate the production of standard biological or chemical warfare agents*. Examples include the application of synthetic genomics to construct dangerous viruses from scratch, circumventing the physical access controls on pathogens of bioterrorism concern.

Second, dual-use technologies could help to identify or develop *novel biological or chemical warfare agents* that either have traditional lethal or incapacitating effects or entirely new ones. For example, it may eventually become possible to synthesize artificial pathogens or toxins that are resistant to standard medical countermeasures. Advances in neuroscience and psychopharmacology could also lead to the development of drugs that can affect human memory, cognition, and emotion in highly specific ways and on a mass scale. Beyond the potential military applications, rulers of autocratic or totalitarian states might seek to employ such agents against their own populations to repress dissent and control unrest. Along these lines, molecular biologist Matthew Meselson of Harvard University has warned, "As our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life but will also be able to manipulate it—including the processes of cognition, development, reproduction, and inheritance. A world in which these capabilities are widely employed for hostile purposes would be a world in which the very nature of conflict had radically changed. Therein could lie unprecedented opportunities for violence, coercion, repression, or subjugation."[21]

Third, dual-use biological/chemical technologies may lead to *harmful applications that undermine international legal norms*. Although the CWC bans all use of toxic chemicals on the battlefield, Article II, paragraph 9 (d) permits the development, production, and use of chemical agents for "law enforcement including domestic riot control."[22] Because the treaty does not

[21] Matthew S. Meselson, "Averting the Hostile Exploitation of Biotechnology," *CBW Conventions Bulletin*, June 2000, pp. 1-2.
[22] Alan M. Pearson, Marie Isabelle Chevrier, and Mark Wheelis, eds., *Incapacitating Biochemical Weapons: Promise or Peril?* (Lanham, MD: Lexington Books, 2007).

specify the types and quantities of toxic chemicals that may be used for this purpose, however, the law-enforcement exemption creates a potential loophole. If the exemption is interpreted broadly to cover chemicals more potent than riot-control agents, it could lead to the development and deployment of a new generation of psychochemical weapons and undermine the ban on chemical warfare. For example, military scientists might exploit advances in psychopharmacology to develop novel incapacitants and calmatives for counterterrorism and peacekeeping operations, blurring the distinction in the treaty between permitted activities (domestic riot control) and prohibited ones (warfare). A 2007 report by the International Union of Pure and Applied Chemistry (IUPAC) warned that the large-scale development and production of incapacitating agents for law-enforcement purposes could have the effect of undermining the basic prohibitions of the treaty because the agents would actually be weaponized and thus hard to distinguish from military weapons.[23] British chemical weapons analyst Julian Perry Robinson has also warned, "A regime that allows weaponization of one form of toxicity but not another cannot, under the circumstances, be stable."[24]

Hostile applications of chemical and biological agents might conceivably move beyond warfare to include systematic violations of human rights and international humanitarian law. Examples include the use of "mind-control" drugs to aid in coercive interrogation, or the possible development of "ethnic weapons"—engineered biological agents that can selectively target and harm certain ethnic or racial groups based on their genetic makeup. Although genetic warfare is not a practical option today, information from ongoing research into the human genome might eventually be exploited for this purpose. If and when it becomes possible to distinguish DNA sequences between ethnic groups and target them in a way produces a harmful outcome, a genetic weapon will become possible.[25]

The potential dark side of the revolution in the life sciences has been recognized for many years. According to a 1999 report by the British Medical Association titled *Biotechnology, Weapons and Humanity*:

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[23] Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention (IUPAC Technical Report)," p. 185.
[24] Julian P. Perry Robinson, "Ensuring that OPCW implementation of the CWC definition of chemical weapons remains fit for purpose," discussion paper for the 54th Pugwash CBW Workshop, *The Second CWC Review Conference and After* (Noordwijk, The Netherlands, April 5-6, 2008).
[25] British Medical Association, *Biotechnology, Weapons and Humanity* (Amsterdam: Harwood Academic Publishers, 1999), p. 60.

> [W]e are concerned that the emerging sciences of genetic engineering and biotechnology may be developed for malign purposes. The social and ethical safeguards which may prevent the escalation of conflict and weapons development therefore need to be discussed urgently. This report hopes to stimulate debate and raise civic awareness of the potential abuse of biotechnology and the important steps we can take to minimize the risk of the development of biological weapons.[26]

In 2003, an expert panel chaired by biology professor Gerald Fink of the Massachusetts Institute of Technology (M.I.T.), convened under the auspices of the U.S. National Academy of Sciences, produced a landmark study titled *Biotechnology Research in an Age of Terrorism.* This report identified seven types of experiments in the fields of microbiology and molecular biology that entail potential dual-use risks and warrant a security review before being approved and funded.[27] In response to the Fink Committee report, the U.S. government established a federal advisory committee called the National Science Advisory Board for Biosecurity (NSABB) with the mandate to develop a policy framework for the oversight of "dual-use research of concern" in the life sciences.[28]

Other prominent organizations have issued warnings about the potential misuse of advances in the life sciences, such as synthetic genomics and the mapping of the human genome. In 2004, the World Health Organization warned, "[E]very major new technology of the past has come to be intensively exploited, not only for peaceful purposes but also for hostile ones. Prevention of the hostile exploitation of biotechnology therefore rises above the security interests of individual states and poses a challenge to humanity generally."[29] That same year, the International Committee of the Red Cross (ICRC) launched an *Appeal on Biotechnology,*

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[26] British Medical Association, *Biotechnology, Weapons and Humanity* (Amsterdam: Harwood Academic Publishers, 1999), p. 1.

[27] National Research Council, *Biotechnology Research in an Age of Terrorism* (Washington, DC: National Academies Press, 2004).

[28]The NSABB's definition of "dual-use research of concern" (DURC) is as follows: "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." NSABB, *Proposed Framework for the Oversight of Dual-Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information* (June 2007), available online at: http://www.oba.od.nih.gov/biosecurity/biosecurity_documents.html

[29]World Health Organization, *Public Health Response to Biological and Chemical Weapons: WHO Guidance*, 2nd edition (Geneva, Switzerland: WHO, 2004), Executive Summary.

Weapons and Humanity, which urged governments, the scientific and medical communities, the military, industry, and civil society "to strengthen their commitment to the international humanitarian law norms which prohibit the hostile uses of biological agents and to work together to subject potentially dangerous biotechnology to effective controls."[30]

Proposals to ban emerging dual-use biological or chemical technologies outright are not realistic because doing so would sacrifice major benefits for public health, agriculture, and economic development. A better approach is to design policies that prevent misuse for harmful purposes while permitting legitimate applications. To date, however, a rigorous methodology for assessing the dual-use risk of emerging technologies and designing tailored governance strategies has yet to be widely adopted. Absent such a framework, dual-use technologies and expertise have continued to proliferate, increasing the risk that they could fall into the hands of states, groups, or individuals with malign intent. Creating a practical analytical approach to managing the dual-use problem is the central purpose of this book.

Structure of This Book

In addition to this Introduction, the book is organized into three parts and an Appendix. To provide an empirical basis for analyzing the problem of dual-use, the volume includes case studies of 14 contemporary dual-use technologies and two historical ones. Drawing on the case studies, the book develops a methodology to assess the risk of misuse, identify the types and combinations of governance options most likely to be effective, and tailor these measures to the specific characteristics of each technology.

Part I, "The Problem of Dual-Use," contains four chapters. Chapter 2, "Review of the Literature on Dual-Use," summarizes the academic literature on technological risk assessment and governance measures to provide a foundation for the comparative analysis of the case studies. Chapter 3, "Dual-Use Governance Measures," surveys the wide variety of existing approaches to technology governance, which can be divided into three categories: *hard-law* measures (legally binding laws and treaties), *soft-law* measures (voluntary agreements and guidelines), and *normative* measures (codes of conduct and awareness-raising). Chapter 4, "Lessons from History," uses the two historical cases in the Appendix to discuss sociological

[30] International Committee for the Red Cross, "Appeal on Biotechnology, Weapons and Humanity," September 25, 2002, Geneva, Switzerland, available online at: http://www.icrc.org/Web/eng/siteeng0.nsf/htmlall/5EAMTT

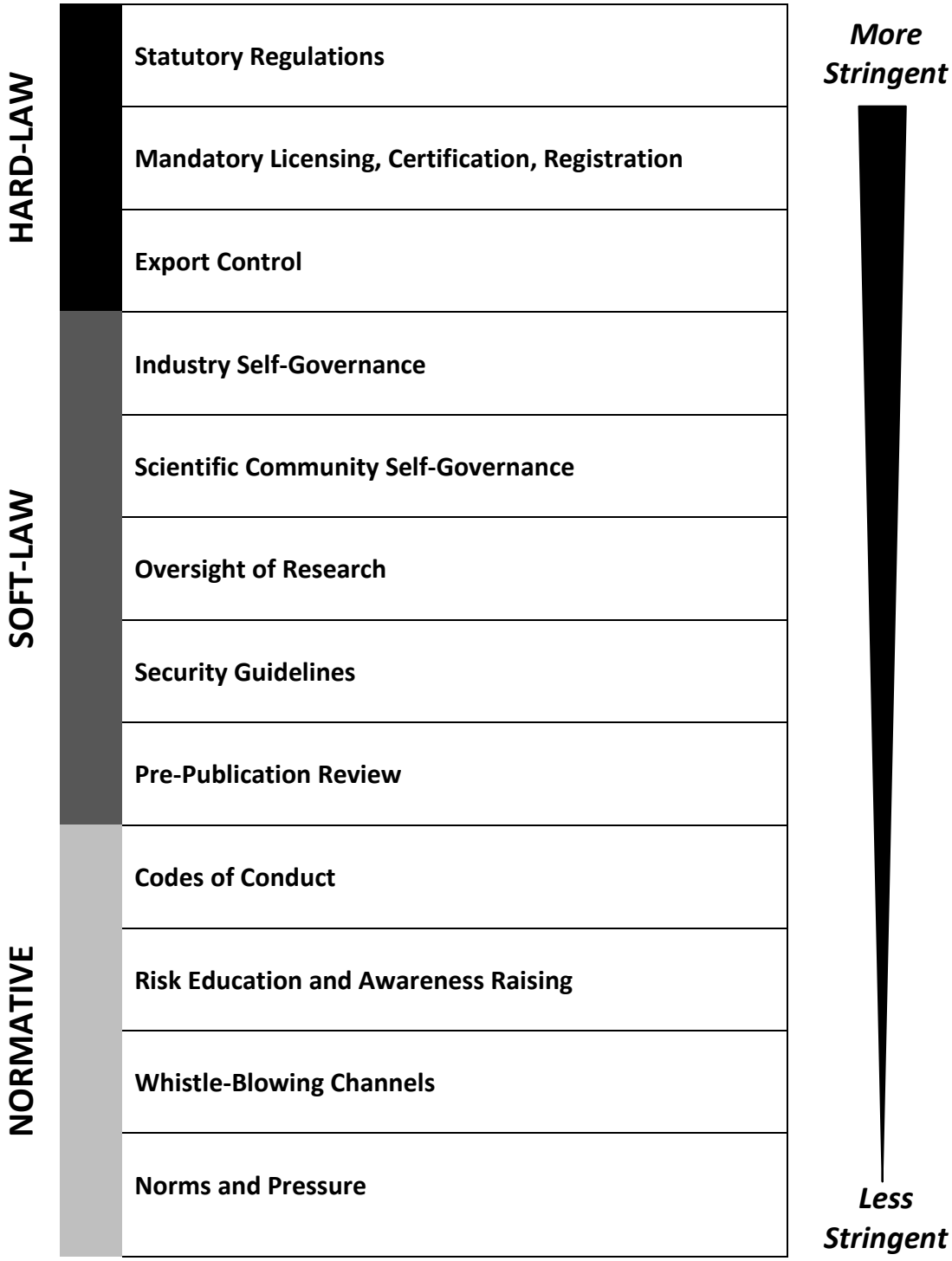
theories of how dual-use technologies are "translated" from peaceful to hostile applications. Chapter 5, "Case Study Template," sets out the standard framework that the case study writers used to analyze the 14 contemporary dual-use technologies, thereby facilitating cross-case comparison and inductive model-building. This template examines two key dimensions of each technology—the risk of misuse and susceptibility to governance—and ranks each on the basis of several parameters.

Part II contains the detailed case studies of 14 dual-use technologies in the biological and chemical fields that have emerged in recent years or are still emerging. Because many of these technologies will continue to evolve, the case studies should be viewed as "snapshots" at a given point in time. Accordingly, the proposed governance measures should be flexible enough to adapt to changing circumstances. Finally, Part III, "Findings and Conclusions," performs a comparative analysis of the case studies and uses it to develop a general model for governing the risks of emerging dual-use technologies while preserving the benefits. Chapter 20 discusses the need to develop tailored packages of hard-law, soft-law, and normative measures that are implemented at the individual, institutional, national, or international levels. The chapter concludes with a basic decision algorithm to help policymakers manage the risks of emerging dual-use technologies, both today and in the future.

Acknowledgments

Generous funding for the case studies and the two authors' workshops was provided by the British Foreign and Commonwealth Office's Strategic Counter-Proliferation Programme Fund and the U.S. Defense Threat Reduction Agency's Advanced Systems and Concepts Office. Particular thanks are due to Professor William C. Potter, director of the James Martin Center for Nonproliferation Studies (CNS) at the Monterey Institute of International Studies, and Leonard S. Spector, head of the CNS Washington office, for their encouragement and support, and to CNS research assistants Kirk Bansak and Michael Tu for their outstanding organizational and editorial help. Several reviewers provided helpful comments on some or all of the draft chapters, including Gregory Koblentz, Filippa Lentzos, [MORE TO COME]. Finally, Edith Bursac, the manager of Conference and Event Services at CNS, did a superb job of making travel arrangements for the two authors' workshops, which were held in Washington, D.C. in September 2009 and at Oxford University in March 2010.

Figure 2.1: Spectrum of Governance Measures



PART I: THE PROBLEM OF DUAL-USE

Chapter 2: Review of the Literature on Dual-Use

Jonathan B. Tucker

Many emerging biological and chemical technologies have the potential to be misused for warfare, terrorism, and other harmful purposes by state or non-state actors. Policy responses to this security challenge have two major components: (1) assessing the risk of misuse; and (2) devising effective governance strategies to minimize the risk. To provide some background for the comparative analysis of the case studies, this chapter reviews the academic literature on risk assessment and technology governance.

Assessing Uncertain Risks

A prerequisite for effective governance is the ability to assess the safety and security risks of an emerging technology. Although traditional definitions of technology emphasize hardware, equipment, and tools, the term also encompasses people, processes, and intangible information.[1] The scope of various emerging technologies also differs. Whereas nanotechnology is a large, complex field that includes multiple applications with varying degrees of risk and benefit, technologies such as synthetic genomics are more narrow and focused.

Assessing safety and security risks at an early stage in the development of an emerging technology is challenging because so little hard information is available. Parts-based synthetic biology, for example, is a new discipline that envisions the design and construction of novel microorganisms based on a "toolkit" of genetic parts (DNA segments) known as "BioBricks" that have been well characterized, have a standard interface, and behave in predictable ways. Eventually it may be possible to assemble these genetic elements like Lego blocks to create circuits and modules that can perform useful functions. So far, however, only small genetic circuits such as oscillators and switches have been created, and even these constructs are "noisy" and have unexpected

[1] Keith Grint and Steve Woolgar, *The Machine at Work: Technology, Work and Organization* (Cambridge: Polity Press, 1997).

properties. As much larger genetic constructs are assembled from hundreds of pieces of DNA with known functions, the components may begin to interact with one another in nonlinear and synergistic ways, possibly resulting in "emergent" properties that could pose safety hazards in ways that are impossible to predict in advance.[2]

Given these uncertainties, it is difficult to ascertain at an early stage of development what questions to ask about an emerging technology like parts-based synthetic biology, let alone what broader social values are at stake.[3] Denise Caruso argues that traditional probabilistic approaches to risk assessment are not suitable for new fields such as synthetic biology, which has no historical precedent other than by analogy. To assess such unprecedented risks, she advocates an approach that combines data analysis with a deliberative process that draws on a broad representation of relevant scientific expertise. This methodology involves the use of scenario narratives to develop risk models that are computable over time as hard scientific data become available. Caruso suggests that this approach can help government officials decide when existing regulations are suitable for emerging processes and products, and when they are inappropriate.[4]

David Guston and Daniel Sarewitz address the problem of uncertainty in assessing the risks of emerging technologies by calling for a system of "anticipatory governance" as an integral part of the research and development (R&D) cycle. In their view, the key to dealing with knowledge gaps when assessing risk is to create a process that is "continuously reflexive, so that the attributions of and relations between co-evolving components of the system become apparent, and informed incremental response is feasible."[5] Such a capability requires building a capability for "real-time technology assessment" into the R&D cycle, encouraging communication among potential stakeholders, and allowing for the modification of development paths and outcomes in response to the ongoing risk analysis.

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[2] Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," *The New Atlantis*, No. 12 (Spring 2006), pp. 25-45, http://www.thenewatlantis.com/archive/12/tuckerzilinskas.htm.
[3] National Research Council, Committee on Risk Characterization, *Understanding Risk: Informing Decisions in a Democratic Society* (Washington, DC: National Academy Press, 1996).
[4] Denise Caruso, *Synthetic Biology: An Overview and Recommendations for Anticipating and Addressing Emerging Risks* (Washington, DC: Center for American Progress, November 2008), p. 10.
[5] David H. Guston and Daniel Sarawitz, "Real-Time Technology Assessment," *Technology in Society*, vol. 24 (2002), p. 100.

Daniel Barben and his colleagues disaggregate the concept of anticipatory governance into three components: foresight, engagement, and integration. *Foresight* involves anticipating the implications of an emerging technology through methods such as forecasting, scenario development, and predictive modeling. *Engagement* entails public involvement that goes beyond opinion polls to include substantive "upstream" consultation with a variety of stakeholders, using vehicles such as museum exhibits, public forums, internet sites, and citizens' panels. *Integration* involves encouraging natural scientists to engage with societal issues as an integral part of their research.[6] Barben and his colleagues conclude that anticipatory governance "comprises the ability of a variety of lay and expert stakeholders, both individually and through an array of feedback mechanisms, to collectively imagine, critique, and thereby shape the issues presented by emerging technologies before they become reified in particular ways."[7]

M. Granger Morgan calls for engaging the public in the process of risk assessment. "Laypeople have different, broader definitions of risk, which in important respects can be more rational than the narrow ones used by experts," he writes. "Furthermore, risk management is, fundamentally, a question of values. In a democratic society, there is no acceptable way to make these choices without involving the citizens who will be affected by them." Morgan urges risk managers to allow ordinary citizens to become involved in the process in a significant and constructive way, working with experts and with adequate time and access to information.[8] Along similar lines, Richard Sclove has advocated that the United States adopt "participatory technology assessment" as practiced in Denmark, where it involves panels made up of ordinary citizens as well as substance-matter experts.[9]

In summary, the academic literature suggests that methods for assessing the safety and security risks of emerging technologies must be both flexible and capable of integrating information about ongoing developments as they unfold. The most effective

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[6] Daniel Barben, Erik Fisher, Cynthia Selin, and David H. Guston, "Anticipatory Governance of Nanotechnology: Foresight, Engagement, and Integration," in Edward J. Hackett, Olga Amsterdamska, Michael Lynch, and Judy Wajcman, eds., *The Handbook of Science and Technology Studies*, 3rd ed. (Cambridge, MA: MIT Press, 2007), pp. 979-1000.
[7] Ibid., pp. 992-993.
[8] M. Granger Morgan, "Risk Analysis and Management," *Scientific American*, July 1993, pp. 32-41.
[9] Richard Sclove, *Reinventing Technology Assessment: A 21st Century Model* (Washington, DC: Woodrow Wilson International Center for Scholars, April 2010).

way to achieve this objective is to incorporate an iterative process of technology assessment into the research and development cycle.

Risk Perception and Communication

A separate literature from risk assessment deals with "risk communication," which has been defined by the National Research Council as "an interactive process of exchange of information and opinion among individuals, groups, and institutions."[10] The field grew out of methods for estimating the risk to humans exposed to toxic materials, as well as research on how individuals perceive risk.[11] In the mid-1980s, risk communication was recognized as a key component of risk management and community decision-making in the fields of environmental and occupational health, including topics such as hazardous wastes, nuclear power plants, and toxic chemicals. Conflict resolution plays a key role in risk communication because the assessment of risks tends to be controversial. Indeed, community members, activists, government officials, scientists, and corporate executives often disagree about the nature, magnitude, or severity of the risk in question.[12]

Psychological research has also identified a set of mental strategies, or heuristics, that people use to make sense of an uncertain world. These rules often lead to large and permanent biases in risk perception that tend to be resistant to change. Chauncey Starr observed in 1969, for example, that the public accepts risks from voluntary activities such as skiing that are roughly 1,000 times as great as it will tolerate from involuntary hazards such as toxic pollution.[13] Paul Slovic notes that the public's perception of risk is not based on unidimensional statistics, such as the expected number of deaths or injuries per unit time, but acts as a surrogate for other social and ideological concerns. Risks that evoke a high level of "dread" elicit more calls for government regulation than familiar risks that actually cause a higher rate of death or injury. For example, the public tends to

[10] National Research Council, Committee on Risk Perception and Communication, *Improving Risk Communication* (Washington, DC: National Academy Press, 1989), p. 2.
[11] U.S. Public Health Service, "Risk Communication: Working with Individuals and Communities to Weigh the Odds," *Prevention Report*, February/March 1995.
[12] Ibid.
[13] Chauncey Starr, "Social benefit versus technological risk: What is our society willing to pay for safety?" *Science*, vol. 165, no. 3899 (September 19, 1969), pp. 1232−1238.

view the risks of nuclear power as unacceptably great because they are "unknown, dread, uncontrollable, inequitable, catastrophic, and likely to affect future generations."[14]

Building on Slovic's work, Jessica Stern notes that biological weapons fall into the category of "dread risks" because they possess characteristics (such as involuntary exposure, invisibility, and indiscriminate effects) that elicit a disproportionate level of fear, disgust, and horror. As a result, politicians and the public tend to overestimate the probability and consequences of bioterrorism compared to other, more likely threats.[15]. Thus, risk communication requires active outreach and engagement with the scientific community and the broader public, including an awareness of the psychology of risk.

Assessing the Risk of Deliberate Misuse

Assessing the dual-use risk of emerging technologies poses an even greater challenge than health and safety risks because deliberate misuse for hostile purposes depends as much on the intent and capabilities of the user as on the characteristics of the technology itself. Moreover, little empirical evidence is available to provide a solid basis for dual-use risk assessment. The number of cases of biological and chemical terrorism in the historical record is extremely small—a puzzling fact, given the supposed ease with which such attacks can be carried out.[16] As Gregory Koblentz has observed, this paradox suggests that few terrorist groups are motivated to conduct such attacks, that the capability to do so is harder than is generally assumed, or both. Also unclear is the importance of intangible factors such as tacit knowledge and intra-group dynamics for the ability of terrorists to build and utilize a biological or chemical weapon capable of causing mass casualties.[17]

Risk assessments of deliberate misuse must take into account the potential actors and their motivations, as well as the likely targets and scale of an attack. Moreover, in contrast to an unthinking act of nature, an intelligent actor can adapt and modify his

[14] Paul Slovic, "Perception of Risk," *Science*, vol. 236 (April 17, 1987), pp. 280-285.
[15] Jessica Stern, "Dreaded Risk and the Control of Biological Weapons," *International Security*, vol. 27, no. 3 (Winter 2002/03), pp. 89-123.
[16] For case studies of historical incidents of bioterrorism, see Jonathan B. Tucker, ed., *Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons* (Cambridge, MA: MIT Press, 2000).
[17] Gregory D. Koblentz, "Biosecurity Reconsidered: Calibrating Biological Threats and Responses," *International Security*, vol. 34, no. 4 (Spring 2010), p.131.

behavior in order to circumvent or neutralize defensive countermeasures.[18] Another key element in assessing the risk of deliberate misuse is the vulnerability of the potential targets, including (in the case of biological and chemical terrorism) the availability of effective medical countermeasures such as antidotes, vaccines, and therapeutic drugs. Some analysts have tried to operationalize the risk of deliberate misuse of a technology for hostile purposes by describing it as the product of threat, vulnerability, and consequences, where threat is the likelihood of an attack, vulnerability is the probability of its successful execution, and consequences are the losses that would result (fatalities, injuries, direct and indirect economic impacts, and so forth).[19]

Aside from the need for improved methods of risk assessment, it will always be difficult to calculate the odds that a specific individual or group will misuse a particular scientific discovery or a technological innovation for harmful purposes. Experts have rarely identified in advance a particular discovery or innovation in the life sciences that poses a high risk of misuse. For example, the National Research Council committee that prepared the influential 2004 report *Biotechnology Research in an Age of Terrorism* examined several cases of "contentious" research in the life sciences (such as the Australian mousepox experiment and the laboratory synthesis of poliovirus), yet the panel did not identify a single case in which the research was so security-sensitive that it should not have been published.[20] Of course, consensus among experts about individual cases is not necessarily a prerequisite for identifying dual-use research of concern. A better approach, Brian Rappert argues, is to examine the cumulative development of a dual-use technology and assess the extent to which incremental improvements in capability increase the potential for, and the consequences of, deliberate misuse.[21]

It may also be instructive to examine cases in which a dual-use technology has *not* been employed for hostile purposes in order to obtain insights into the motivational factors that may contribute to misuse. Examples of biotechnologies that appear to pose few if any dual-use concerns include fluorescent probes, gene chips, green fluorescent

[18] British Royal Society, *New Approaches to Biological Risk Assessment* (London, 2009), p. 11.
[19] Barry Charles Ezell, Steven P. Bennett, Detlof von Winterfeldt, John Sokolowski, and Andrew J. Collins, "Probabilistic Risk Analysis and Terrorism Risk," *Risk Analysis*, vol. 30, no. 4 (2010), p. 577.
[20] National Research Council, *Biotechnology Research in an Age of Terrorism* (Washington, DC: National Academies Press, 2004), pp. 24-29.
[21] Brian Rappert, "The Benefits, Risks, and Threats of Biotechnology," *Science and Public Policy*, vol. 35, no. 1 (February 2008), pp. 1-6.

protein, and the polymerase chain reaction (PCR), a widely used technique that can amplify any given DNA sequence several million-fold. PCR was developed in the early 1980s, yet no reports in the public domain indicate that states or terrorist groups have ever used PCR for hostile purposes. Although the Japanese doomsday cult Aum Shinrikyo actively sought to develop biological weapons and did possess a PCR machine, that piece of equipment apparently served only a ceremonial function. According to an account by Milton Leitenberg, "The Aum had invented a religious initiation rite utilizing the 'DNA and lymphocytes' of the group's leader, Shoko Asahara, which they introduced in January 1989. Asahara had asked Endo to find a method to replicate his 'DNA and lymphocytes,' and the purchase of the "DNA machine" [a PCR thermal cycler] was the result."[22]

The 14 contemporary case studies of emerging dual-use technologies included in this volume take a first cut at assessing the risk of deliberate misuse by aggregating several measurable parameters, which are introduced in Chapter 5. At the same time, the case study methodology recognizes the need for iterative risk assessment as technologies continue to evolve over time.

Explicit vs. Tacit Knowledge

Assessments of dual-use risk must take account of the fact that the use of sophisticated technologies normally requires an extensive support infrastructure, including state-of-the-art research facilities, funding, teamwork, and effective management.[23] Another key requirement is access to two types of knowledge, explicit and tacit. Explicit knowledge is information that can be codified and written down, such as a recipe or a laboratory protocol. In contrast, tacit knowledge involves skills and know-how that cannot be reduced to writing and must be acquired through hands-on practice and experience. Because tacit knowledge is not available from the published literature, technologies whose mastery demands a good deal of tacit knowledge will not diffuse as rapidly as those that are easily codified.

[22] Milton Leitenberg, "The Experience of the Japanese Aum Shinrikyo Group and Biological Agents," in *Hype or Reality: The "New Terrorism" and Mass Casualty Attacks*, Brad Roberts, ed. (Alexandria, VA: Chemical and Biological Arms Control Institute, 2000), pp. 159-172..

[23] Ralph Baric, "Synthetic Viral Genomics: Risk and Benefits for Science and Society," commissioned paper for the study *Synthetic Genomics: Options for Governance*, February 22, 2006, p. 24.

There are two subtypes of tacit knowledge, *personal* and *communal*. Personal tacit knowledge refers to skills acquired either by person-to-person transfer ("learning by example") or trial-and-error problem-solving ("learning by doing"). The amount of time required to acquire such knowledge depends on the complexity of a task and the level of skill needed to execute it.[24] Communal tacit knowledge is more complex because it resides in interdisciplinary teams of scientists made up of specialists from different fields. The tacit knowledge that resides in such teams is particularly difficult to acquire and transfer because of its important social dimension.[25]

The fact that many emerging dual-use technologies in the biological and chemical fields require personal and/or communal tacit knowledge impedes the ability of states or terrorist groups to exploit these technologies for harmful purposes. Chemical genome synthesis, for example, demands a high level of tacit knowledge and experience. In a case study of the laboratory synthesis of poliovirus, Kathleen Vogel found that the researchers did not rely exclusively on written protocols but made use of extensive tacit knowledge, particularly with respect to the preparation of the cell-free extracts needed to convert the synthetic viral genome into infectious virus particles.[26] Given these obstacles, Vogel calls into question the alarmist assumption that terrorists could easily exploit genome synthesis to recreate pathogenic viruses in the laboratory. The important role of tacit knowledge in many areas of biotechnology helps to explain the problems that scientists frequently encounter when attempting to move a technological innovation from the research bench to the commercial market. Based on her empirical research, Vogel concludes that biotechnology is a "*sociotechnical* assemblage," that is, an activity with interwoven technical and social dimensions.[27]

The same principle applies to the misuse of biotechnology for hostile purposes. In general, the development and production of a biological weapon requires communal tacit knowledge in the form of an interdisciplinary team of scientists and engineers who have

[24] Michael Polyani, *Personal Knowledge* (London: Routledge and Kegan Paul, 1958).
[25] Kathleen M. Vogel, "Bioweapons Proliferation: Where Science Studies and Public Policy Collide," *Social Studies of Science*, vol. 36, no. 5 (October 2006), pp. 659-690.
[26] Kathleen M. Vogel, "Framing Biosecurity: An Alternative to the Biotech Revolution Model?" *Science and Public Policy*, vol. 35, no. 1 (2008), pp. 45-54.
[27] Kathleen M. Vogel, "Biodefense: Considering the Sociotechnical Dimension," in Andrew Lakoff and Stephen J. Collier, eds., *Biosecurity Interventions: Global Health and Security in Question* (New York: Columbia University Press, 2008), pp. 240-241.

specialized knowledge and experience in a variety of fields, including microbiology, aerobiology, weaponization, formulation, and delivery. States are more likely to be capable of organizing and sustaining such a team than are non-state actors. In addition, empirical evidence from the study of terrorist organizations that have tried unsuccessfully to acquire biological or chemical weapons suggests that dysfunctional group dynamics can create obstacles to interdisciplinary collaboration.[28]

The De-skilling Agenda

Scholars who emphasize the importance of personal and communal tacit knowledge for the development and use of emerging dual-use technologies tend to downplay the risk that terrorists and other malicious actors could exploit these capabilities to cause significant harm. But other scholars disagree, noting that the evolution of many emerging technologies entails a process of "de-skilling" that reduces the amount of tacit knowledge required for their use. Christopher Chyba argues, for example, that as dual-use technologies such as genome synthesis become increasingly automated and "black-boxed," they will become more accessible to terrorists and criminals with basic scientific skills.[29] Along similar lines, Gerald Epstein notes that genetic-engineering techniques that a few decades ago were found only in sophisticated laboratories are now available in the form of kits and commercial services, making them accessible to individuals with limited scientific training and experience.[30]

Indeed, an explicit goal of synthetic-biology visionaries such as Drew Endy of Stanford University and Tom Knight of the Massachusetts Institute of Technology is to develop a "tool kit" of standardized biological parts called BioBricks—pieces of DNA with known coding and regulatory functions that behave in a predictable manner and can be assembled like Lego blocks into functional circuits and modules. At least in theory, the de-skilling of biological engineering, combined with the development of techniques to alter living systems using modular design, would significantly reduce the need for tacit

[28] Anthony Stahelski, "Terrorists are Made, Not Born: Creating Terrorists Using Social Psychological Conditioning," Journal of Homeland Security, March 2004, available online at: http://www.homelandsecurity.org/journal/Articles/stahelski.html

[29] Christopher F. Chyba, "Biotechnology and the Challenge to Arms Control," *Arms Control Today*, vol. 36, no. 8 (October 2006), pp. 11-17.

[30] Gerald Epstein, "The Challenges of Developing Synthetic Pathogens," *Bulletin of the Atomic Scientists* website, May 19, 2008.

knowledge. As Gautam Mukunda, Kenneth Oye, and Scott Mohr point out, "Synthetic biology includes, as a principal part of its agenda, a sustained, well-funded assault on the necessity of tacit knowledge in bioengineering and thus on one of the most important current barriers to the production of biological weapons. . . . Deskilling and modularity . . . have the potential to both rapidly increase the diffusion of skills and decrease the skill gradient separating elite practitioners from non-experts."[31]

Freeman Dyson has gone even further by envisioning a future in which synthetic biology has been "democratized" by amateur scientists who are motivated by curiosity and the joy of learning.[32] In fact, Dyson's vision is already beginning to materialize. In May 2008, a group of amateur biologists founded an organization called DIYbio ("do-it-yourself biology"), with the goal of using synthetic biology techniques to carry out personal projects.[33] Although the intent of many DIYbio practitioners appears benign, past experience with malicious computer hackers has raised concerns about the possible emergence of "biohackers" who seek to exploit synthetic biology for harmful purposes or engage in reckless experimentation.[34] According to Gaymon Bennett and his colleagues, "The good news is that open access biology, to the extent that it works, may help actualize the long-promised biotechnical future: growth of green industry, production of cheaper drugs, development of new biofuels and the like. The bad news, however, is that making biological engineering easier and available to many more players also makes it less predictable, raising the specter of unknown dangers."[35]

In order to move beyond anecdotal examples, more sociology-of-science research is needed on the nature of tacit knowledge and the processes by which certain emerging technologies become de-skilled. This task will require disaggregating specific technologies into their component parts and assessing the importance of tacit knowledge

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[31] Gautam Mukunda, Kenneth A. Oye, and Scott C. Mohr. "What rough beast? Synthetic biology, uncertainty, and the future of biosecurity," *Politics and the Life Sciences*, vol. 28, no. 2 (September 2009), pp. 14-15.
[32] Freeman Dyson, "Our Biotech Future," *New York Review of Books*, vol. 54, no. 12 (July 19, 2007), http://www.nybooks.com/articles/20370
[33] Marcus Wohlsen, "Amateurs Are Trying Genetic Engineering at Home," Associated Press, December 25, 2008; Carolyn Y. Johnson, "As Synthetic Biology Becomes Affordable, Amateur Labs Thrive," *Boston Globe*, September 16, 2008; Phil McKenna, "Rise of the Garage Genome Hackers," *New Scientist*, No. 2689 (January 7, 2009), pp. 20-21. See also, http://diybio.org/blog/
[34] Anonymous, "Hacking Goes Squishy," *Economist*, vol. 392, no. 8647 (September 5, 2009), pp. 30-31.
[35] Gaymon Bennett, Nils Gilman, Anthony Stavrianakis, and Paul Rabinow, "From Synthetic Biology to Biohacking: Are We Prepared?" *Nature Biotechnology*, vol. 27, no. 12 (December 2009), p. 1109.

for each element.[36] Preliminary evidence suggests that some technologies are more amenable to de-skilling than others. For example, scientists commonly use genetic-engineering "kits" containing all of the materials and reagents needed for a particular process to perform tedious or difficult laboratory procedures. Recent studies have shown, however, that these kits do not necessarily remove the need for tacit knowledge when applied in the context of a particular experiment.[37] In addition, analysts who contend that de-skilling is lowering barriers to the misuse of biotechnology for hostile purposes may be overestimating the risk because they focus on one or two steps in what is actually a complex, multi-step process. Practitioners of *de novo* viral synthesis, for example, point out that the most challenging steps are "downstream" of DNA synthesis, namely the assembly of dozens of DNA fragments into a functional genome, followed by the expression of the viral proteins. These operations remain more of an art than a science and demand extensive tacit knowledge.[38]

Developing an effective biological weapon also requires far more than simply acquiring a deadly viral pathogen from nature or synthesizing it from scratch. Additional steps include: (1) growing sufficient quantities of the virus to carry out an attack, without infecting oneself accidentally in the process, (2) processing the agent into a concentrated slurry or a dry powder with the appropriate particle size; (3) "formulating" the wet or dry agent with a mixture of chemical additives to extend its shelf-life and facilitate its dissemination as a windborne aerosol, and (4) devising an efficient delivery system. These downstream steps entail far greater technical hurdles than acquiring the agent itself.[39] Michael Levi has made a similar argument about the hypothetical ability of terrorists to construct an improvised nuclear device. He notes that the process involves a complex series of technical tasks, all of which the perpetrators must perform correctly in order to succeed.[40] Thus, when assessing the risk that gene synthesis could be misused to

[36] Kathleen Vogel contends that the role of tacit knowledge must be evaluated either through in-depth historical analysis based on archival research or through in-depth interviews with practicing scientists and ethnographies of laboratory work.
[37] Michael Lynch, "Protocols, Practices, and the Reproduction of Technique in Molecular Biology," *British Journal of Sociology*, vol. 53, no. 2 (June 2002), pp. 203-220.
[38] Baric,"Synthetic Viral Genomics."
[39] In the case of anthrax spores, which are inherently rugged and can persist for hours in aerosol form, the agent does not have to be formulated or weaponized but can be disseminated as is, albeit at some cost in efficacy.
[40] Michael A. Levi, *On Nuclear Terrorism* (Cambridge, MA: Harvard University Press, 2009).

create a biological weapon, one must break the problem down into its component steps and calculate the overall probability of success as the product of the individual probabilities of performing each of the intermediate steps correctly.

It is also important to disaggregate the risk of misuse by distinguishing among different types of perpetrators, who vary markedly in resources and technical know-how. Possible actors include states with advanced biowarfare programs, terrorist organizations of varying size and sophistication, and "lone-wolf" individuals motivated by ideology or personal grievance. Apart from the question of motivation, which is difficult to assess a priori, the task of developing a mass-casualty biological weapon would exceed the technical and financial resources of the vast majority of individuals and terrorist groups. It is far more likely, for example, that a state could recruit a multidisciplinary team with all of the relevant areas of expertise.

In rare cases, however, a scientist who is deeply familiar with a particular dual-use technology might conceivably decide—or be coerced—to exploit it for harmful purposes. According to the Federal Bureau of Investigation (FBI), the perpetrator of the 2001 anthrax letter attacks was Dr. Bruce E. Ivins, a leading anthrax researcher who worked at the U.S. Army's premier biodefense lab at Fort Detrick, Maryland, until his suicide in July 2008.[41] Although some continue to harbor doubts about Ivins' guilt, the case has prompted new concerns about lone-wolf terrorists and the "insider threat."

Approaches to Technology Governance

The prevalence in the technology-policy literature of the word "governance" reflects a paradigm shift from the earlier focus on "governing," or top-down efforts by the state to regulate the behavior of people and institutions. Governance includes a range of approaches to the management of technology that are not limited to top-down, command-and-control regulation. Jan Kooiman, for example, argues that responsibility for the oversight of new technologies is no longer based exclusively in the state but increasingly shared with the private sector and non-governmental organizations.[42] R.A.W. Rhodes notes that the various social actors engaged with emerging technologies

[41] U.S. Department of Justice, *Amerithrax Investigative Summary* (Washington, DC, February 19, 2010).
[42] Jan Kooiman, ed., *Modern Governance* (London: Sage Publishers, 1993).

exchange resources and negotiate shared purposes. Thus, while governing involves goal-directed interventions by the state, governance is the result of complex socio-political-administrative interactions.[43] The key actors in this process are (1) the scientists and engineers developing a new technology; (2) the policymakers and regulators involved in promoting innovation or in regulating its products; and (3) the citizens and advocacy groups that promote a technology or express concerns about its risks.

Gerry Stoker argues that a governance structure or order cannot be imposed in a top-down manner but arises from the interaction of multiple actors distributed across society.[44] When this interaction achieves a high level of mutual understanding and shared vision, it results in a "self-governing network" in which a coalition of actors and institutions coordinate their resources, skills, and purposes.[45] For a self-governing network to be sustainable over time, it must be capable of evolution, learning, and adaptation. The state may attempt to "steer" the network indirectly through facilitation, accommodation, and bargaining, an approach that Stoker terms "managed governance."[46]

A good example of managed governance was the creation by the National Institutes of Health of the *NIH Guidelines for Research involving Recombinant DNA Molecules*. This process began when concerns over the possible safety hazards of genetic engineering led the leading scientists in the field to impose a voluntary moratorium on the research. The relevant scientific community then organized the 1975 Asilomar Conference in Pacific Grove, California, where practitioners developed a set of voluntary biosafety rules for experiments involving recombinant DNA molecules. These rules were largely adopted by the NIH, which transformed them into a more formal set of biosafety guidelines for recipients of federal research grants. Over the next few decades, the *NIH Guidelines* went through a series of revisions in response to real-world experience with the technology and have been adopted by countries around the world. Thus, the evolution

[43] R. A. W. Rhodes, "The New Governance: Governing without Government," *Political Studies*, vol. 44, no. 4 (Sept. 1996), pp. 657, 660.
[44] Gerry Stoker, "Governance as Theory: Five Propositions," *International Social Science Journal*, vol. 50, no. 155 (1998), p. 17.
[45] Ibid., pp. 22-23.
[46] Ibid., p. 23-24.

of the *NIH Guidelines* remains an iconic example of self-governance by the scientific community, as well as managed governance by the state.[47]

In general, strategies to manage the risk of emerging dual-use technologies must seek out a delicate balance. Although inadequate regulation can result in harm to human health, the environment, or national security and undermine public confidence, excessive regulation can smother a promising technology in the cradle and thus deprive society of its benefits. Effective governance of emerging technologies is particularly challenging because it involves multiple stakeholders and the need to assess risks at an early stage of development, when scientific uncertainties are high. Joyce Tait has called for "appropriate risk governance," by which she means policies that *enable* technological innovation, *minimize* risk to people and the environment, and *balance* the interests and values of the relevant stakeholders. To achieve these goals, governance should be based as much as possible on evidence of harm, accommodate the values and interests of all affected societal groups, and maximize the scope for choice among a range of technology options.[48]

Another generic problem is to make sure that a governance mechanism, once established, is capable of adapting to rapid technological change. The challenge for policymakers is to create a system of "adaptive" governance that allows them to consider the risks and benefits of emerging technologies and respond flexibly to new developments. Achieving a sufficient level of flexibility usually requires an iterative process of technology assessment, meaning a cycle of data-gathering, evaluation, and rule modification as the technology evolves and the scientific understanding of its risks matures.[49] Unfortunately, institutional and legal hurdles, such as the bureaucratic requirements of the U.S. Administrative Procedures Act, tend to impede the establishment of adaptive governance mechanisms.[50]

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[47] Marcia Barinaga, "Asilomar Revisited: Lessons for Today?" *Science*, vol. 287, no. 5458 (March 3, 2000), pp. 1584-1585; Gregory A. Petsko, "An Asilomar Moment," *Genome Biology*, vol. 3, no. 10 (September 25, 2002), available online at: http://genomebiology.com/2002/3/10/comment1014.1

[48] Joyce Tait, "Systemic Interactions in Life Science Innovation," *Technology Analysis & Strategic Management*, vol. 19, no. 3 (May 2007), pp. 257-277.

[49] Gregory Mandel, "Nanotechnology Governance," *Alabama Law Review*, vol. 59 (2008), p. 1379.

[50] The Administrative Procedures Act (APA) mandates a complex and length process for revising final rules after they have been promulgated. First, the APA requires agencies to publish in the *Federal Register* a notice of proposed rulemaking that references the legal authority under which the rule is proposed and a description of the subjects and issues to be addressed by the proposed rule. Second, the APA instructs

One possible solution to this problem is to incorporate multiple options or contingencies into a regulation, thereby providing a degree of flexibility in its implementation. For example, both the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) have designed regulations that can be updated and corrected as new information becomes available. The EPA's National Ambient Air Quality Standards program has revised its air-quality standards for particulate matter several times after a systematic review of the latest health-effects information. Similarly, the FDA's post-marketing surveillance program tracks the adverse health effects of new drugs based on information collected after the drugs have been approved and marketed. Thus, both sets of regulations are able to accommodate new scientific findings and other knowledge into an iterative decision-making process.[51] The problem with applying this approach to emerging technologies is that it is almost always difficult to predict with any precision how a new technology will evolve and hence what regulatory options will be needed in the future. Another approach is to create an expedited process for making technical amendments so that the rules can be modified rapidly in response to new scientific evidence about risks and benefits.[52]

In biotechnology, there are often several alternative paths for achieving a given goal, and multiple ways of implementing each of these paths. Thus, if a regulation blocks one path but not the alternate routes, it may not be effective. Policymakers should therefore try to identify "chokepoints" or critical steps in the development or production of a technology at which control measures can be brought to bear, thereby providing a degree of leverage. If suitable chokepoints do not exist, effective regulatory options may not be available, regardless of their desirability.

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agencies to give the public an opportunity to submit comments on the proposed rulemaking, and the final rulemaking must address all significant comments. Finally, if affected parties believe a Federal regulatory agency has made an unlawful decision due to procedural and/or substantive error, they may seek a review of the decision in a disciplined process of judicial review under the APA. See Executive Office of the President, Office of Management and Budget, Office of Information and Regulatory Affairs, *Informing Regulatory Decisions: 2003 Report to Congress on the Costs and Benefits of Federal Regulations and Unfunded Mandates on State, Local, and Tribal Entities* (Washington, DC: U.S. Government Printing Office, 2003), pp. 52-53.

[51] Lawrence E. McCray, Kenneth A. Oye, and Arthur C. Petersen, "Planned adaptation in risk regulation: An initial survey of US environmental, health, and safety regulation," *Technological Forecasting and Social Change* , vol. 77, no. 6 (July 2010), pp. 951-959.

[52] Mandel, "Nanotechnology Governance," p. 1379.

Modes of Technology Governance

Current approaches to dual-use technology governance comprise a broad spectrum of measures, ranging from "hard-law" measures (mandatory, statute-based) at one end to "soft-law" measures (voluntary, non-binding) and "normative" measures (ethically based) at the other. (See **Figure 2-1**.) Examples of hard-law approaches include licensing, certification, civil liability, insurance, indemnification, testing, labeling, and oversight. Such regulations range from minimalist (such as the requirement to report a new technology prior to marketing it) to extremely stringent (such as the U.S. Food and Drug Administration's rules for pre-market testing and approval of pharmaceuticals). Soft-law mechanisms include voluntary guidelines and industry best practices, and normative measures include education and awareness programs, codes of conduct, and transparency measures. A related metaphor is a "web of prevention," made up of mutually reinforcing risk-management strategies at multiple levels, from the individual (e.g., codes of conduct) to the international (e.g., multilateral treaties).[53] (For a detailed discussion, see Chapter 3.) An important factor is how the governance process is framed. A strictly "top-down" approach brings with it the danger of excessive government control and limited connection to public concerns. Yet an excessive emphasis on "bottom-up" approaches may enable stakeholder groups to "hijack" the issue, resulting in a tenuous connection to actual decision-making.

Policy analysts disagree over the merits of formal, top-down regulation versus community self-regulation for the governance of emerging dual-use technologies. In the case of synthetic biology, for example, Stephen Maurer and Laurie Zoloth argue that voluntary guidelines have the advantage that they can be developed in months rather than years. Maurer and Zoloth also contend that consensus-based solutions are less disruptive and more likely to be respected by practitioners.[54] Other advocates of self-regulation claim that government intervention can have unintended harmful consequences. Robert Carlson, for example, argues that the top-down regulation of synthetic biology would foster a black market in synthetic DNA that would be harder to monitor and control than

[53] Jez Littlewood, "Managing the Biological Weapons Problem: From the Individual to the International," Commissioned Paper No. 14, WMD (Blix) Commission, August 2004, available online at http://www.wmdcommission.org.

[54] Stephen M. Maurer and Laurie Zoloth, "Synthesizing Biosecurity," *Bulletin of the Atomic Scientists*, vol. 63, no. 6 (November/December 2007), pp. 16-18.

the current unfettered market. "Our best potential defense against biological threats," he concludes, "is to create and maintain open networks of researchers at every level, thereby magnifying the number of eyes and ears keeping track of what is going on in the world."[55] Nevertheless, the transparency of private-sector activities cannot be assured because companies protect trade secrets to retain a competitive advantage.

Advocates of legally binding regulation argue that voluntary governance measures are inadequate because there is no guarantee that all of the relevant players will participate voluntarily. As a result, cheaters and free-riders will exploit a system that lacks formal sanctions for noncompliance. Another problem with self-governance is that scientists have a strong professional and intellectual interest in promoting and publishing their research, and they often lack the ability to assess its security implications.[56] Jan van Aken writes, for example, that "scientists hesitate to place any restrictions on each other's work and regard oversight mechanisms largely as a bureaucratic burden."[57] While this statement is perhaps exaggerated, it is clear that without buy-in and active participation by the affected community, formal regulations will not be effective. A cooperative rather than a coercive approach to governance is particularly important in a fast-moving field like synthetic biology, where regulation cannot keep pace with technological change.

Finally, it is widely assumed that scientists and companies view formal regulation as burdensome because it inevitably entails additional paperwork, unpaid mandates, and rigid performance standards. Nevertheless, the existence of rules that apply to all members of a given industry can be beneficial by creating a predictable framework for technology development and a level playing field for competition. Formal regulations also tend to build public confidence in an emerging technology, creating a favorable political environment for its adoption.[58] Because scientists and companies are aware of these advantages, they are rarely as anti-regulation as is generally assumed. Rather than opposing regulation in principle, they object instead to poorly informed or technically incompetent regulation.

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[55] Rob Carlson, "The Pace and Proliferation of Biological Technologies," *Biosecurity and Bioterrorism*, vol. 1, no. 3 (September 2003), pp. 203-214
[56] Parliamentary Office of Science and Technology, "The Dual-Use Dilemma," p. 3.
[57] Jan van Aken, "When Risk Outweighs Benefit," *EMBO Reports*, vol. 7 (Special Issue), 2006, p. S13.
[58] Merchant and Sylvester, "Transnational Models for Regulation of Nanotechnology," p. 715.

Hybrid Approaches to Governance

The choice between formal regulation and self-regulation is rarely clear-cut and in many cases the best solution may be a hybrid of the two approaches. Indeed, Filippa Lentzos calls the debate over "top-down" versus "bottom-up" governance a false dichotomy and advocates a multiplicity of approaches.[59] She identifies three different modes of regulation: *coercive*, *normative*, and *mimetic*. The coercive mode involves statutory regulations that draw upon the authority of the state and are accompanied by penalties for noncompliance. The normative mode is less formal and involves conceptions of what is socially desirable, along with behavioral standards such as codes of conduct and professional self-regulation. Finally, the mimetic mode involves the emulation of successful practices and models of behavior through peer observation and mentoring.[60]

Lentzos argues that for technology governance to be effective, the coercive mode must be integrated with the normative and mimetic modes. In addition, the relative importance of the three modes will vary depending on a particular technology's level of maturity as it moves through the research and development process. During the early stages of R&D, the normative and mimetic modes tend to predominate, but when a new technology approaches the market, the importance of coercive regulation increases.[61] In the case of synthetic biology, Gabrielle Samuel and colleagues contend that neither self-governance nor formal regulation alone is sufficient. Instead they favor either an independent oversight authority or a hybrid of institutional and governmental regulation to achieve an optimal balance between academic freedom and public safety.[62]

Normative measures implemented by the life sciences community (universities, medical and veterinary schools, trade associations, and biotechnology and pharmaceutical companies) also have an important role to play in mitigating the dual-use risks of biotechnology. According to the 2008 report of the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, biological scientists must

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[59] Filippa Lentzos, "Countering Misuse of Life Sciences through Regulatory Multiplicity," *Science and Public Policy*, vol. 35, no. 1 (Feb. 2008), p. 62.
[60] Ibid.
[61] Ibid., p. 64.
[62] Gabrielle N. Samuel, Michael J. Selgelid, and Ian Kerridge, "Managing the Unimaginable," *EMBO Reports*, vol. 10, no. 1 (2009), p. 9.

foster a "bottom-up effort to sensitize researchers to biosecurity issues and concerns, and to strive to design and conduct experiments in a way that minimizes safety and security risks."[63] To foster a culture of security awareness, a number of international organizations have launched their own biosecurity initiatives, including the International Criminal Police Organization (Interpol) and the Organization for Economic Cooperation and Development (OECD).

In implementing these governance measures, the timing of policy interventions is important. The early stages of research and development provide a window of opportunity to introduce new regulations before vested interests and sunk costs reinforce the status quo, yet early intervention may be problematic because political interest is low and little is known about the risks and benefits of the technology.[64] As Gerald Epstein has pointed out, the best time to introduce governance measures is during the brief period—if it exists—between "too early to tell" and "too late to change."[65]

International Governance Regimes

Mihail Roco writes that organizations and measures for technology governance are often "stove-piped" by area of jurisdiction, product or process, and level of interaction. Accordingly, an integrated approach, comprising both anticipatory and corrective measures, is needed for the governance of emerging technologies, particularly those with trans-border and global implications.[66] Commercial gene-synthesis providers, for example, are located not only in the United States, Europe, and Japan but also in China, India, and other emerging economies. For this reason, applying a regulatory framework selectively to a few countries would yield limited security benefits and might well be counterproductive by driving illicit users to unregulated suppliers. As biotechnology continues to globalize, harmonized governance must be implemented on

[63] Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, *World at Risk* (New York: Vintage Press, 2008).
[64] Mandel, "Nanotechnology Governance," p. 1378.
[65] Gerald L. Epstein, "The Challenges of Developing Synthetic Pathogens,' *Bulletin of the Atomic Scientists* website, May 19, 2008, http://www.thebulletin.org/web-edition/features/the-challenges-of-developing-synthetic-pathogens.
[66] Mihail Roco, "Possibilities for Global Governance of Converging Technologies," *Journal of Nanoparticle Research*, vol. 10, no. 1 (January 2008), pp. 11-29.

an international basis, either through outreach to the affected industry or the negotiation of guidelines under the auspices of the United Nations or some other multilateral body.[67]

Although the BWC and the CWC seek to prevent the misuse of biology and chemistry writ large for hostile purposes, treaties designed to manage the risks of specific technologies are rare. Chyba observes that the impediments "lie both in the mismatch between the rapid pace of technological change and the relative sluggishness of multilateral negotiation and verification, as well as the questionable suitability of monitoring and inspections with a widely available, small-scale technology."[68] Because formal international agreements take a great deal of time, effort, and political will to negotiate, they are normally pursued only for the most serious and urgent threats to health and security, such as global warming, nuclear proliferation, and persistent organic chemical pollutants. Gary Merchant and Douglas Sylvester discuss several alternatives to formal treaties for regulating dual-use technologies at the international level, including forums for transnational dialogue and information-sharing, civil society-based monitoring, international consensus standards, and confidence-building measures involving incremental steps to build trust in the context of an enduring dispute.[69] Informal international arrangements have also been developed for a few highly specialized areas of dual-use science and technology, such as oversight by the World Health Organization of research with live variola virus, the causative agent of smallpox.[70]

Traditional export controls on dual-use chemical and biological technologies are declining in effectiveness as these technologies become increasingly globalized and pervasive. Elizabeth Turpen argues that technology denial alone is no longer a viable strategy because the international trade in dual-use technologies has outpaced the ability of the United States and other like-minded countries to control access.[71] United Nations Security Council Resolution 1540 (April 2004), for example, seeks to prevent terrorist

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[67] Kendall Hoyt and Stephen G. Brooks, "A Double-Edged Sword: Globalization and Biosecurity," *International Security*, vol. 28, no. 3 (Winter 2003/04), pp. 123-148.
[68] Christopher F. Chyba, "Biotechnology and the Challenge to Arms Control," *Arms Control Today*, October 2006, http://www.armscontrol.org/act/2006_10/BioTechFeature.
[69] Gary E. Merchant and Douglas J. Sylvester, "Transnational Models for Regulation of Nanotechnology," *Journal of Law, Medicine and Ethics* (Winter 2006), pp. 715-723.
[70] Jonathan B. Tucker, "Preventing the Misuse of Biology: Lessons from the Oversight of Smallpox Virus Research," *International Security*, vol. 31, no. 2 (Fall 2006), pp. 116-150.
[71] Elizabeth Turpen, "Achieving Nonproliferation Goals: Moving from Denial to Technology Governance," *Policy Analysis Brief* (Muscatine, IA: Stanley Foundation, June 2009).

groups from acquiring nuclear, biological, or chemical weapons. In Turpen's view, implementing this resolution requires "a new grand bargain whereby the developing world gains access to critical technologies while being fully vested in a comprehensive nonproliferation and global control regime." Although state-level governance is crucial for achieving nonproliferation objectives, she notes that "industry and other nongovernment organizations must increasingly work in concert with governments to meet the burgeoning proliferation challenges."[72]

An example of effective self-governance at the international level has been the biosecurity regime established by the gene-synthesis industry. Two consortia of companies from the United States, Germany, and China have adopted voluntary guidelines for screening gene-synthesis orders sent in via the Internet to ensure that they do not contain pathogenic sequences, such as toxin genes and virulence factors. The industry developed these rules out of a sense of enlightened self-interest, and they were later reinforced by a set of similar guidelines developed by the U.S. government.[73] In some cases, however, competition among countries or firms seeking to extract unilateral economic advantage from an emerging technology may prevent them from cooperating to manage safety and security risks, resulting in lax or inconsistent standards or practices.[74]

Another approach to international technology governance, advocated by scholars such as Anne-Marie Slaughter, Jean-François Rischard, and Caroline Wagner, is the creation of informal "global issues networks." These networks link scientists in various parts of the world to each other, as well as to representatives of governments, non-governmental organizations, and the private sector. By generating an international consensus on specific issues, global issue networks can foster "rapid norm production" and pressure states to behave responsibly.[75] In the area of dual-use technologies, it may be possible to create a network of informed scientists, connected through the Internet,

[72] Ibid.
[73] Jonathan B. Tucker, "Double-Edged DNA: Preventing the Misuse of Gene Synthesis," *Issues in Science and Technology*, vol. 26, no. 3 (Spring 2010), pp. 23-32.
[74] Roco, "Possibilities for Global Governance."
[75] Caroline S. Wagner, *The New Invisible College: Science for Development* (Washington, DC: Brookings Institution Press, 2008); Anne-Marie Slaughter, *A New World Order* (Princeton, NJ: Princeton University Press, 2005); Jean- François Rischard, "Global Issue Networks," *Washington Quarterly*, vol. 26, no. 1 (Winter 2002-03), p. 17.

who recognize when knowledge or technology is being used inappropriately and report their concerns to national law-enforcement or intelligence agencies.[76]

Conclusion

This review of the scholarly literature suggests that a one-size-fits-all approach to managing the risk of misuse is not feasible, and that for each emerging technology, it is possible to identify a tailored package of governance measures—a mix of hard-law, soft-law, and normative options that provides a reasonable balance between risks and benefits and ensures an equitable distribution of both across the various stakeholders.[77] To that end, the book develops a consistent methodology for assessing dual-use risk and addressing the question of governance in a consistent manner across a wide variety of technologies.

[76] National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences*, pp. 251-256.
[77] Parliamentary Office of Science and Technology, "The Dual-Use Dilemma," p. 2.

Chapter 3: Dual-Use Governance Measures

Lori P. Knowles

As the previous chapter made clear, the governance of emerging dual-use technologies in the biological and chemical fields is a complex task. Many of these technologies are—or have the potential to be—beneficial for human health, biomedical research, industrial production, energy production, or environmental protection, making it necessary to balance these benefits against the need to prevent or limit the potential harm caused by deliberate misuse. Another characteristic of emerging dual-use technologies is that they evolve and converge in ways that are often unexpected.[1] A case in point is the new discipline of synthetic biology, which has emerged from two different convergences: of biology and chemistry, and of engineering principles and living systems.

The effective governance of dual-use technologies requires a multifaceted approach that includes three types of measures: hard law (treaties, statutes, and regulations), soft law (voluntary standards and guidelines), and normative measures (ethical norms such as professional codes of conduct). These three types of governance are not mutually exclusive. For example, voluntary standards and guidelines aimed at promoting biosafety and biosecurity can be bolstered by criminal laws or tort laws that impose penalties for breaches of legal standards or the harm caused by accidental or deliberate misuse.[2]

Recent trends in dual-use governance measures include an increased emphasis on criminal law, efforts at international harmonization, monitoring of dual-use scientific research, and attempts to create an ethics-based "culture of responsibility" in the life sciences. Employing a variety of governance tools creates a "web of prevention" that is

[1] National Academies of Science, Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, Workshop Report, An International Perspective on Advancing Technologies and Strategies for Managing Dual-Use Risks (Washington, DC: National Academies Press, 2005), pp. 57-71.
[2] Filippa Lentzos, "Countering Misuse of Life Sciences through Regulatory Multiplicity," Science and Public Policy, vol. 35, no. 1 (Feb 2008), pp. 55-64.

dynamic and adaptable.[3] Indeed, emerging technologies such as synthetic genomics require flexible governance strategies because the technology is evolving so rapidly that more rigid measures would soon become obsolete. This chapter reviews current technology governance measures at the international, regional, and national levels and assesses their effectiveness.

Arms Control and Disarmament Treaties

Arms control and disarmament treaties provide an important example of hard law at the international level. Such regimes seek to prevent the development, production, acquisition, deployment, and use of certain categories of weapons and technologies. Although international treaties have limitations, their importance in codifying and harmonizing international norms—sometimes through customary international law—cannot be overstated.[4] Indeed, in cases where penal sanctions do not exist or cannot be enforced, international norms with respect to the handling of dual-use technologies may provide an effective deterrent to misuse.

1925 Geneva Protocol

A foundational instrument of the international law of armed conflict is the Geneva Protocol of 1925, which bans the use in war of chemical and biological weapons.[5] Although the Hague Conventions of 1899 and 1907 had similar provisions, the Geneva Protocol was the first widely accepted prohibition on the military use of asphyxiating gases and bacteriological agents.[6] Still, the treaty had many weaknesses: it was limited to a ban on use and did not prevent states from continuing to develop and stockpile chemical and biological weapons, and it lacked verification and enforcement measures.

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[3] Brian Rappert and Caitriona McLeish, eds., Web of Prevention: Biological Weapons, Life Sciences, and the Governance of Research (London: Earthscan, 2007).
[4] Catherine Jefferson, "The Chemical and Biological Weapons Taboo: Nature, Norms and International Law," D.Phil. dissertation, University of Sussex, 2009.
[5] Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or other Gases and of Bacteriological Methods of Warfare [Geneva Protocol], 1925.
[6] Daniel H. Joyner, International Law and the Proliferation of Weapons of Mass Destruction (London: Oxford University Press, 2009) p. 88.

Moreover, many countries that ratified the Geneva Protocol reserved the right to retaliate in kind if they were attacked with chemical or biological weapons, in effect turning the treaty into a "no-first-use declaration."[7] Finally, because the Protocol was structured as a contract among the parties, it did not bind the participating states with respect to non-parties. (Today this structure is less of a weakness because the treaty has arguably risen to the status of customary international law, making it binding on all nations, whether or not they have formally ratified or acceded to it.)

A major impediment to U.S. ratification of the Geneva Protocol was a disagreement over whether or not the treaty bans the use in war of non-lethal chemicals, such as riot-control agents and defoliants. Contrary to the view of the large majority of member countries, the United States does not consider riot-control agents (such as CS tear gas) to be chemical weapons. Because of this controversy, Washington did not ratify the Geneva Protocol until 1975, at which time President Gerald Ford issued an Executive Order reserving the right to employ riot-control agents with presidential authorization "in defensive military modes to save lives," such as rescuing downed pilots behind enemy lines or when civilians are used to mask or screen attacks.[8] Today the debate continues because several states are interested in developing incapacitating or calmative agents for counterterrorism operations, which blur the line between law enforcement and warfare.[9]

1972 Biological Weapons Convention

During the Cold War, the Soviet Union and the United States engaged in a biological arms race until President Richard M. Nixon decided in 1969 to renounce the U.S. offensive biological weapons program and limit all further activity in this area to

[7] Nicholas Sims, "Legal Constraints on Biological Weapons," in Mark Wheelis, Lajos Rózsa, and Malcolm Dando, eds., Deadly Cultures: Biological Weapons since 1945 (Cambridge, MA: Harvard University Press, 2006), p. 330.
[8] President Gerald R. Ford, "Executive Order 11850—Renunciation of Certain Uses in War of Chemical Herbicides and Riot-Control Agents," April 8, 1975.
[9] William H. Boothby, Weapons and the Law of Armed Conflict (New York: Oxford University Press, 2009) pp. 135-139.

defensive research and development.[10] Nixon's decision, and Moscow's agreement in 1971 to pursue separate treaties to control biological and chemical arms, created a positive political climate for the negotiation of the Biological and Toxin Weapons Convention (BWC), which was concluded in 1972 and entered into force in March 1975.[11] The BWC built upon the Geneva Protocol by prohibiting the development, production, possession, and transfer of biological weapons and creating an obligation to destroy all existing stockpiles and production facilities.

At the same time, the dual-use nature of biological pathogens precluded the BWC from imposing a comprehensive ban on activities involving such materials.[12] Instead, the treaty's definition of a biological weapon is based largely on intent. Article I of the BWC prohibits "microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes." This purpose-based definition, known as the General Purpose Criterion, gets to the heart of the dual-use problem. Compliance with the BWC depends on how a member state uses a biological agent, in what quantities, and with what types of equipment. Yet because the treaty lacks formal declaration or inspection measures, there is no effective way to monitor, verify, or enforce compliance.

Although Article VI of the BWC empowers states to report suspected violations of the treaty to the United Nations Security Council for investigation, this provision has never been used because the permanent members of the Security Council can veto an inquiry. Indeed, confidence in BWC compliance was severely shaken when defectors revealed in the early 1990s that the Soviet Union had secretly maintained a vast biological warfare program in violation of its treaty commitments. In 1995, concern about the treaty's lack of formal verification measures led the member states to launch the

[10] Federation of American Scientists, Weapons of Mass Destruction, Biological Weapons, <http://www.fas.org/nuke/guide/usa/cbw/bw.htm>.
[11] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, April 10 1972.
[12] The BWC does not ban research, in part because of the difficulty of assessing whether or not it is being conducted for (illegal) offensive or peaceful purposes. Some commentators believe that research was excluded because a ban on offensive research would not be verifiable. See Nicholas Sims, "Banning Germ Weapons: Can the Treaty Be Strengthened?" *Armament & Disarmament Information Unit,* vol. 8, no. 5 (September-October 1986), pp. 2-3.

negotiation of a compliance protocol to the BWC that was designed to enhance transparency and deter violations. The talks lasted until summer 2001, when the United States rejected the draft protocol on the grounds that it would be ineffective at detecting violations and overly burdensome for the U.S. pharmaceutical and biotechnology industries. Whether or not effective verification is technically feasible remains at the heart of the ongoing debate about how best to strengthen the BWC.[13]

Despite the lack of a compliance protocol, efforts have continued to strengthen the Convention. Review conferences are held every five years to survey the operations of the treaty and assess the impact of advances in science and technology. Since 2002, the member states have also pursued an "intersessional work program" that consists of annual meetings of experts and diplomats to discuss topics related to BWC implementation and the prevention of bioterrorism, such as securing dangerous pathogens and creating codes of conduct for life scientists. The combination of the annual meetings and the five-year review conferences has helped to keep international attention focused on the biological disarmament regime. A major focus of efforts to strengthen the BWC has been on national implementation, including the adoption of penal legislation to make the treaty prohibitions binding on the citizens of each state party. UN Security Council Resolution 1540, adopted in 2004, also calls on all UN members—whether or not they are parties to the BWC—to adopt national measures to prevent bioterrorism and the proliferation of biological weapons-related materials.[14]

1993 Chemical Weapons Convention

A few years after the BWC was concluded, the UN Conference on Disarmament in Geneva launched what proved to be a quarter-century of negotiations on a separate treaty banning chemical arms. The Chemical Weapons Convention (CWC), which entered into force in April 1997, requires the declaration and destruction of all existing

[13] Nicholas A. Sims, "Toward the BWC Review Conference, Disarmament Still in the Doldrums" Disarmament Diplomacy, no. 82 (Spring 2006), available online at: <http://www.acronym.org.uk/dd/dd82/82ns.htm>

[14] United Nations Security Council Resolution 1540, April 28, 2004, <http://daccess-dds-ny.un.org/doc/UNDOC/GEN/N04/328/43/PDF/N0432843.pdf?OpenElement>.

chemical weapons stockpiles and prohibits any future development, production, stockpiling, transfer, and use of such weapons.[15] To avoid being overtaken by technological change, the CWC includes a broad, purpose-based definition of chemical weapons as "toxic chemicals and their precursors, except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes."[16] Non-prohibited uses of toxic chemicals include industrial, agricultural, research, medical, pharmaceutical, and other peaceful applications, the development of defenses against chemical and toxin weapons, and "law enforcement including domestic riot control."[17]

In contrast to the BWC, the CWC has extensive verification measures to monitor compliance with its provisions, including the declaration and routine inspection of chemical industry plants that produce dual-use chemicals. As a basis for routine verification, the treaty includes three lists (Schedules) of toxic chemicals and precursors in an Annex on Chemicals. The drafters of the CWC recognized that the Schedules were not comprehensive and would require periodic updating as science and technology evolved. In practice, however, the three Schedules have never been amended since the CWC entered into force in April 1997. The treaty also requires member states to pass domestic implementing legislation making the terms of the treaty binding on their citizens, both at home and abroad, and imposing penal sanctions for violations.

The organization responsible for implementing the international aspects of the CWC is the Organization for the Prohibitions of Chemical Weapons (OPCW) in The Hague. The OPCW has three main organs: the Technical Secretariat, which conducts inspections and helps member states to meet their treaty obligations; the Conference of the State Parties, a plenary body that meets annually to make policy decisions related to the CWC; and the 41-country Executive Council, responsible for carrying out the decisions of the Conference of the State Parties. The OPCW monitors advances in

[15] Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction (CWC), September 3, 1992, United Nations Treaty Series (1974), p. 317.
[16] CWC, Article II, paragraph 1(a).
[17] Ibid., Article II, paragraph 9.

science and technology relevant to the CWC through a Scientific Advisory Board, which can recommend updates to the Annex on Chemicals or improvements in verification technologies.

Together the Geneva Protocol, the BWC, and the CWC constitute the backbone of international law with respect to the governance of dual-use technologies in the chemical and biological fields. The three treaties not only embody important international norms against the use of toxic chemicals and disease as a method of warfare, but they have been augmented with national implementing legislation.

National Governance Measures

The legitimate use of biological and chemical agents entails both safety and security risks. Biosafety governance seeks to keep scientific personnel safe from accidental exposures to the hazardous biological agents they are working with, and to prevent risks to public health and the environment from the accidental escape of pathogens from the laboratory. Biosecurity measures, in contrast, seek to prevent the deliberate theft, diversion, and malicious release of pathogens for hostile purposes.[18]

Incidents of chemical and biological terrorism in Japan in 1994 and 1995, and the fall 2001 anthrax mailings in the United States, called attention to the need to expand biosecurity measures beyond nation-states to address threats from non-state actors, such as terrorist groups and "lone-wolf" individuals. This broadened threat perception has prompted efforts to augment the BWC and the CWC with domestic laws relating to dual-use exports, pathogen security, and the oversight of dual-use research in the life sciences.

U.S. Biosafety Governance

[18] BIOSAFETY-EUROPE CONSORTIUM, "Final Considerations: Coordination, harmonization and exchange of biosafety and biosecurity practices within a pan-European network," November 2008, <http://www.biosafety-europe.eu/FinalConsiderations_171208.pdf>; Foot and Mouth Disease 2007: A Review and Lessons Learned, HC 312 (London: The Stationery Office Ltd) November 11, 2008., <http://archive.cabinetoffice.gov.uk/fmdreview/documents/fmd_2007_review_full.pdf>; Biosecurity in Research Laboratories, HC 360-1 (London: The Stationery Office Ltd) June 25, 2008, p. 9. <http://www.publications.parliament.uk/pa/cm200708/cmselect/cmdius/360/360i.pdf>

The United States has a large number of laws, regulations, and guidelines pertaining to the safe handling of hazardous biological and chemical agents, including the Occupational Safety and Health Act of 1970, the Clean Air Act of 1970, and the Toxic Substances Control Act of 1976.[19] The U.S. Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) jointly publish a manual titled Biosafety in Microbiological and Biomedical Laboratories (BMBL), which sets out a graduated risk assessment and containment model for work with dangerous pathogens. The levels of precaution range from Biosafety Level 1, for research on microbes not known to cause human disease, to Biosafety Level 4, for research on dangerous and exotic agents that pose a high risk of life-threatening infection and person-to-person spread, and for which no vaccines or treatments are available. The four biosafety levels demand increasingly stringent measures for handling, containment, and disposal of biohazardous materials, as well as risk-management efforts involving equipment, facilities, and personnel.[20]

The BMBL is not legally binding on U.S. laboratories but serves as an advisory document that codifies best practices rather than prescriptive regulations. Laboratories are expected to adhere to the standards if they receive federal funds, although many commercial labs and private pharmaceutical firms adhere voluntarily because of liability concerns and the strict regulations associated with licensing and marketing of new drugs and vaccines.[21] Because the BMBL sets performance standards without prescribing the means to meet them, however, various U.S. institutions implement the guidelines in different ways and thus achieve inconsistent levels of biosafety.

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[19] Michael John Garcia, "Biological and Chemical Weapons: Criminal Sanctions and Federal Regulations," CRS Report for Congress (Washington, DC: Congressional Research Service, 2004).
[20] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, Biosafety in Microbiological and Biomedical Laboratories, 5th ed. (Washington, D.C.: U.S. Government Printing Office, 2007), <http://www.cdc.gov/OD/ohs/biosfty/bmbl5/BMBL_5th_Edition.pdf>.
[21] Amy E. Smithson, "Chapter 4: Considering US Proposals for Enhanced Biosafety, Biosecurity, and Research Oversight," Compliance through Science: U.S. Pharmaceutical Industry Experts on a Strengthened Bioweapons Nonproliferation Regime, Henry L. Stimson Center Report No. 48 (September 2002), p. 45. <http://www.stimson.org/cbw/pdf/CTS-Chapter4.pdf>.

Partially filling this legal gap is tort law under actions for negligence, for which the BMBL provides standards of reasonable (non-negligent) behavior. The plaintiffs in a negligence suit might use the accused party's failure to follow the biosafety guidelines to demonstrate that it exercised a lack of due care resulting in harm, potentially leading to a judgment for damages. In addition to civil liability for personal injury or loss, regulations pursuant to the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 require anyone who works with Select Agents (a list of more than 80 microbial pathogens and toxins of bioterrorism concern) to follow biosafety guidelines such as those in the BMBL.[22] By referencing the BMBL guidelines, the Act effectively makes them legally binding because a failure to comply could lead to a finding of civil or criminal liability.

Genetic engineering in the United States is governed by the *NIH Guidelines on Research involving Recombinant DNA Molecules*.[23] These guidelines specify safe laboratory practices and appropriate levels of physical and biological containment for basic and clinical research with recombinant DNA, including the creation and use of organisms containing foreign genes.[24] The NIH Guidelines classify research into four risk categories based on the pathogenicity of the agent in healthy adult humans, with increasingly stringent safety and oversight precautions.[25] Recent attempts have been made to harmonize the risk levels in the *NIH Guidelines* with the biosafety levels in the BMBL by cross-referencing them.[26]

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[22] Department of Health and Human Services, *Possession, Use and Transfer of Select Agents and Toxins*, 42 CFR Part 72 and 73.

[23] National Institutes of Health, NIH Guidelines for Research involving Recombinant DNA Molecules (NIH Guidelines), as amended, Federal Register, vol. 74, no.182, September 22, 2009. <http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm >.

[24] In 2009, in response to developments in synthetic biology, the NIH published proposed changes to the *Guidelines* that would extend coverage to molecules constructed outside living cells by joining pieces of synthetic DNA to DNA molecules that can replicate in a living cell.

[25] Julie Gage Palmer, "Government Regulation of Genetic Technology, and the Lessons Learned," in Lori P. Knowles and Gregory E. Kaebnick, eds. , Reprogenetics: Law, Policy, and Ethical Issues (Baltimore MD: Johns Hopkins University Press, 2007), pp. 20-63.

[26] Notice pertinent to the September 2009 revisions of the NIH Guidelines for Research involving Recombinant DNA Molecules, <http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm#_Toc7261555>.

Proposed experiments with recombinant DNA are reviewed at the local level by an Institutional Biosafety Committee (IBC), which assesses the potential harm that might occur to public health and the environment. Based on this risk assessment, the IBC determines the appropriate level of biocontainment, evaluates the adequacy of training, procedures, and facilities, and assesses the compliance of the investigator and the institution with the NIH Guidelines. The local IBC also reviews human gene transfers and the use of recombinant DNA in whole animals. For research proposals lacking a clear precedent, the IBC may refer the decision to a federal-level body called the Recombinant DNA Advisory Committee (RAC), which then develops appropriate guidelines, and in exceptional cases to the NIH Director. Depending on the level of risk associated with a proposed recombinant DNA experiment, a researcher or institution may be required to simply notify the local IBC, obtain approval from the IBC before starting work, or seek a combination of approvals from the IBC, the RAC, and the NIH Director. In principle, failure to comply with the *NIH Guidelines* may lead to the revocation of federal funding for recombinant DNA research projects.

A serious weakness of the U.S. biosafety system is that the source of the research funding—private or public—determines whether the rules are binding or advisory. Like the BMBL, the *NIH Guidelines* apply only to laboratories that receive federal funding for recombinant DNA research and to other institutions that accept the rules voluntarily. However, whereas the BMBL and *NIH Guidelines* serve as de facto research standards for all entities that conduct research with biological pathogens or recombinant DNA, some private institutions have chosen not to follow the rules in situations where they would have been desirable.[27] The U.S. approach differs from that of Canada, where the biosafety guidelines apply regardless of the source of funding and, when referenced by a regulation, acquire the status of hard law.[28] The value of this approach is that it ensures a

[27] Lori P. Knowles, "The Governance of Reprogenetic Technologies: International Models," in Knowles and Kaebnick, eds.., Reprogenetics, pp. 127-129.
[28] This is currently the case with the Human Pathogen Importation Regulations, SOR/94-558. The Public Health Agency of Canada is currently in the process of creating regulations to the new Human Pathogens and Toxins Act, S.C. 2009, c.24, and it is not clear which biosafety guidelines will be referenced.

level playing field, more consistent oversight, and greater assurance that all laboratories will comply with the guidelines.[29]

A separate set of local oversight bodies called Institutional Review Boards (IRBs) weigh the potential risks and benefits of human-subjects research and ensure that volunteers are given full informed consent. Whereas IBCs are based on the *NIH Guidelines*, IRBs were created by statute and are mandatory for institutions that receive federal research funding.[30] Both IBCs and IRBs are staffed by volunteers and have been criticized for their heavy workload and lack of expertise in key areas. The growing number of research protocols that raise complex biosafety and bioethical issues have strained the ability of some IBCs and IRBs to make careful, informed decisions.[31] Nevertheless, performing research oversight at the local level provides certain advantages over centralized or national oversight. In particular, local reviewers tend to have an institutional memory and valuable personal knowledge of the community and individuals. In addition to leveraging institutional expertise, the use of local review committees is more economical and less bureaucratic than creating a parallel oversight system. These efficiencies result in a more streamlined review process for research and impose fewer administrative burdens.

Biosafety standards have also been the object of international harmonization efforts by groups such as the World Health Organization[32] and the European Committee for Standardization (CEN).[33] In 2008, CEN created a system of biorisk management for

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[29] Knowles, "The Governance of Reprogenetic Technologies," pp. 127-143.
[30] U.S. Department of Health and Human Services, Protection of Human Subjects, 45 Code of Federal Regulations 46, revised July 14, 2009. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>.
[31] Tora K. Bikson, Ricky N. Blumenthal, Rick Eden, and Patrick P. Gunn, eds., Ethical Principles in Social-behavioral Research on Terrorism: Probing the Parameters, RAND Working Paper, WR-490-4-NSF/DOJ (January 2007), p. 119. <http://www.rand.org/pubs/working_papers/WR490-4/>; American Association for the Advancement of Science (AAAS), News Archives, "AAAS Meeting Explores Ways to Improve Ethics Panels that Oversee Social Science Research", October 7, 2008. <http://74.125.113.132/search?q=cache:vFjPLo-YCL0J:bakser.aaas.org/news/releases/2008/1007irb.shtml+lack+of+expertise+IRB+biosecurity&cd=1&hl=en&ct=clnk&gl=us&client=safari>.
[32] In 2004, the United States provided funding to the World Health Organization (WHO) to develop guidelines for laboratory biosecurity. This effort led to the WHO manual *Biorisk Management: Laboratory Biosecurity Guidance*, WHO/CDS/EPR/2006.6, 2006, <www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf>.
[33] European Committee for Standardization (CEN), "Laboratory Biorisk Management

laboratories that handle dangerous pathogens, including a scheme to certify laboratory compliance with the CEN standards and applicable national regulations. Each country that adopts the CEN standards is responsible for selecting its own certification method and agency. Although harmonized standards may require the use of specified equipment, which can be burdensome and expensive, the existence of common standards facilitates technology transfer and collaboration among legitimate researchers in the participating countries. Over time, the harmonization of biosafety standards can reduce costs and increase efficiencies through mutual recognition and reciprocity agreements.

U.S. Biosecurity Governance

The United States is a leader with respect to the extent and detail of its biosecurity legislation.[34] Shortly after the terrorist attacks of September 11, 2001 and the subsequent anthrax mailings, the U.S. Congress passed the Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (USA PATRIOT Act), which prohibits "restricted persons" from shipping, possessing, or receiving Select Agents and Toxins.[35] The definition of "restricted persons" includes citizens of countries on the State Department's list of state sponsors of terrorism, individuals with a criminal background or a history of mental instability or drug abuse, and persons connected with organizations suspected of domestic or international terrorism. The *USA PATRIOT Act* also criminalizes the possession of Select Agents in types or quantities that cannot be justified for prophylactic, protective, or peaceful purposes and makes it a federal crime for convicted felons, illegal aliens, or fugitives to possess or transport Select Agents in any quantity, for any reason. Although the Act is controversial in the way it balances national security and law enforcement needs against the protection of individual civil rights, it illustrates an important trend in biosecurity: the

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Standard," CEN Workshop Agreement 15793 (Brussels: CEN, 2008), <ftp://ftp.cenorm.be/PUBLIC/CWAs/wokrshop31/CWA15793.pdf>.

[34] Jonathan B. Tucker, "Preventing the Misuse of Pathogens: The Need for Global Biosecurity Standards," Arms Control Today, June 2003, <http://www.armscontrol.org/act/2003_06/tucker_june03>.

[35] Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (USA PATRIOT Act), Pub. L. No. 107-56, Oct. 12, 2001.

increasing use of criminal law as a tool in the fight against biological weapons proliferation and terrorism.[36]

The Department of Health and Human Services originally established the Select Agent Program under the Antiterrorism and Effective Death Penalty Act of 1996,[37] but the initial regulations covered only U.S. laboratories that transferred or received Select Agents and overlooked facilities that merely possessed or worked with such agents without transferring them. Congress later closed this loophole with a provision in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 that requires all institutions that possess, use, or transfer Select Agents that affect humans to register with and notify the CDC. [38] Entities that work with plant or animal pathogens on the Select Agent List must notify the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture.[39]

The cornerstone of the Select Agent Rules is the registration of institutions and personnel that use, possess, or transfer Select Agents. In addition, all persons who store, use, transfer, or receive Select Agents must undergo a "security risk assessment" by the Federal Bureau of Investigation (FBI) that includes fingerprinting and screening against terrorist and other databases. This vetting process aims to identify "restricted persons" and others who are legally denied access to Select Agents. Once registered, institutions and personnel are required to report any release, loss, theft, or accident involving Select Agents. The regulations also require that the Select Agent List be reviewed and updated every two years. Eventually, the list may be replaced by a system for specifying microbial pathogens and toxins based on DNA sequence rather than microbial species so that it can keep pace with rapid advances in biotechnology.

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[36] David P. Fidler and Lawrence O. Gostin, Biosecurity in the Global Age: Biological Weapons, Public Health and the Rule of Law (Stanford, CA: Stanford University Press, 2008), pp. 59-73.
[37] *The Antiterrorism and Effective Death Penalty Act of 1996*, Public Law No. 104-132, 110 Stat. 1214.
[38] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 42 U.S.C. §262a. CDC certifies facilities to receive and handle dangerous pathogens and toxins that affect humans (as regulated in 42 CFR 72 and 42 CFR 71 and 71.54).
[39] Agricultural Bioterrorism Protection Act of 2002, 7 U.S.C. §8401. APHIS oversees regulations regarding the importation of etiological agents of livestock, poultry, and other animal diseases and the federal plant pest regulations (respectively, see 9 CFR 92, 94, 95, 96, 122 and 130 and 7 CFR 330).

In recent years, biosecurity concerns have extended to certain areas of basic research in the life sciences that could yield dangerous bioengineered pathogens or knowledge with a potential for misuse. Because researchers, reviewers, funders, and publishers must be able to recognize "dual-use research of concern" (DURC) when they see it, a shared definition is essential. The National Science Advisory Board for Biosecurity (NSABB), a U.S. federal advisory committee, has defined DURC as "[r]esearch 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, agriculture, plants, animals, the environment, or material."[40]

The NSABB has recommended that IBCs be charged with the oversight of dual-use research, in addition to their current responsibility for ensuring the biosafety of recombinant DNA experiments.[41] If this path is taken, it will be necessary to develop a set of criteria for identifying DURC that can be applied consistently by different institutions. The National Research Council, for example, has identified seven types of "experiments of concern" that may warrant dual-use review, such as those aimed at rendering vaccines ineffective, impairing the immune system, or making a pathogen more virulent.[42]

Another element of biosecurity governance concerns possible restrictions on the publication of sensitive information. In 2003, the editors of several major scientific journals issued a joint statement calling for the review of security-sensitive research papers submitted for publication, with the default position favoring public release. In response to concerns over dual-use information, however, the editors could ask the

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[40] National Science Advisory Board for Biosecurity, Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information (Bethesda, MD: National Institutes of Health, June 2007), p. 17, <http://oba.od.nih.gov/biosecurity/pdf/Framework%20for%20transmittal%200807_Sept07.pdf>.

[41] U.S. Congress, Congressional Research Service, "Oversight of Dual-Use Biological Research: The National Science Advisory Board for Biosecurity," CRS RL 333-42, April 27, 2007., available at: <http://fas.org/sgp/crs/natsec/RL33342.pdf>.

[42] National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, Biotechnology Research in an Age of Terrorism, (Washington D.C.: National Academies Press, 2004), pp. 114-115. <http://www.nap.edu/catalog.php?record_id=10827>.

authors to modify an article, delay publication, or reject it entirely.[43] In 2004, an expert panel of the U.S. National Academies considered restrictions on the publication of certain pathogen genomes but ultimately decided not to endorse them.[44] A major problem with pre-publication security reviews is that it can be difficult to identify which research findings are associated with dual-use risks. Critics also argue that scientific freedom and access to information are crucial to technological innovation and that restricting publication would slow or hamper the development of medical countermeasures against biological threats.[45]

Export Control Regulations

Dual-use export controls are designed to prevent states seeking nuclear, biological, or chemical arms or that sponsor terrorism from obtaining access to relevant materials and equipment. The Australia Group (AG), for example, is an informal group of like-minded states, formed in 1985, that are in full compliance with the BWC and the CWC and work to harmonize their national export regulations on dual-use materials and technology related to chemical and biological weapons. Made up of more than 40 exporting countries, the AG has developed common control lists of chemical weapons precursors, biological pathogens and toxins, and dual-use chemical and biological production equipment.[46] Harmonized dual-use export controls imposed by like-minded states can help to slow proliferation while facilitating trade among legitimate users.

UN Security Council Resolution 1540 also obligates all UN member states to adopt and implement national legislation to prevent the proliferation of nuclear, chemical, or biological weapons and their means of delivery, particularly to terrorists. Countries

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[43] Journal Editors and Authors Group, "Statement on Scientific Publication and National Security," Science, vol. 299 (February 21, 2003), p. 1149.
[44] National Research Council, Committee on Genomics Databases for Bioterrorism Threat Agents, Seeking Security: Pathogens, Open Access, and Genome Databases, (Washington, DC.: National Academies Press, 2004).
[45] U.S. National Academies, Committee on a New Government-University Partnership for Science and Security, Science and Security in a Post 9/11 World: A Report Based on Regional Discussions between the Science and Security Communities, (Washington, DC: National Academies Press, 2007) <http://www.nap.edu/catalog/12013.html>.
[46] Australia Group, <http://www.australiagroup.net/en/index.html>.

must do so by establishing "appropriate [export] controls over related materials" and by passing laws that prohibit efforts by "non-states to manufacture, acquire, possess, develop, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery, in particular for terrorist purposes."[47] The legislative details are left to the individual states.

Although export controls are an important tool of dual-use governance, they suffer from a number of weaknesses. First, their effectiveness depend on exporters' knowing when they must obtain an export license. Second, monitoring, enforcement, and sanctions are key and require considerable investment by governments. Third, export controls must be harmonized internationally because the alternative is "an uneven patchwork of regulations, creating pockets of lax implementation or enforcement."[48]

U.S. export controls on dual-use items and materials have been promulgated pursuant to several laws, including the USA PATRIOT Act of 2001, the Homeland Security Act of 2002,[49] and the Export Administration Act of 1979.[50] The Commerce Control List (CCL), established by Part 738 of the Export Administration Regulations (EAR), specifies the combinations of dual-use goods and destinations for which an exporter must obtain a license. The CCL also provides "Reasons for Control" for each item, ranging from counterterrorism and crime prevention to national security and regional stability. Under the EAR, an exporter must obtain a license from the Department of Commerce's Bureau of Industry and Security (BIS), which enters all license information into a database. Other rules govern transfers of sensitive information to foreign nationals within the United States, which are referred to as "deemed exports."[51]

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[47] UN Security Council Resolution 1540 of April 28, 2004, <http://daccess-dds-ny.un.org/doc/UNDOC/GEN/N04/328/43/PDF/N0432843.pdf?OpenElement>.
[48] Jonathan B. Tucker, "Strategies to Prevent Bioterrorism: Biosecurity Policies in the United States and Germany," Disarmament Diplomacy, no. 84 (Spring 2007), <http://www.acronym.org.uk/dd/dd84/84jt.htm>.
[49] Homeland Security Act of 2002, Pub. L. 107-296, November 25, 2002.
[50] The Export Administration Act of 1979 lapsed in August 2001 and has not been renewed by Congress. However, the Export Administration Regulations have remained in effect under Executive Order 13222 issued on August 17, 2001 pursuant to the International Emergency Economic Powers Act and extended annually by the President.
[51] Export Administration Regulations §734.2(b)(2)(ii).

According to the EAR, the Department of Homeland Security's Customs and Border Protection (CBP) agency is responsible for ensuring that licensable exports from U.S. ports comply with non-proliferation export controls.[52] For a number of reasons, however, the U.S. export system is more porous than it might seem.[53] Greater industry awareness of dual-use export requirements, coupled with more advanced information-sharing systems, would facilitate enforcement efforts.

Biosafety and Biosecurity in the European Union

Despite European leadership in promoting the norms embedded in the BWC and the CWC, efforts are still needed to strengthen and reinforce those norms through biosecurity governance at the regional and national levels. In contrast to the United States, where biosafety and biosecurity have been developed on separate tracks, the European Union (EU) has pursued both forms of governance in tandem.

In general, the EU has been less preoccupied than the United States with the threat of bioterrorism compared to other biological risks.[54] For example, European concerns over food safety are high because of controversies over genetically modified foods, incidents of food contamination, and outbreaks of BSE (mad cow disease) and its human variant in the United Kingdom. This backdrop has made the Europeans more skeptical about the genetic manipulation of biological organisms and assurances of safety from developers and regulators. Another factor influencing biosafety governance in Europe has been the EU's embrace of the "precautionary principle," which promotes a cautious approach to uncertain risks by requiring proof that serious hazards will either not materialize or can be controlled before a technology is approved for broad release.

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[52] Authority of the Office of Export Enforcement, the Bureau of Industry and Security, Customs offices and Postmasters in clearing shipments, 15 C.F.R. Part 758.7

[53] Office of Inspector General, Department of Homeland Security, Review of the Controls over the Export of Chemical and Biological Commodities, < http://www.dhs.gov/xoig/assets/mgmtrpts/ OIGr_05-21_Jun05.pdf>.

[54] See Alexander Kelle, "Synthetic Biology & Biosecurity Awareness in Europe," Bradford Science and Technology Report, no. 9 (November 2007), citing Markus Schmidt, p. 9, <http://www.synbiosafe.eu/uploads///pdf/Synbiosafe-Biosecurity_awareness_in_Europe_Kelle.pdf>

A number of EU directives on biosafety provide guidelines for national implementation by member states. For example, EU Directive 2000/54/EC of September 18, 2000 sets out a legislative framework for protecting workers from risks related to occupational exposures to biological agents.[55] The directive includes a list of animal and human pathogens (but not genetically modified organisms), provides a model for risk assessment and biocontainment, and outlines employer obligations for worker safety and reporting. Individual EU countries have also adopted their own biosafety regulations, most of which involve lists of pathogens, risk assessment methods, and four biocontainment levels of increasing stringency. In recent years, the EU has made export-control legislation a focal area of biosecurity governance and has also participated in interdiction exercises and actual operations coordinated by the U.S.-led Proliferation Security Initiative.[56]

In recent years, a series of terrorist attacks, including the transportation bombings in Madrid in 2004 and in London in 2005, have caused the EU countries to become more concerned about biosecurity threats emanating from non-state actors. As McLeish and Nightingale observe, "The increased perception of threat from bioterrorists and the diffusion of dual-use biological technologies has meant that non-state actors are now seen as both sources of threat and as sources of technological capabilities. As a result, the regime has evolved and governments are now . . . introducing new controls on people, experiments and the flow of information, technology and materials."[57]

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[55] Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC), *Official Journal* L 262 , 17 October 2000, pp. 21-45.<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32000L0054:EN:HTML>.

[56] Launched in 2003 and spearheaded by the United States, the Proliferation Security Initiative is a global effort to interdict trafficking in WMD, their delivery systems, and related materials to and from states and non-state actors of proliferation concern. See U.S. Department of State, "Proliferation Security Initiative," <http://www.state.gov/t/isn/c10390.htm>.

[57] Caitríona McLeish and Paul Nightingale, "Biosecurity, bioterrorism and the governance of science: The increasing convergence of science and security policy," Research Policy, vol. 36 (2007), p. 1640 <http://www.steps-centre.org/PDFs/biosecurityresearchpolicy_PN.pdf>.

In response to UN Security Council Resolution 1540, the EU adopted Regulation 428/2009 in August 2009.[58] This regulation creates lists of controlled goods that are subject to export restrictions and licensing, including dual-use biological and chemical materials and production equipment, and restricts the brokering and transit of such goods through EU territory. Member countries are legally bound to incorporate the EU regulation into their national law, although they are free to adopt export controls that are stricter than the EU standard. The national export controls of EU member states are also harmonized by the Australia Group and other multilateral export control regimes, such as the Nuclear Suppliers Group and the Wassenaar Arrangement.

The EU customs security program, adopted in 2006, aims to create a harmonized customs system that can identify hazardous goods entering EU territory.[59] This system seeks to identify illicit shipments by requiring companies to submit information on exports prior to their arrival; it also includes an EU-wide secure electronic system for exchanging risk information. By creating one of the largest systems in the world for monitoring the dual-use goods leaving its territory, the EU will remove impediments to trade in such items among its member states. Although the tightening of European customs regulations promises to enhance security in a region that has many borders and ports, effective implementation of the new system will require the adoption of common standards and the investment of substantial financial resources.

Biosafety Governance in the United Kingdom

Like other EU member states, the United Kingdom seeks to minimize the harm caused by accidental releases of pathogens and chemicals. The Health and Safety at Work etc Act 1974[60] and the Biological Agents and Genetically Modified Organisms (Contained Use) Regulations are the main statutes covering pathogens and genetically

[58] Council Regulation (EC) No 428/2009 of 5 May 2009 setting up a Community regime for the control of exports, transfer, brokering and transit of dual-use items, Official Journal L 134/1, 29/05/2009. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:134:0001:0269:en:PDF>.
[59] Regulation (EC) No. 648/2005 of the European Parliament and the Council of 13 April 2005 amending Council Regulation (EEC) No 2913/92 establishing the Community Customs Code.
[60] Health and Safety at Work etc Act 1974, c.37, available at <http://www.hse.gov.uk/legislation/hswa.pdf>.

modified microorganisms. A new version of the regulations went into effect in April 2011, updating the earlier version from 2000.[61] The revised regulations create a risk-assessment framework of four hazard groups, depending on a pathogen's ability to infect humans and cause disease. A similar set of regulations for toxic chemicals, called the Control of Substances Hazardous to Health Regulations 2002[62], are designed to assess and manage the risk of exposure in the workplace.

The governing body responsible for implementing these regulations is the Health and Safety Executive (HSE), a quasi-autonomous non-governmental organization ("quango") that was created by statute but has devolved powers, along with its own staff and budget. Although the HSE reports upward to the Minister of Health, it operates at arm's length from the British government, insulating it from political pressure and partisan policies. The HSE's Advisory Committee on Dangerous Pathogens (ADCP) is responsible for the classification of hazardous biological agents and publishes an Approved List of Biological Agents.[63] Listed pathogens are normally classified according to hazard group and the corresponding level of biocontainment. In some cases, however, the risks of a proposed experiment are assessed on a case-by-case basis to allow for additional variables, such as the quantity and intended use of the pathogen in question. Another regulatory body, the Scientific Advisory Committee on Genetically Modified Organisms, provides technical and scientific advice on the human and environmental risks associated with the contained use of GMOs.

The British biosafety regime is built on a system of notifications, inspections, acknowledgements, and enforcement. A research institution that intends to handle a listed pathogen or a GMO must notify the HSE before launching an experiment. Depending on the risk category of the agent, the HSE may require an inspection before allowing the work to begin. The agency's Biological Agents Unit employs experienced inspectors to

[61] Genetically Modified Organisms (Contained Use) Regulations 2000, as amended, S.I. 2000, no. 2831, November 15, 2000, available at <http://www.opsi.gov.uk/si/si2000/20002831.htm>.
[62] The Control of Substances Hazardous to Health Regulations 2002, S.I. 2002, no.2677, November 21, 2002, available at <http://www.opsi.gov.uk/SI/si2002/20022677.htm#1>.
[63] Health and Safety Executive, Advisory Committee on Dangerous Pathogens, Approved List of Biological Agents, <http://www.hse.gov.uk/PUBNS/misc208.pdf>.

review notifications and applications and visit laboratories that are working with potentially dangerous pathogens and GMOs.[64] Because of the non-governmental status of the HSE, regulators can exercise a degree of discretion and work closely with the regulated institutions to ensure a safe working environment.[65]

The United Kingdom experienced devastating outbreaks of Foot and Mouth Disease (FMD) in livestock in 2001 and 2007, resulting in severe economic losses and the mass slaughter of animals. Investigators later traced the strain of FMD virus involved in the 2007 outbreak to a faulty drainage pipe at a British government laboratory, the Institute for Animal Health (IAH) in Pirbright, England. The evidence that the outbreak had originated at Pirbright came as a shock both to the government and the general public. An inquiry into the incident led by Dr. Iain Anderson found serious breaches of the biosafety regulations and concluded that "the facilities of IAH fall well short of internationally recognized standards. . . . There have been many warning signs that all was not well at Pirbright."[66]

The FMD outbreak has since led to a number of reforms. Sir Bill Callaghan chaired a committee that conducted a comprehensive review of the regulatory framework for handling animal pathogens. The resulting report recommended creating a single set of biosafety rules for work with human and animal pathogens, including those that have been genetically modified.[67] The Callaghan report also recommended that the HSE be made the regulatory body for both human and animal pathogens, with responsibility for inspections and enforcement.[68] In the new, reformed regulatory system, the ACDP will

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[64] Filippa Lentzos, "Regulating Biorisks: Developing a Coherent Policy Logic (Part II)," Biosecurity and Bioterrorism, vol. 5, no. 1 (2007), pp. 55-61.
[65] Lentzos, "Regulating Biorisks," pp. 59-61.
[66] Dr. Iain Anderson, chair, Foot and Mouth Disease 2007: A Review and Lessons Learned, HC 312, (London: The Stationery Office Ltd), November 11, 2008, p. 19 <http://archive.cabinetoffice.gov.uk/fmdreview/documents/fmd_2007_review_full.pdf>
[67] Sir Bill Callaghan, chair, "A Review of the Regulatory Framework for Handling Animal Pathogens," presented to the Secretary of State for Environment, Food and Rural Affairs, December 13, 2007, <http://www.defra.gov.uk/animalh/diseases/fmd/pdf/callaghan-reviewreport071213.pdf>.
[68] Health and Safety Executive, "Implementing Sir Bill Callaghan's recommendations for a single regulatory framework for handling human and animal pathogens and GMOs," <http://www.hse.gov.uk/biosafety/callaghan.htm>.

be responsible for preparing a centralized set of containment guidelines for both human and animal pathogens.[69]

To the extent that biosecurity concerns are not already covered by the biosafety regulations, they are chiefly the responsibility of the Home Office through provisions in the *Anti-Terrorism, Crime and Security Act 2001* pertaining to the security of human and animal pathogens and toxins.[70] Schedule 5 of this Act creates a list of human pathogens and toxins that was amended in May 2007 to include animal pathogens. The use or storage of the listed agents may require the notification of, and inspection by, the Secretary of State. The *Anti-Terrorism Act* also requires that information about persons granted access to dangerous substances be supplied if requested. In conjunction with the Home Office, the agency responsible for overseeing Schedule 5 pathogens is a specialized police organization called the National Counter-Terrorism Security Office. This office issues guidelines for physical and personnel security at laboratories that handle listed pathogens.[71] In addition, the Civil Contingencies Act 2004 empowers local emergency responders to act in a biological emergency, which could range from a natural outbreak of an animal disease to an act of bioterrorism.

Security checks for personnel working with biological pathogens and toxins are not centralized in the United Kingdom as they are in the United States.[72] The Academic Technology Approval Scheme, operated by the Foreign and Commonwealth Office, subjects all foreign students who work in sensitive fields to security screening before they can apply for a visa to study in Britain.[73] This vetting system seeks to balance the need to prevent the proliferation of dual-use knowledge against the goal of fostering a global

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[69] The Department of the Environment, Food and Rural Affairs (Defra), the British government agency that oversees animal research, grants licenses to laboratories seeking to store, handle, and transfer certain animal pathogens under the Specified Animal Pathogens Orders of England, Scotland, and Wales.
[70] Antiterrorism, Crime and Security Act of 2001, c. 24, Part 7, Schedule 5. <http://www.opsi.gov.uk/acts/acts2001/ukpga_20010024_en_18#sch5>.
[71] National Counter Terrorism Security Office, "Security of Pathogens and Toxins," <http://www.nactso.gov.uk/pathogens.php>.
[72] For a good discussion of security screening at UK universities, see McLeish and Nightingale, "Biosecurity, bioterrorism and the governance of science," p. 1641.
[73] House of Commons, Foreign Affairs Committee, Fourth Report of Session 2008-09, Global Security: Non-Proliferation, June 14, 2009, Evidence, pp. 261-263. A similar U.S. system, called Visa Mantis, reviews foreign student applications and research proposals.

science commons through the free flow of students and researchers between countries and institutions.

Soft-Law and Normative Measures

The previous sections have illustrated that one of the leading trends in the governance of dual-use technologies is to reinforce international treaties with national biosafety and biosecurity measures implemented through national legislation. A complementary set of governance tools is based on "soft-law" measures, such as voluntary guidelines and self-governance mechanisms. For such measures to succeed at controlling dual-use risks, however, there must be a community of practitioners to which individuals can self-identify.

A profession is a "legally-mandated association granted a monopoly over specialized practices" that is both state-regulated and self-governed because it requires a license and a certain level of knowledge or skill to join.[74] The state grants each profession certain powers of self-governance, which are intended to align the expertise of its practitioners with the public good. The value of professionalism as a mode of governance lies in its ability to bridge science and public values. Although virologists have a sense of professional identity, that is not the case for researchers working in less specialized fields such as nanotechnology, medical research, chemistry, or engineering. The fact that dual-use biological and chemical technologies are so diverse means that no one group can form the basis of a professional ethos. This lack of group identity makes professionalization ineffective as a governance scheme for dual-use technologies writ large.

In addition to soft-law measures to prevent misuse such as voluntary guidelines, a number of normative measures are directed mainly at individuals, such as awareness-raising programs for practicing scientists and professional codes of conduct. Normative measures augment legally binding controls on materials and equipment through a focus

[74] Laura Weir and Michael J. Selgelid, "Professionalization as Governance Strategy for Synthetic Biology," Systems and Synthetic Biology, vol. 3 (2009) pp. 91-97.

on the people who use them.[75] Such people-centric governance measures reflect the recognition that individuals are ultimately responsible for accidents and deliberate misuse. The International Union of Microbiological Societies[76], following the lead of the American Society for Microbiology[77], has issued a code of ethics for its members that prohibits the development of biological weapons. International organizations such as the United Nations Educational, Scientific and Cultural Organization (UNESCO) have also studied and recommended the use of ethical codes.[78] Nevertheless, the codes of conduct developed by various scientific societies and international organizations have not yet been integrated into scientific education, professional development, or certification requirements.[79]

In the absence of a self-regulatory scheme based on professional identity, ethics education can help to create a culture of responsibility in the life sciences. In 2009, the Federation of American Societies for Experimental Biology (FASEB) issued a statement that "scientists who are educated about the potential dual-use nature of their research will be more mindful of the necessary security controls which strike the balance between preserving public trust and allowing highly beneficial research to continue."[80] Surveys indicate, however, that many life-science researchers lack an awareness of dual-use concerns, including the risk of misuse associated with their own work.[81] Overcoming this deficit will require a commitment to ethics education for all science and engineering students, as well as training in identifying and managing dual-use risks. This task is

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[75] Interacademy Panel on International Issues, Statement on Biosecurity, November 7, 2005, available online at: <http://www.interacademies.net/Object.File/Master/5/399/Biosecurity%20St..pdf>.
[76] International Union of Microbiological Societies, *Code of Ethics against Misuse of Scientific Knowledge: Research and Resources*, http://www.iums.org/about/Codeethics.html.
[77] American Society for Microbiology, *Code of Ethics*, revised and approved by the Council, 2005, http://www.asm.org/ccLibraryFiles/FILENAME/000000001596/ASMCodeofEthics05.pdf
[78] See, for example, the work of the World Commission on the Ethics of Scientific Knowledge and Technology, http://portal.unesco.org/shs/en/ev.php-URL_ID=10157&URL_DO=DO_TOPIC&URL_SECTION=201.html
[79] Brian Rappert, Marie Chevrier, and Malcolm Dando, "In-depth Implementation of the BTWC: Education and Outreach," http://www.brad.ac.uk/acad/sbtwc/briefing/RCP_18.pdf.
[80]Federation of American Societies for Experimental Biology, *Statement on Dual Use Education*, http://www.faseb.org/portals/0/pdfs/opa/2009/FASEB_Statement_on_Dual_Use_Education.pdf.
[81] Malcolm R. Dando, "Dual-Use Education for Life Scientists," Disarmament Forum: Ideas for Peace and Security, no. 2, (2009), pp. 41-44.

daunting, however, because of the difficulty of defining dual-use and the lack of experts in the field.[82]

Perhaps the most difficult step in teaching ethics and awareness to those who work with dual-use technologies is to inculcate a sense of personal responsibility. Although medical students are bound by the Hippocratic Oath to "do no harm," science is often presented as a search for objective truth that it is value-neutral and unconstrained by ethical norms. In fact, this belief is neither true nor defensible. As the InterAcademy Panel on International Issues has observed, "Scientists have an obligation to do no harm. They should always take into consideration the reasonably foreseeable consequences of their own activities. They should therefore: always bear in mind the potential consequences—possibly harmful—of their research and recognize that individual good conscience does not justify ignoring the possible misuse of their scientific endeavor."[83]

To help contain dual-use risks, ethics education must be coupled with mechanisms for reporting risks once they have been identified. When a student or researcher suspects that a colleague is misusing a technology for harmful purposes, there should be a confidential channel for passing this information to law enforcement so that it can be acted upon. Although medical students in the United States, Canada, Australia, and Europe are trained in professional ethics, it remains unclear how to motivate them to identify and report ethical breaches in view of the hierarchical culture prevailing in laboratories and medical schools.

Conclusions

The governance of dual-use biological and chemical technologies is grounded in international treaties such as the BWC and the CWC, which prohibit the use of these technologies for hostile purposes. Informal forums of like-minded states, such as the Australia Group, have also bolstered the nonproliferation regime by harmonizing national export controls on dual-use materials and technologies relevant to biological and

[82] National Science Advisory Board for Biosecurity, Strategic Plan for Outreach and Education on Dual Use Issues (Washington D.C.: NSABB, 2008).
[83] InterAcademy Panel on International Issues, Statement on Biosecurity, November 7, 2005, p. 1.

chemical weapons. In recent years, a series of high-profile terrorist attacks have shifted the focus of biosecurity activities from states to non-state actors. National legislation to implement the BWC and the CWC, and UN Security Council Resolution 1540, have fostered efforts to harmonize and strengthen the domestic safety and security regulations governing the use of biological pathogens, toxic chemicals, and GMOs. Although the EU has focused primarily on biosafety measures and placed a lesser emphasis on biosecurity, the United States has created a dedicated set of laws and regulations to strengthen laboratory security.

With the exception of professional licensing requirements, soft-law measures such as voluntary guidelines and self-governance schemes lack strict enforcement mechanisms. For this reason, critics of self-regulation seek to bolster soft-law approaches with enforceable standards to reduce risk. In general, EU member states do not consider self-governance and norm-building as politically viable alternatives to hard law.[84] In the United States, by contrast, historical deference to the scientific community has created more space for self-regulation instead of binding legislation. Even so, some analysts believe that the biosecurity risks of synthetic genomics are sufficient to warrant mixed-governance approach.[85]

In conclusion, ongoing efforts to build a "web of prevention" through multiple, overlapping governance measures must include a greater awareness on the part of individual researchers about the dual-use risks of many emerging technologies and the fact that they are the ultimate gate-keepers. If education is to become a powerful tool for technology governance, it must be coupled with the recognition that science is a morally-bounded enterprise and those who practice it have a responsibility to ensure that it is used for good and not for ill.

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[84]Agomoni Ganguli-Mitra, Markus Schmidt, et al., "Of Newtons and Heretics," Nature Biotechnology, vol. 27 (2009), pp. 321-322.

[85] For a discussion of governance options for synthetic genomics, including mixed approaches, see Michele Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, *Synthetic Genomics: Options for Governance* (J. Craig Venter Institute, October 2007), available at <http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf>.

Chapter 4: Lessons from History

Michael Tu

At first glance the work of historians, reconstructing events from archived documents decades after the fact, appears to offer little of relevance to policymakers seeking to manage the risks of emerging dual-use technologies. According to the British Parliamentary Office of Science and Technology, however, the study of history offers several benefits for current decision-making. First, it provides background and context for policy debates and identifies lessons from the past that can be applied to the present. Second, historical research helps to dispel myths and misconceptions and ensures that current policy is based on an informed understanding of events. Although decisions involving science and technology may appear inevitable in retrospect, historical analysis can identify the factors that led to specific policy choices and explore the alternatives that were available at the time. Of course, it is also important to recognize the differences as well as the similarities between historical and contemporary cases and to avoid crude or superficial analogies that could be misleading.[1]

With respect to the topic of this book, historical cases can shed light on the process by which technologies developed for peaceful, civilian purposes are adapted by state or non-state actors for hostile ends, such as warfare, covert operations, coercive interrogation, or terrorism. Although determinist theories view dual-use potential as an inherent property of certain technologies, another school of analysis contends that the *social context* in which a technology arises plays a key role in shaping the way it is developed and utilized. According to this view, interested actors and institutions facilitate the transfer of technology from the civil to the military sector. Because historical case studies can trace social processes over time, they provide a nuanced picture of how new technologies emerge, develop, and evolve as a function of economic, bureaucratic, and other contextual factors.

Risk assessments of emerging dual-use technologies have traditionally revolved around the materials, methods, and products that facilitate misuse. Governance strategies

[1] Parliamentary Office of Science and Technology, "Lessons from History," *Postnote*, No. 323 (January 2009), pp. 1-2.

have also relied on an artifact-centric approach by seeking to restrict the availability of dual-use products and services. This traditional paradigm has serious limitations, however. Because many emerging technologies are based largely on intangible information and employ standard materials and equipment, imposing stringent controls on access stifles legitimate research and commerce. In addition, dual-use biological and chemical technologies are increasingly diffuse, globalized, and multidisciplinary, reducing the effectiveness of traditional regulatory approaches such as export controls. An alternative governance strategy, geared towards influencing the social chronology of a technology as it unfolds, may offer more a effective approach.[2]

Technology Transfer as a Social Process

Scholars in the field of Science and Technology Studies have long discussed "the circulation of knowledge," meaning the process by which knowledge from one context is translated, modified, and reconstructed in another.[3] Such knowledge transfers may take different forms depending on *how* the transfer occurs (between disciplines, geographic locations, or institutions), *what* is being transferred (material items called "artifacts," ideas, or techniques), and *who* is performing the transfer.[4] Technology transfers between the civilian and military sectors, or from legitimate use to deliberate misuse, are a type of knowledge circulation in which the technological artifact is reinterpreted as an instrument for causing harm and then modified within that context.

Analyzing the *how* of civil-military transfer is informed by the theories of the social construction of technology developed by Trevor Pinch and Wiebe Bijker.[5] These theories view technological development as an "open process that can produce different

[2] Kathleen Vogel, "Framing biosecurity: an alternative to the biotech revolution model?" *Science and Public Policy*, vol. 35, no. 1, pp. 45-
[3] Bruno Latour, *Science in Action* (Cambridge, MA: Harvard University Press, 1987).
[4] The various forms of "circulation of knowledge" can be inferred from the conference program of *"Circulating Knowledge": Fifth British-North American Joint Meeting of the British Society for the History of Science, the Canadian Society for the History and Philosophy of Science, and the History of Science Society*, held at the University of King's College, Halifax, Canada, August 5-7, 2004.
[5] Trevor J. Pinch and Weibe E. Bijker, "The Social Construction of Facts and Artifacts: Or How the Sociology of Science and the Sociology of Technology Might Benefit Each Other," in Wiebe E. Bijker, Thomas P. Hughes, and Trevor J. Pinch, eds., *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology* (Cambridge, MA: MIT Press, 1987), pp. 17-50.

outcomes depending on the social circumstances of development."[6] Social constructivists posit that science and technology are not objective and value-neutral but instead reflect the political agendas of those who practice them.[7]

In general terms, the social constructivist model consists of the following elements.[8] A technological artifact inspires multiple interpretations that provide alternative paths of development. Various interest groups and institutions coalesce around the different interpretations, which are then contested and negotiated through a social process that reflects the power relationships of the players and the rules governing their interactions. The interpretation of the technology is also shaped by the "technological frame," meaning the theories, questions, and protocols that dominate scientific thinking during a given time in history. The legitimized interpretation of the technology defines the subsequent paths of its development and use. Once a technological artifact has been created that fits the specifications flowing from the legitimized interpretation, "closure" has been achieved and the development process comes to an end.

A good historical example that illustrates the lack of inevitability in technological development and the role of different interpretations is the QWERTY keyboard, which is now used in all typewriters and computers in the English-speaking world. Although the QWERTY keyboard is not the most efficient layout for typing English, it was introduced on manual typewriters to make typists *less* efficient so that they would not type too fast and jam the keys. By the time more efficient keyboard layouts were proposed, managers

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[6] Hans K. Klein and Daniel Lee Kleinman, "The Social Construction of Technology: Structural Considerations," in *Science, Technology, and Human Values*, vol. 27, no. 1 (Winter 2002), pp. 29.

[7] Susan Leigh Star, *Ecologies of Knowledge: Work and Politics in Science and Technology* (Albany, NY: State University of New York Press, 1995), p. 3. Other seminal works on the social construction of technology include Daryl Chubin and Ellen Chen, *Science Off the Pedestal: Social Perspectives on Science and Technology* (Belmont, CA: Wadsworth Publishing, 1989); Bruno Latour and Steve Woolgar, *Laboratory Life: The Social Construction of Scientific Facts* (Beverly Hills, CA: Sage Publications, 1979); Karin Knorr-Cetina, *The Manufacture of Knowledge: An Essay on the Constructivist and Contextual Nature of Science* (Oxford: Pergamon Press, 1981); and Andrew Pickering, ed., *Science as Practice and Culture* (Chicago: University of Chicago Press, 1992).

[8] For a full treatment of "social construction of technology" as traced through three case studies, see Wiebe E. Bijker, *Of Bicycles, Bakelites, and Bulbs: Towards a Theory of Technological Change* (Cambridge, MA: MIT Press, 1995). Some scholars have critiqued the theory. Stewart Russell contends that Pinch and Bijker's conception of "greater social context" is oversimplified, while Langdon Winner notes the omission of the social consequences of technological change and the imprecision in defining who constitutes a "relevant" social group. See Stuart Russell, "The Social Construction of Artifacts: A Response to Pinch and Bijker," *Social Studies of Science*, vol. 16 (May1986), pp. 331-345; Langdon Winner, "Upon Opening the Black Box and Finding it Empty: Social Constructivism and the Philosophy of Technology," *Science, Technology, and Human Values*, vol. 16, no. 3 (Summer 1993), pp. 362-378.

and office staff had already invested time and money in training personnel to type with the QWERTY keyboard and thus had no incentive to switch to a different layout. QWERTY keyboards, of course, remain in place today, even though jamming is no longer a problem with electronic keyboards. This case suggests that there is nothing inevitable about technological development and that what is interpreted as the "best" design depends on one's perspective. "Best" from an efficiency perspective is not necessarily "best" from the standpoint of the time and resources invested in training.[9]

The Appendix contains two historical case studies of civil-military technology transfer, "The Development of the V-Series Nerve Agents" by Caitríona McLeish and Brian Balmer, and "The Use and Misuse of LSD by the U.S. Army and the CIA" by Mark Wheelis. Both of these cases suggest the relevance of social constructivist theory to the analysis of civil-military technology transfer. All dual-use technologies, by definition, inspire multiple interpretations. Thus, civil-military transfer involves a process in which a social actor reinterprets a peaceful technology as having a hostile purpose. This interpretation is then negotiated through a socio-scientific network and ultimately gains legitimacy. Although a social network is required to mediate civil-military technology transfers, the structure and composition of the network varies from one technology to the next.

Analyzing the social context for technology development is not only useful for understanding the process of civil-military transfer but may reveal avenues for policy intervention to reduce the risk of misuse.[10] For example, it may be possible to modify the structure of the socio-scientific network in order to delegitimate misuse. To derive practical applications from theories of the social construction of technology, however, one must first obtain an understanding of how socio-scientific networks develop, how expertise travels through such networks, and how the civilian and military interpretations of a technology are negotiated. Historical case studies can shed useful light on these processes.

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[9] Robert Pool, *Beyond Engineering: How Society Shapes Technology* (Oxford, England: Oxford University Press, 1997).

[10] Jennifer Croissant and Sal Restivo, "Science, Social Problems, and Progressive Thought: Essays on the Tyranny of Science," in Star, *Ecologies of Knowledge*, pp. 57.

Because the V-agents and LSD were once emerging technologies, they can provide useful lessons for contemporary dual-use dilemmas. Drawing on the theoretical tools summarized above, it is possible to analyze the two historical case studies as examples of the social construction of technology. In both cases, a particular institution reinterpreted an artifact or technique from the civil to the military sphere, successfully promoted this interpretation, and then obtained the consent of other interested parties. In other words, knowledge was not simply passed along like a baton in a relay race. In the case of the V-agents, Porton Down took a failed pesticide (Amiton) and reinterpreted it as a chemical weapon; in the case of LSD, the CIA became aware of the experimental use of this drug to treat the delusions of psychiatric patients, and thus reinterpreted LSD as a potential instrument of "mind control" to support coercive interrogation and covert operations. By tracing the processes by which each technology was recast from the civil to the military sphere, the two historical cases illuminate the social construction of technology and provide insights into the structural factors that facilitate misuse.

The V-Agents Case (Appendix A)

McLeish and Balmer argue that there was nothing inevitable about the transfer of the agricultural pesticide Amiton from the civil to the military sphere. Contrary to determinist theories of technology, the weapons application did not emerge automatically from the inherent properties of the chemical—its high toxicity to humans and ability to penetrate the skin—but instead required the active intervention of military officials. For several years after World War II, scientists at the British chemical warfare (CW) establishment at Porton Down languished under limited government funding, which impeded their ability to develop new CW agents. Seeking to make the best use of scarce resources, Porton officials identified the British chemical industry as an inexpensive source of front-end development—the difficult and costly process of identifying new compounds as candidate CW agents. To this end, Porton reached out to chemical companies, both directly and through the British chemical trade association, and urged them to submit information about toxic compounds that they may have stumbled across in the course of developing commercial drugs, dyes, and pesticides.

In seeking the assistance of the chemical industry, Porton officials sought to legitimate the solicitation by framing it disingenuously in "defensive" terms. The aim of this approach was to create a mutually acceptable mode of discourse between scientists in the military and the private sector. Another ploy to gain the cooperation of chemical companies was the creation of a new chemical classification scheme designed to safeguard commercial trade secrets and preserve confidentiality. Despite these efforts, however, many chemical firms resisted the British government's outreach efforts because they lacked a financial incentive to study chemicals that were too toxic to market commercially. As a result, Porton's initiative failed to generate the expected flood of research leads. The only useful product to emerge from the outreach effort was a commercial pesticide (Amiton) that had been developed and marketed by Imperial Chemical Industries but had then proved too toxic for agricultural use. Within months, Porton reconfigured the industry-government network into a channel for technology transfer and recast the failed pesticide as VG, the first of the V-series nerve agents. This new generation of chemical weapons offered a potent blend of rapid action, stability, and persistence. (The "V" code reportedly stood for the word "venomous" because of the agent's lethality and ability to penetrate the skin.)

The proactive role of British defense officials in transforming a failed pesticide into a CW agent challenges the determinist view of dual-use as an inherent characteristic of a technological artifact that leads inevitably to its application for hostile purposes. Amiton did not automatically become a chemical weapon from the moment its toxic properties were recognized. Instead, its transfer from the civil to the military sphere required the active intervention of a socio-scientific network, which reinterpreted the purpose of the chemical and defined a new path of inquiry within the military context. This socio-scientific network involving government and the private sector was subject to strong internal tensions and required an active effort to maintain.

With respect to policies for the governance of dual-use technologies, McLeish and Balmer highlight policies that focus on intent as an alternative to the traditional artifact-centric approach. For example, the General Purpose Criterion in Article II, paragraph 1(a) of the Chemical Weapons Convention (CWC) is designed to ensure that the treaty will not be overtaken by technological change by banning the development, production,

transfer, and use of all toxic chemicals *except* for nonprohibited purposes, as long as the types and quantities are consistent with those purposes. This intent-based, rather than artifact-based, governance system aims to direct technical change along a trajectory that is incompatible with misuse.

The LSD Case (Appendix B)

Mark Wheelis's case study of the use and misuse of LSD chronicles the efforts by the U.S. Army and the CIA during the 1950s and 1960s to reinterpret a civilian technology as a military one. The LSD case study also emphasizes the contextual nature of the concept of misuse. Wheelis makes a clear distinction between the Army's attempted development of the drug as an incapacitating chemical weapon and the CIA's Project MKULTRA, which sought to develop LSD as a tool for mind control, covert operations, and coercive interrogation. Although the Army research program did not violate any existing treaties to which the United States was a party and thus did not constitute "misuse" in the context of the time, the CIA's experimentation with LSD on unwitting human subjects violated the ethical principles in the Nuremberg Code.

The CIA, by successfully negotiating between the civilian and military interpretations of LSD, was able to pressure medical personnel to participate in abusive experiments. Whenever the goals of MKULTRA came in conflict with the Hippocratic oath and other norms that guide the medical profession, the CIA overcame these ethical barriers through appeals to patriotism and claims of Communist brainwashing. Although several of the physicians involved had serious moral qualms about their work, they had no recourse because of the intense secrecy shrouding the program and the lack of safe channels for principled dissent or whistle-blowing. Thus, the development of LSD as a mind-control drug continued in secret for years and only reached closure when the CIA finally recognized that it was not a reliable tool for that purpose.

Wheelis contends that the CIA's ethical abuses during Project MKULTRA resulted from a lack of organizational checks and balances. Although the Director of Central Intelligence authorized the special-access "black" program, only a few senior agency officials were aware of it. This high level of secrecy and compartmentalization precluded effective external or internal oversight, enabling a "rogue element" within the

CIA to pursue an illegal activity that was accountable to no one and became increasingly corrupt over time. Wheelis offers four explanations for this failure of governance: (1) the agency's intense preoccupation with the Soviet military and ideological threat during the Cold War, which eroded moral barriers; (2) the lack of formal or informal oversight mechanisms to monitor the activities of the clandestine service; (3) the extensive compartmentalization of the program of human experimentation in a deliberate bid to circumvent ethical controls; and (4) the reluctance of professional medical societies to discipline members who participated in unethical activities.

Despite the inherent conflict between secrecy and governance, Wheelis contends that it is possible to have effective oversight even in a highly classified environment through measures such as independent legal analysis, ombudsmen, whistle-blower protections, and Institutional Review Board (IRB) review of human-subjects research. Unfortunately, governments sometimes reinterpret their own rules to allow these internal oversight systems to fail. During the George W. Bush administration, for example, the Justice Department's Office of Legal Counsel reinterpreted the existing legal guidance banning torture to permit the development and use of "enhanced" interrogation techniques such as water-boarding.[11]

Wheelis concludes that a more equitable balance of power between CIA program managers and the medical professionals they supervised would have constrained the agency's ability to reinterpret LSD as an instrument of mind control, impose this interpretation on the medical community, and conduct unethical human experiments. The LSD case also suggests that the misuse of emerging technologies can go beyond military applications to include violations of human rights and international humanitarian law. Other governments are known to have employed potent drugs against their own people (e.g., Soviet and Chinese misuse of psychiatric medications to suppress dissidents[12]) or external enemies (e.g., Israel's use of the synthetic opiate fentanyl as an assassination weapon[13]). Preventing a government from abusing its own citizens, even within highly classified programs, requires a high degree transparency and accountability, including

[11] Jane Mayer, *The Dark Side: The Inside Story of How the War on Terror Turned into a War on American Ideals* (New York: Anchor Books, 2009).
[12] Richard J. Bonnie, "Political Abuse of Psychiatry in the Soviet Union and in China: Complexities and Controversies," *Journal of the American Academy of Psychiatry and the Law*, vol. 30 (2002), pp. 136-144.
[13] Alan Cowell, "The Daring Attack That Blew Up in Israel's Face," *New York Times*, October 15, 1997.

internal channels for dissent and whistle-blowing—consistent, of course, with national security. Beyond formal oversight mechanisms, codes of ethics and the more active engagement of professional societies can help to prevent physicians, psychiatrists, or scientists from contributing to unethical applications of emerging dual-use technologies.

Comparing the Two Cases

When the chronologies of the V-agent and LSD cases are compared, the events fall into two categories: development milestones along the path toward the hostile application of the technology, and the formation and maintenance of the socio-scientific networks through which the technology was reinterpreted and transferred. In practice, these two types of events reinforced each other, producing interwoven narratives of technological development and social motivation that are difficult to tease apart.[14]

Some notable parallels exist between the two historical case studies. Both the development of the V-agents and of LSD were motivated by fears of similar programs in the Communist bloc and the deep-seated belief that the Soviet Union or Red China posed an existential threat to the West. Both cases also involved government collaboration with civilian scientists or private companies. Because the military framing of the technology ran counter to the ethical standards of the civilian participants, this conflict had to be overcome through careful marketing and outright deception about the state's intended goals. In the V-agents case, Porton Down's translation of "Amiton the pesticide" into "VG the nerve agent" was mediated by personal networks and repeated solicitations of the chemical industry, including efforts to address companies' concerns about confidentiality and the protection of trade secrets. In the LSD case, the CIA compartmentalized information about the program in a deliberate bid to evade both internal and external oversight.

The two cases differ, however, in some important respects. First, the achievements of the CIA pale in comparison with those of Porton Down. Whereas the CIA studied LSD in its original form, Porton scientists translated a failed commercial

[14] Sociologists of science and technology have observed that "any attempt to separate the social and the nonsocial . . . is . . . quite simply, impossible, because the social runs throughout the technical and thus cannot be separated from it." John Law and Michael Callum, "Engineering and Sociology in a Military Aircraft Project," in Star, *Ecologies of Knowledge*, p. 282.

pesticide into a new class of highly potent nerve agents. Second, although the larger goals of Project MKULTRA remained hidden from the civilian participants, the commercial chemical industry was informed of the British government's search for highly toxic compounds for military use—although Porton initially mischaracterized the program as "defensive" in nature.[15] Finally, whereas the CIA gleaned information about LSD from the scientific literature, Porton Down solicited information directly from the chemical industry.

Policy Implications

Although the geopolitical environment has changed dramatically since the Cold War era when the two historical cases occurred, some of the same concerns still exist. For example, much as the Soviet Union was believed to pose an existential threat to the United States that arguably justified the use of extreme and even unethical measures, some current policymakers view the threat of global Islamic terrorism in equally stark terms. At the same time, it is important to view the lessons for current policy of the historical cases with caution because times have indeed changed in important ways. For one thing, transfers of technology from the civilian to the military sector are no longer unusual, and collaboration between civil and military institutions has become routine at all levels of technology research and development. Although these changes prevent one from drawing definitive lessons from the historical case studies, some general principles continue to be relevant.

The two cases suggest that the contemporary policy discourse may be missing some important dimensions. First, whereas current policy focuses almost exclusively on the hostile exploitation of dual-use technologies by terrorist organizations, the risk of misuse by governments—either against other countries or their own citizens—remains a serious concern. Historically, states have been more likely than non-state actors to adapt emerging technologies for hostile purposes because they possess far greater financial resources and technical expertise. In some cases, rogue elements within intelligence agencies or the military have appropriated dual-use technologies for their own use

[15] A large number of documents on MKULTRA were eventually declassified and made public. In contrast, fewer documents from Porton Down on the V-agent development program are publically available and even the dates are not known precisely.

without the authorization of the government as a whole. In apartheid South Africa, for example, the South African Defense Force had a secret chemical and biological weapons program (code-named Project Coast) that tried, but ultimately failed, to develop "ethnic weapons" that could selectively kill non-whites.[16] A new source of the potential misuse of chemical agents is the growing interest in applications in counterterrorism and counterinsurgency.

Both historical cases challenge the traditional concept of effective governance and suggest a need to go beyond a narrow focus on tangible goods and artifacts. Narratives focusing exclusively on artifacts often miss the mark because dual-use technologies do not pose an inherent or inevitable threat but depend instead on social processes to reinterpret and translate them into hostile use. As policymakers grapple with the difficult task of managing the dual-use risks of emerging technologies, they should not overlook the structural relationships both between and within the civilian and military sectors. While approaches based on technology denial, such as export controls and interdiction strategies, may be useful in early stages of technology development when few suppliers exist, the rapid diffusion and globalization of dual-use technologies have inexorably reduced the effectiveness of such measures.

The case studies also suggest that the motivational and social aspects of technology transfer between and within the civil and military sectors are difficult to sustain and are potentially subject to disruption. It may therefore be possible to reduce the risk of misuse by shaping the structural features that govern the social construction of a dual-use technology, for example, by promoting a civilian rather than a military interpretation. Skeptics note, however, that since governments frequently exploit civilian technologies for military purposes they consider legitimate, they may be unable or unwilling to rein in dual-use technologies that entail a risk of misuse.

By highlighting the social mechanisms that mediate civil-military technology transfers, the authors suggest that policy interventions designed to alter the social context of a technology or to influence the technological frame may prevent its reinterpretation in a military context. For example, McLeish and Balmer call for regulating intent through

[16] Chandré Gould and Alastair Hay, "The South African Biological Weapons Program," in Mark Wheelis, Lajos Rózsa, and Malcolm Dando, eds., *Deadly Cultures: Biological Weapons since 1945* (Cambridge, MA: Harvard University Press, 2006), pp. 191-212.

the CWC by fully implementing the General Purpose Criterion, rather than by basing verification exclusively on static lists of chemical warfare agents and precursors. Wheelis, for his part, proposes to restrict or break up the socio-scientific networks that support militarization by establishing stronger mechanisms for institutional review, creating a safe reporting channel for whistle-blowers, closing legal loopholes that could legitimate the use of incapacitating agents, and paying greater attention to the ethical and moral dimensions of emerging technologies. Finally, both historical cases emphasize the continued importance of a mixed but tailored approach to governance that integrates hard-law, soft-law, and normative measures. Although the socio-scientific approach to the dual-use problem stresses the importance of influencing intent, hard-law measures may still be desirable and effective in some cases.

Chapter 5: Case Study Template

Jonathan B. Tucker

To assess the risk of misuse of emerging biological and chemical technologies and develop tailored governance strategies, the study took an inductive approach by commissioning case studies of 14 different technologies, which were analyzed in a comparative manner using a template, or common set of research questions. This chapter describes how the cases were selected, and the basic conceptual framework that was used to analyze them.

Selection of Cases

The starting point for selecting the technologies for analysis was a 2006 report by the National Research Council (NRC), a policy-analysis arm of the U.S. National Academy of Sciences, titled *Globalization, Biosecurity, and the Future of the Life Sciences*. This study, directed by microbiologists Stanley Lemon and David Relman, looked beyond research with dangerous pathogens to examine a variety of emerging dual-use biological and chemical technologies that might be exploited for hostile purposes.[1] The Lemon-Relman report classified these technologies into four categories based on their shared characteristics:

(1) *Technologies that generate collections of molecules with greater structural and biological diversity than those found in nature* (e.g., DNA synthesis, combinatorial chemistry, and directed molecular evolution);

(2) *Technologies that create novel but predetermined molecular or biological diversity* (e.g., the rational design of small molecules that bind to protein targets, genetic engineering of bacteria or viruses, and synthetic biology);

(3) *Technologies that facilitate the manipulation of complex biological systems* (e.g., systems biology, RNA interference, genomic medicine, modification of homeostatic systems, and bioinformatics); and

[1]National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006).

(4) *Technologies for the production, delivery, and packaging of biological products* (e.g., production of drugs in transgenic plants, aerosol drug-delivery systems, microencapsulation, microfabrication technologies, nanotechnology, and gene therapy).[2]

For the present study, several emerging technologies indentified in the Lemon-Relman report were augmented with additional cases from the fields of chemistry, biochemistry, molecular genetics, biomedicine, and neuroscience. Because of the central importance of two emerging fields, synthetic genomics and synthetic biology, separate case studies were commissioned of these technologies despite their extensive overlap. A key selection criterion was to ensure that the technologies being analyzed were directly comparable. In fact, emerging biological and chemical technologies vary widely in scope and impact: some provide incremental improvements to an existing field, while others create a new subfield within an established discipline or launch an entirely new area of application. An example of the latter is nanobiotechnology, the manipulation of biological materials at the nanometer scale. Because it is an extremely broad discipline that encompasses numerous applications with different levels of dual-use risk, however, nanobiotechnology was not included in the list of case studies.

Another criterion in selecting the technologies for comparative analysis was to ensure a high level of variance across several parameters, making it possible to group the cases into distinct categories. Accordingly, the cases were selected to include (1) technologies having different levels of maturity, from the early phases of research and development to wide commercial availability; (2) technologies based primarily on hardware, on intangible information, or a hybrid of the two; and (3) technologies that are advancing and diffusing at different rates. Finally, some of the technologies chosen for case-study analysis are based on cutting-edge science, whereas others are applications of existing knowledge.

An important characteristic of the life sciences today is that the traditional distinction between science and technology is increasingly blurred. The standard paradigm states that advances in scientific knowledge (the understanding of how nature works) lead to technological innovations (the application of scientific knowledge to solve practical problems). In fields such as molecular biology, however, the distance between knowledge and application is so short as to make it difficult to distinguish between them. Emerging technologies such as RNA interference,

[2]Ibid., pp. 140-141.

for example, began as science-based laboratory techniques but soon found their way into wide variety of scientific and industrial applications, some of them with dual-use potential.

The scholars who prepared the case studies for this volume were asked to employ a Case Study Template consisting of a standard set of research questions, in order to facilitate the process of cross-case comparison. The initial version of the template was based on a working analytical framework for technology governance that was subsequently refined over a period of several months. Because some of the parameters included in the original template proved to be of minimal explanatory value, they were later dropped, while other variables were identified as useful and incorporated into the model. For example, one of the original parameters was to determine if an emerging technology was "evolutionary," meaning that its dual-use implications became apparent gradually over time as its speed, throughput, accuracy, or other characteristics improved, or "revolutionary," meaning that its dual-use potential emerged practically overnight as a result of an unexpected breakthrough. This variable proved to be overly vague or misleading, however, and was therefore discarded.

Additional parameters, such as the role of tacit knowledge in exploiting a technology for harmful purposes, and the amount of capital needed to acquire it, were later incorporated into the template. Over the course of the study, the parameters for assessing dual-use risk and governability were gradually pared down, yielding an analytical framework that is more parsimonious. Because of the changes to the Template, the case study authors had to revise their chapters in midstream to accommodate changes in variables and terminology. Finally, the case studies were edited to ensure that they all employ the same headings and parameters, thereby ensuring the greatest possible degree of comparability.

As illustrated in **Figure 5.1**, the Template used to analyze the contemporary case studies has two basic elements: *Assessing the Risk of Misuse* and *Assessing Susceptibility to Governance*. Each of these elements is in turn defined by several parameters that, when averaged together, provide an ordinal ranking of risk and governability. In addition, the authors were asked to propose tailored governance strategies for their respective technologies. It soon became clear that the chosen strategies involved a mix of hard-law, soft-law, and normative approaches. The following sections describe the specific parameters used in the Case Study Template and the rationale for including each of them in the assessment process.

Assessing the Risk of Misuse

The process of analyzing an emerging dual-use technology begins with assessing the *risk of misuse*. For the purpose of creating a manageable analytical framework, the assessment of risk is based on four parameters:

1. *Ease of misuse*. This parameter includes the level of expertise and tacit knowledge required to master the technology, as well as the extent to which it is gradually being "de-skilled" and becoming more available to less expert individuals.
2. *Accessibility*. This parameter measures how easy it is for non-specialists to access the technology, which may be either commercially available, proprietary (if developed in the private sector), or restricted because of classification or some other reason. This variable also includes the amount of capital needed to acquire the technology and whether the level of expenditure is within the means of an individual, group, or nation-state. (It is important to note that a scientist in an established laboratory who is working with a dual-use technology could potentially exploit it for harmful purposes at minimal expense.)
3. *Magnitude of potential harm resulting from misuse*. This variable is a function both of the technology itself and the vulnerability of the potential targets. Potential harm encompasses a variety of different parameters, including the approximate number of deaths and injuries resulting from an attack, the economic costs caused by an incident and its mitigation, the societal effects of an attack, including disruption, terror, and persistent psychological trauma; and the political or normative effect on the international nonproliferation regimes.
4. *Imminence of the risk of misuse*. This parameter indicates how rapidly a malicious actor seeking to cause harm could exploit the technology in its current state of development. For example, whereas the *de novo* synthesis of existing viral pathogens is feasible with existing technologies, the design and assembly of artificial genomes through the use of standardized genetic parts ("BioBricks") is still a long way from becoming a practical field.

Because there was a direct relationship between the four parameters and the risk of misuse, each parameter was ranked on a three-level ordinal scale (HIGH, MEDIUM, and LOW) and the four values were averaged together to provide a rough estimate of the "level of concern." This method provides a good indication of whether or not the technology in question poses a sufficient level of dual-use concern to warrant the introduction of governance measures. An overall value of HIGH means that the technology has an imminent risk of misuse *and* a significant potential for large-scale harm; MEDIUM means that it has an imminent risk of misuse *or* a significant potential for large-scale harm; and LOW means that the risk of misuse is neither imminent *nor* particularly consequential.

For the risk of misuse to be rated MEDIUM or HIGH, an emerging technology must have potential harmful consequences that exceed what is already possible with existing technologies. For example, the capability to synthesize the entire genomes of dangerous viral pathogens, such as the SARS virus or the 1918 strain of influenza virus, represents a new and salient threat that warrants a governance response—particularly with respect to viruses such as variola (smallpox) that no longer exist in nature and are restricted to a few high-security labs. In contrast, the risk of misuse of transcranial magnetic stimulation (TMS) is low because this technology could only be used to harm one person at a time. Thus, the possibility of misuse is more of a human-rights concern than a national security threat. For those technologies whose risk of misuse is currently low and unlikely to materialize for some time, it would be prudent to put the technology on a "watch list" and monitor how it evolves, so that appropriate controls can be introduced later on if warranted.

Assessing Susceptibility to Governance

If the initial analysis determines that an emerging technology has a HIGH or MEDIUM risk of misuse, the analysis should go on to the next step: determining the extent to which the technology is susceptible to governance measures. As with the risk of misuse, the factors that define governability can be ranked on an ordinal scale (HIGH, MEDIUM, and LOW) and then averaged to give a rough overall value. The assessment of governability is based on the following five parameters:

1. *Embodiment of the technology*. Some emerging technologies consist primarily of hardware, others are based largely on intangible information, and still others are a hybrid of the two. DNA shuffling and RNA interference are both techniques that require specialized know-how but no dedicated equipment beyond that found in standard molecular-biology laboratories. Chemical microreactors, in contrast, are a hardware-based technology, while combinatorial chemistry and high-throughput screening are a hybrid technology.
2. *Maturity of the technology*. The second parameter affecting governability is the *maturity* of a technology, meaning its current position in the research and development (R&D) pipeline extending from basic research to commercialization or commoditization. Maturity refers to whether the technology is still under development, has been prototyped, has recently been marketed, or is widely available from commercial outlets. Customized sequences of synthetic DNA, for example, are currently available from commercial suppliers around the world, whereas micro process devices are produced by only a small number of manufacturers.
3. *Degree of convergence of the technology*. Convergence refers to the number of different disciplines that are brought together to create a new device or capability. So-called "NBIC" technologies, for example, combine elements of nanotechnology, biotechnology, information technology, and cognitive neuroscience.[3] Similarly, the field of "nanobiotechnology" involves the convergence of nanotechnology and biotechnology to develop engineered bioparticles, for example to deliver drugs to certain cells or tissues in a targeted manner.[4] Synthetic biology is also a highly convergent technology because it combines elements of nanoscale biology, bioinformatics, and engineering into a new discipline for the design and construction of biological parts and devices that perform useful tasks.[5] Because highly convergent technologies draw on multiple fields, each with its own practitioners, culture, jargon,

[3]Mihail C. Roco, "Possibilities for Global Governance of Converging Technologies," *Journal of Nanoparticle Research*, vol. 10, no. 1 (January 2008), pp. 11-29.
[4]Alfred Nordmann, *Converging Technologies – Shaping the Future of European Societies* (Brussels: European Commission, Directorate-General for Research, 2004), p. 3.
[5] Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," *The New Atlantis*, Spring 2006, online at: http://www.thenewatlantis.com/publications/the-promise-and-perils-of-synthetic-biology

and awareness of dual-use issues, such technologies are more difficult to govern than unitary technologies derived from a single discipline. Nevertheless, even a highly convergent technology may include a critical element that provides an effective intervention point, thereby increasing its governability. Synthetic biology, for example, hinges on the availability of automated DNA synthesis, a technology that is already the focus of several national and international governance measures.

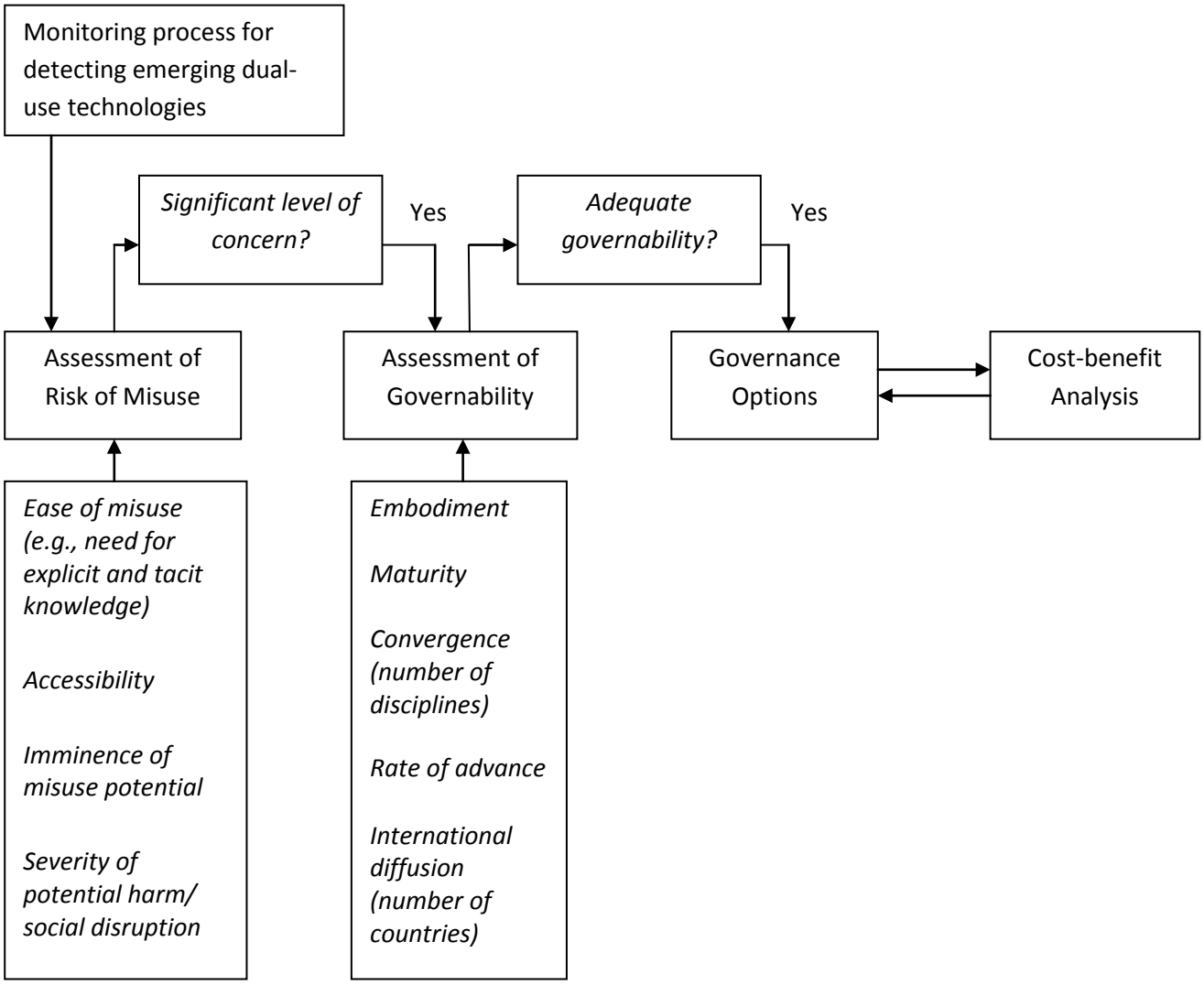
4. *Rate of advance of the technology*. This parameter refers to whether the utility of a technology (as measured by speed, throughput, accuracy, or cost) is increasing linearly, exponentially, stagnating, or declining over time. In general, the faster a technology advances, the harder it is for governance measures to keep pace. Some technologies, however, progress incrementally until they reach a threshold of speed, throughput, or capacity at which their dual-use potential becomes manifest.
5. *Extent of the international diffusion of the technology*. Emerging technologies vary greatly in the extent to which they are available on international markets. Some technologies are limited to one or a few countries, which keep them under wraps or patent protection, while other technologies are more widely available. The global diffusion of synthetic biology, for example, has accelerated in recent years because of the annual International Genetically Engineered Machines (iGEM) competition sponsored by the Massachusetts Institute of Technology, which has attracted the participation of student teams from countries around the world. In general, the fewer the number of countries that have access to a technology, the easier it is to govern. In the case of a widely diffused technology, governance requires the international harmonization of regulations or guidelines, which can be a difficult task. Chemical micro process technology, for example, is currently limited to a small number of suppliers capable of manufacturing high-tech devices, creating a window of opportunity for the industry to develop harmonized approaches to governance.

For each of the 14 technologies included in the study, the five parameters of governability were graded on the ordinal scale of HIGH, MEDIUM, or LOW and then averaged to give a rough assessment of the technology's susceptibility to governance. The meaning of these rankings is less clear-cut than is the case with the risk of misuse because the five variables

do not show a direct linear correlation with the governability of a technology. Three of the variables—convergence, rate of advance, and international diffusion—are inversely related to governability. The other two variables—embodiment and maturity—also do not relate directly to governability. In general, hardware-based technologies are more governable than those based on intangible information, which can be shared in an undetectable manner, with hybrid technologies in an intermediate position. Similarly, with respect to technological maturity, emerging technologies are most susceptible to governance at certain times in their development. Early in the R&D process a technology is usually too immature to permit a clear assessment of its dual-use risk, yet after a technology has diffused widely is usually too late to exercise effective control. Thus, the "sweet spot" of maximum governability is during the period extending from advanced development and prototyping to early commercialization, when the number of manufacturers and consumers is still extremely limited. Accordingly, if maturity is used as a measure of governability, the advanced development phase would be ranked HIGH, the commercialization phase MEDIUM, and the early research and development phase LOW. Although it is unlikely that a given technology will fulfill all five criteria, meeting most of them is indicative of high governability.

In general, a HIGH overall rank for governability means that the technology in question is susceptible to the full range of governance strategies, including hard-law measures such as legally binding regulations. A MEDIUM value means that only soft-law and normative measures are feasible, such as voluntary guidelines and self-regulatory regimes, while a LOW value means that only normative options are possible, such as awareness-raising and professional codes of conduct. Emerging dual-use technologies that have a HIGH or MEDIUM risk of misuse and a HIGH or MEDIUM level of governability are considered ripe for some type of regulatory intervention. In such cases, the analysis proceeds to the selection of specific governance measures, which are then subjected to an iterative cost-benefit analysis. (For a description of this process, see Chapter 20.) The next section contains the 14 detailed case studies, which are grouped together according to scientific discipline. Finally, Chapter 20 converts the Case Study Template into a general decision algorithm that can be used with any emerging technology to select a package of governance measures tailored to its specific characteristics.

Figure 5.1: Analytical Framework for Governance of Dual-Use Technologies Study



PART II: CONTEMPORARY CASE STUDIES

Chapter 6: Combinatorial Chemistry and High-Throughput Screening

Jonathan B. Tucker

Traditionally, the discovery of new drugs was a labor-intensive process in which medicinal chemists synthesized thousands of different compounds, which were tested for biological activity to identify promising "leads" for further development. The 1980s saw the advent of a new approach to drug discovery called combinatorial chemistry, or "combi-chem," which involves the mixing and matching of chemical building blocks to generate large collections of structurally related compounds called "libraries." A second technique called high-throughput screening (HTS) rapidly tests the compound library for a desired biological activity. Whereas a traditional organic chemist can synthesize between 100 and 200 different compounds per year, combinatorial chemistry and HTS can generate and screen tens of thousands of structurally related molecules in a matter of weeks.

Although combinatorial chemistry and HTS were initially conceived as a brute-force method for discovering new lead compounds, today the two techniques are used primarily to optimize the structure-function relationship after a lead has been identified. Highly toxic substances created inadvertently during combinatorial synthesis are normally discarded because they lack commercial value. Nevertheless, combi-chem and HTS might be employed deliberately to identify and optimize highly toxic compounds as chemical warfare (CW) agents. This chapter describes the technologies, assesses their potential for misuse, and suggests some possible approaches to governance.

Overview of the Technology

Combi-chem emerged initially from the solid-phase method for synthesizing peptides (short chains of amino acids) developed in the early 1960s by R. Bruce Merrifield at the Rockefeller University. Merrifield devised a cycle of chemical reactions that added amino acids one by one, in any desired sequence, to growing polypeptide chains anchored to tiny plastic

beads.[1] In the early 1980s, H. Mario Geysen adapted this method to create a combinatorial technique called "parallel synthesis," in which a molecular scaffold anchored to beads is reacted with various mixtures of amino acids to generate a library of structurally related peptides. An advantage of using beads as the substrate for combinatorial synthesis is that cleaving the end-products from the beads provides high yields without the need for laborious purification steps. Nevertheless, because chemical reactions that are straightforward when performed in solution behave differently in a solid-phase system, re-optimizing the reaction conditions for the solid phase is a time-consuming process.[2]

Parallel synthesis is usually performed on a microtitre plate, a sheet of molded plastic containing 96 tiny wells in an array of 8 rows by 12 columns. Each well contains a few milliliters of liquid in which the reactions occur. By injecting different combinations of amino acids into each well, it is possible to synthesize 96 distinct molecular variants on a single plate.[3] Advanced laboratory robotic systems permit the use of microtitre plates with 384 wells or more, giving chemists the ability to generate large compound libraries in a single synthesis campaign.

In the late 1980s, Árpád Furka developed a second combi-chem method called "split-and-pool" synthesis, which can generate much larger compound libraries. In this case, the polymer beads are reacted with chemical building blocks in several different test tubes, creating mixtures of beads with different molecules attached to them. The contents of the test tubes are pooled in a single vessel, randomly distributing the chemically-modified beads; this mixture is then split into several equivalent portions and reacted with another set of chemical building blocks. The process of pooling and splitting serves as an enormous combinatorial multiplier: the greater the number of reaction cycles, the larger the library of variant molecules produced.[4]

Split-and-pool synthesis routinely generates up to a million different molecular structures. At the end of the process, the synthesized compounds are detached chemically from the beads and the content of each test tube is screened to determine its average biological activity. The mixture with the highest activity is separated into about a hundred different compounds, which are purified and individually screened. The main drawback of the split-and-

[1] R. Bruce Merrifield (1963), "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *Journal of the American Chemical Society*, vol. 85, p. 2149.
[2] Dawn Verdugo, James Martin Center for Nonproliferation Studies, personal communication to the author, August 19, 2009.
[3] Matthew J. Plunkett and Jonathan A. Ellman, "Combinatorial Chemistry and New Drugs," *Scientific American*, vol. 276, no. 4 (April 1997), p. 70.
[4] Mark S. Lesney, "Rationalizing Combi-Chem," *Modern Drug Discovery*, vol. 5, no. 2 (February 2002), pp. 26-30.

pool method is the need for the purification step. Because each variant molecule is present in tiny amounts, it can be difficult to sort through an active mixture and determine which compound is responsible for the detected activity, and the variant molecules may inhibit or inactivate one another. For these reasons, contemporary medicinal chemists tend to avoid the split-and-pool approach and instead create compound libraries by parallel synthesis.[5]

Combi-chem is usually employed in conjunction with high-throughput screening (HTS), which can screen compound libraries for a particular biological activity at a rate commensurate with the speed of combinatorial synthesis. Before the advent of HTS, screening assays were conducted in intact experimental animals and typically measured a general therapeutic effect, such as anti-bacterial or anti-inflammatory action. Today, however, screening is performed against an isolated biomolecular target such as a cell-surface receptor, an enzyme, or an ion channel. Ideally, a drug should bind with high affinity to a specific site in the body to induce a desired physiological change; if the compound binds to multiple sites, it will most likely have unwanted side effects.

HTS systems are well suited to automation with laboratory robots, making it possible to screen thousands of different compounds in parallel. For example, a receptor protein that is a target for drug development can be tagged with a fluorescent molecule that glows in response to binding, so that drug candidates with a high affinity for the receptor can be identified with a fluorescence sorting machine.[6] Because a poorly defined screening target can generate false-positive "hits"—or worse, false negatives, meaning real hits that are not detected—a robust, highly sensitive screening mechanism is essential. When screening a new compound library, a medicinal chemist does not want to miss even a modestly potent lead that could serve as the starting point for creating a more focused combinatorial library.

History of the Technology

In 1988, the entrepreneur Alejandro Zaffaroni founded a company called Affymax in Palo Alto, California, that used combi-chem methods to synthesize large peptide libraries for screening as potential therapeutic drugs.[7] Because peptides are rapidly broken down by enzymes

[5] Ibid.
[6] Joseph Alper, "Drug Discovery on the Assembly Line," *Science*, vol. 264 (June 3, 1994), pp. 1389-1401.
[7] Robert F. Service, "Combinatorial Chemistry: High-Speed Materials Design," *Science*, vol. 277, no. 5325 (July 25, 1997), p. 474.

in the stomach, however, they are not ideal drug candidates. Skeptics doubted that combinatorial synthesis could generate libraries of small-molecule drugs with a molecular weight less than 500 daltons, which can be taken orally, the preferred method of administration, and are more persistent in the body. In 1992, however, Jonathan Ellman and Barry Bunin at the University of California at Berkeley developed a method for the parallel synthesis of an important class of small-molecule drugs: benzodiazepines, which are used to treat anxiety.[8]

During the late 1980s and early 1990s, combi-chem and HTS elicited great interest from the major pharmaceutical companies, nearly all of which established specialized departments devoted to combinatorial synthesis. Numerous drug-discovery firms were also founded to perform contract work.[9] The "golden age" of combi-chem lasted from 1992 to about 1997 and witnessed rapid improvements in the speed and throughput of the technology.[10] After this initial wave of enthusiasm, however, the growth of combi-chem slowed in the late 1990s because the synthesis and screening of large, quasi-random compound libraries failed to yield the expected results. In practice, the method produced low "hit" rates and did not lead to the discovery of new "blockbuster" drugs, producing a sense of disillusionment in the industry. It gradually became clear that the first generation of combinatorial libraries had been ineffective because of their excessive complexity and the low purity caused by the presence of unwanted synthetic byproducts.[11] According to Nobel-laureate chemist K. Barry Sharpless of the Scripps Research Institute in San Diego, combinatorial synthesis generated variant molecules that were too much alike and did not fill enough of the available "molecular space."[12]

In response to the reassessment at the end of the 1990s, many pharmaceutical companies and drug-discovery firms scaled back and reoriented their combi-chem units. Although the initial practice had been to create large, diverse screening libraries for the discovery of lead compounds, drug companies now began to use combi-chem for "optimization," or modifying the molecular structure of a lead compound to enhance its biological activity. Combi-chem was also

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[8] Barry A. Bunin and Jonathan A. Ellman, "A General and Expedient Method for the Solid-Phase Synthesis of 1,4-Benzodiazepine Derivatives," *Journal of the American Chemical Society*, vol. 114 (1992), pp. 10997-10998.
[9] Alper, "Drug Discovery on the Assembly Line."
[10] Stu Borman, "Combinatorial Chemistry," *Chemical & Engineering News*, vol. 80, no. 45 (November 11, 2002), pp. 43-57.
[11] Christopher Lipinski and Andrew Hopkins, "Navigating Chemical Space for Biology and Medicine," *Nature*, vol. 432 (December 16, 2004), pp. 855-861.
[12] Hartmuth C. Kolb and K. Barry Sharpless, "The Growing Impact of Click Chemistry on Drug Discovery," *Drug Discovery Today*, vol. 8, no. 24 (December 2003), pp. 1128-1137.

integrated with rational drug design, which involves the use of computer modeling to generate a more focused library of compounds with a greater probability of possessing the desired biological activity.[13] In rational drug design, a biochemical target in the body is identified as a potential site of drug action. Researchers then use x-ray crystallography to determine the 3-D structure of the molecular complex between a natural body chemical (such as a hormone or a neurotransmitter) and its receptor.[14] From the configuration of the binding site, pharmacologists try to predict the structure of small molecules with the appropriate shape and chemical properties to bind tightly and selectively to the receptor.[15] In this case, combi-chem and HTS represent only about a third of the activity involved in the process of drug development.

Utility of the Technology

According to Dr. William A. Nugent of Vertex Pharmaceuticals (Cambridge, Mass.), "Combinatorial chemistry was originally seen as a powerful tool for lead discovery, but that didn't pan out. Instead, it's become an important tool for optimization."[16] During the optimization process, medicinal chemists use combi-chem to synthesize hundreds of structural variants of a lead molecule in an effort to enhance its biological activity and eliminate unwanted side effects.[17] The resulting compound library is screened with HTS to identify the variant molecules that bind most tightly and selectively to the receptor.[18] Today the pharmaceutical industry focuses on designing libraries of "drug-like" compounds that are suitable for oral administration. Such molecules typically consist of fewer than 30 non-hydrogen atoms, lack toxic or reactive elements, and are stable in the presence of water and oxygen. Other characteristics of small-molecule drugs are the ability to be absorbed through the gastrointestinal tract, solubility in lipids, and a moderate rate of metabolism in the liver, so the drug can have a useful physiological effect before being broken down.[19]

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[13] Borman, "Combinatorial Chemistry."
[14] Mark S. Lesney, "Rationalizing Combi-Chem," *Modern Drug Discovery*, vol. 5, no. 2 (February 2002), pp. pp 26–30.
[15] Robert F. Service, "Combinatorial Chemistry Hits the Drug Market," *Science*, vol. 272 (May 31, 1996), pp. 1266-1268.
[16] Author's telephone interview with Dr. William A. Nugent, Vertex Pharmaceuticals, June 23, 2009.
[17] Konrad H. Bleicher, Hans-Joachim Böhm, Klaus Müller, and Alazander I. Alanine, "Hit and Lead Generation: Beyond High-Throughput Screening," *Nature Reviews Drug Discovery*, vol. 2 (May 2003), pp. 369-378.
[18] Plunkett and Ellman, "Combinatorial Chemistry and New Drugs," p. 73.
[19] Simon J. Teague, Andrew M. Davis, Paul D. Leeson, and Tudor Oprea, "The Design of Leadlike Combinatorial Libraries," *Angewandte Chemie International Edition*, vol. 38, no. 24 (1999), pp. 3743-3748.

Instead of the vast combinatorial libraries once generated by the split-and-pool method, the current approach is to create smaller libraries of drug-like molecules using parallel synthesis with one- or two-step reactions. A method developed by Sharpless known as "click chemistry" uses a few highly efficient reactions to synthesize compound libraries based on generic molecular structures called pharmacophores, as well as existing drugs and natural products. Each derivative is more than 85 percent pure, rather than a mixture of synthetic byproducts.[20]

To constrain the size of combinatorial libraries, researchers often use a computer program to create a "virtual" library of the millions of hypothetical compounds that would result from the reaction of a pharmacophore with various functional groups. Computational filters are then used to reduce the number of virtual compounds to those with the most desirable bulk properties and metabolic and pharmacokinetic profiles. Only this subset of compounds is actually synthesized for screening purposes.[21] Whereas the combinatorial libraries generated by quasi-random synthesis typically contain more than 5,000 variant molecules, those based on virtual screening range from 50 to 100.[22]

Another pharmaceutical application of combi-chem is to develop manufacturing processes for commercial drugs by optimizing the sequence of synthetic reactions to obtain a pure end-product in an economical manner. Combi-chem is also used in the polymer and petrochemical industries for the discovery of new catalysts. [23]

Potential for Misuse

In principle, the capacity to synthesize large libraries of novel compounds and screen them rapidly for biological activity might be exploited to develop novel chemical warfare (CW) agents. Pharmaceutical and agrochemical companies currently employ combi-chem and HTS to build large databases of chemical compounds containing information on their toxicity to humans, animals, and plants, as well as physiochemical properties such as stability, volatility, and persistence. Because private companies are only interested in molecules of commercial value, the development of a new drug or pesticide is normally ends if it is highly toxic in humans.

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[20] Kolb and Sharpless, "The Growing Impact of Click Chemistry on Drug Discovery."
[21] Thierry Langer and Gerhard Wolber, "Virtual Combinatorial Chemistry and In Silico Screening: Efficient Tools for Lead Structure Discovery?" *Pure and Applied Chemistry*, vol. 76, no. 5 (2004), pp. 991-996.
[22] Lesney, "Rationalizing Combi-Chem."
[23] Author's interview with Dr. Joel M. Hawkins, Pfizer Research and Development Center, Groton, CT, June 26, 2009.

Nevertheless, a state or terrorist organization seeking to develop new CW agents might deliberately search a database for toxic compounds have been created unintentionally in the hope of identifying new types of chemicals with lethal or incapacitating properties.[24] Historical precedent exists for such a process. Both the G-series and V-series nerve agents were discovered accidentally during industrial pesticide research and then developed into military CW agents by the German and British armies, respectively.

Ease of Misuse (Explicit and Tacit Knowledge)

Although combi-chem and HTS have some potential for misuse, the magnitude of the risk is difficult to assess. The technique generally works best for optimizing compounds with a fairly high molecular weight (about 700 daltons), yet traditional chemical warfare agents such as mustard or sarin have a molecular weight below 500 daltons. Combi-chem may therefore be best suited for the development of "mid-spectrum" biochemical agents such as peptide bioregulators, provided that the weaponization and delivery challenges associated with these agents can be overcome.[25] (See Chapter 8.)

To gain access to a large compound library to search for highly toxic molecules, a proliferant state or terrorist group might try to penetrate the computer system of a pharmaceutical company, perhaps with the aid of an insider such as a disgruntled employee. A great deal of information on drug development in academic and industrial laboratories is also available in the public domain. Several open-source databases contain data on the pharmacokinetic properties of newly synthesized compounds, and pharmaceutical companies often publish failed drug-discovery campaigns in the scientific literature while keeping their best commercial leads under wraps.[26] If the sole purpose of the development process is to identify candidate CW agents for military use, there is no need to worry about harmful side effects, making it possible to streamline the process of lead identification and optimization.[27]

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[24] George W. Parshall, Graham S. Pearson, Thomas D. Inch, and Edwin D. Becker, "Impact of Scientific Developments on the Chemical Weapons Convention (IUPAC Technical Report)," *Pure and Applied Chemistry*, vol. 74, no. 12 (2002), p. 2331.
[25] Jonathan B. Tucker, "The Body's Own Bioweapons," *Bulletin of the Atomic Scientists*, March/April 2008, pp. 16-22.
[26] Verdugo, personal communication to author.
[27] Author's interview with George W. Parshall, former director of Central Research and Development at the DuPont company, Wilmington, DE, June 8, 2009.

Nevertheless, even in the unlikely event that a terrorist with a good knowledge of pharmacology and synthetic organic chemistry was able to access the relevant information, it would be difficult and expensive to employ combi-chem and HTS to optimize a novel CW agent and produce it in sufficient quantities for a terrorist attack. Although skilled technicians can perform some aspects of combinatorial synthesis, a synthetic organic chemist with Ph.D.-level expertise would have to oversee the process, and a pharmacologist with a good understanding of physiology would have to identify an appropriate biomolecular target for screening. Employing combi-chem and rational-design methods to develop a novel CW agent from scratch would probably require a multidisciplinary team of 40 to 60 people, including biochemists to isolate the target receptor, x-ray crystallographers to determine its molecular structure, and about 20 organic chemists to synthesize lead compounds for optimization.[28]

Accessibility to the Technology

Combi-chem involves the use of specialized hardware and software for the automated synthesis of compound libraries and their screening against biomolecular targets. Fewer than 10 major manufacturers of such equipment exist, and nearly all are based in the United States, the European Union, and Japan. (Leading U.S. suppliers include Symyx, Tecan, and Caliper.) A turnkey combi-chem and HTS system costs about $1 million, and the commercial market consists almost entirely of large pharmaceutical companies and start-ups in industrialized countries. Nevertheless, according to a former researcher at Symyx, company scientists built early prototypes for advanced combi-chem and HTS systems using components purchased at Home Depot.[29] Given this fact, a small team with the right knowledge, experience, and motivation might be able to assemble a crude combi-chem and HTS system fairly cheaply that could perform reasonably well. The greatest obstacle is not access to hardware components but the need for individuals with the appropriate knowledge and experience.

Imminence and Magnitude of Risk

The greatest potential for the misuse of combi-chem and HTS lies with advanced industrial countries that have clandestine CW development programs and could use the

[28] Author's interview with Nugent.
[29] Verdugo, personal communication to author.

technology to identify lethal or incapacitating chemicals that are militarily more effective or less costly to produce than existing agents. Thus, the imminence of risk is fairly high for state programs but low for non-state actors.

Awareness of Dual-Use Potential

The dual-use implications of combi-chem and HTS were first discussed in 2002 at an expert workshop convened by the International Union of Pure and Applied Chemistry (IUPAC) to discuss the implications of scientific and technological advances for the Chemical Weapons Convention (CWC). Although the experts could not rule out the possibility that compound libraries generated by combi-chem and HTS might be exploited to discover novel CW agents, particularly for small-scale or terrorist use, they put the threat in perspective by pointing out the technical hurdles:

> Some new chemicals found by database mining will have toxicity characteristics that could lead to their being considered as chemical weapon agents. . . . Unless the compounds are simple and of low molecular weight, considerable effort will be required to devise practical methods to produce sufficient quantities to constitute a threat. Such quantities are likely to be a few tens of kilograms for research and development (or terror applications) and tens or hundreds of tons for military use. Further, unless the new compounds are gases or liquids with suitable volatility characteristics, all the usual problems of dispersing solids so that they could be used effectively as chemical weapons will apply.[30]

A second IUPAC workshop on chemical technologies and the CWC, held five years later in April 2007, concluded that the risk of misuse of combi-chem and HTS for CW purposes was "increasing." The experts noted that among the large number of bioactive chemicals synthesized and screened during pharmaceutical R&D, there will inevitably be toxic chemicals, some of which may have other properties that could make them candidate CW agents. Here again, however, the experts put the threat in context:

[30] Parshall, Pearson, Inch, and Becker, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 2331.

> . . . [D]espite this dramatic increase in knowledge and in the number of chemicals that could have CW utility given their toxicological and chemical profile, the risk to the object and purpose of the CWC posed by these scientific advances may not have increased as much as one might fear. To use a new toxic compound as an effective CW requires a number of developments before it can successfully be used. However, the risks from such novel toxic chemicals should not be ignored.[31]

A new concern raised at the 2007 IUPAC meeting was the potential use of combi-chem and HTS to develop novel incapacitants—often referred to misleadingly as "non-lethal" agents—for law enforcement and counterterrorism purposes. Such chemicals affect the central nervous system to induce persistent sedation, anesthesia, or unconsciousness, and can be fatal at high doses. Although scientists have tried to expand the safety margin between the lethal and incapacitating effects of these drugs, it is impossible to control exposure precisely during tactical operations. As a result, the effects of these agents are fundamentally unpredictable and dangerous.[32]

Characteristics of the Technology Relevant to Governance

Embodiment. Combi-chem and HTS are a hybrid technology requiring a combination of specialized hardware and software.

Maturity. The technology is mature and commercially available.

Convergence. The technology is moderately convergent because it draws on fundamental advances in miniaturization, laboratory robotics, and drug-screening technologies.

Rate of advance. Combi-chem and HTS have existed since the late 1980s but have undergone a number of changes. These technologies emerged initially as a spinoff from solid-phase peptide synthesis and were generalized to the broader universe of drug-like molecular

[31] Mahdi Balali-Mood, Pieter S. Steyn, Leiv K. Sydnes, and Ralf Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention (IUPAC Technical Report)," *Pure and Applied Chemistry*, vol. 80, no. 1 (2008), p. 184.

[32] For more on chemical incapacitating agents, see Chapter 18 in this volume and Alan M. Pearson, Marie Isabelle Chevrier, and Mark Wheelis, eds., *Incapacitating Biochemical Weapons: Promise or Peril?* (Latham, MD: Lexington Books, 2007).

structures. In the field of drug discovery, combi-chem was originally conceived as a brute-force method for the identification of lead compounds but proved to be of limited value for that purpose. Today its main use is for optimization, or improving the characteristics of promising leads. Although the rate of advance was exponential during the 1990s, it has since plateaued.

International diffusion. Today combi-chem and HTS equipment is available to any country with a modern pharmaceutical research and development infrastructure (such as Australia, Canada, the European Union, Japan, Russia, Singapore, South Africa, and the United States) and, to a lesser extent, countries with a generic drug manufacturing capability (such as China, India, Spain, Israel, Hungary, and Brazil). The quality of Chinese pharmaceutical science in particular is improving rapidly, in part because a large number of Chinese scientists who perform outsourced development work for U.S. pharmaceutical firms. Most countries of CW proliferation concern, such as Syria and North Korea, lack a highly developed pharmaceutical infrastructure and are therefore unlikely to acquire combi-chem and HTS equipment and know-how for that purpose. Iran is a possible exception to the rule, however. According to the U.S. intelligence community, "Tehran maintains dual-use facilities intended to produce CW agent in times of need and conducts research that may have offensive applications."[33]

Past and Current Approaches to Governance

Combi-chem and HTS have been available since the late 1980s and have diffused widely throughout the advanced industrial countries. At present, no restrictions exist on the use or export of such equipment to countries of CW proliferation concern. This lack of regulation is in contrast to the stringent controls imposed by the Australia Group countries on trade in dual-use chemicals (e.g., precursors for mustard and nerve agents) and corrosion-resistant chemical reactors and pipes made of high-nickel steel alloys such as Hastelloy, which have legitimate commercial applications but could be used to produce CW agents. At present, it would not be cost-effective to impose legally binding export controls on combi-chem and HTS technologies. One reason is that a state proliferator or sophisticated terrorist group could generate and screen a large number of molecular variants by means of labor-intensive methods such as manual organic synthesis, or simply by screening compounds from a historical collection. Moreover, any country

[33] J. Michael McConnell, Director of National Intelligence, "Annual Threat Assessment of the Intelligence Community for the House Permanent Select Committee on Intelligence," February 7, 2008, p. 13.

sophisticated enough to conduct drug-discovery research probably has the capacity to reverse-engineer its own combi-chem and HTS equipment, should it decide to do so.[34]

Options for Future Governance

If a decision was made to regulate combi-chem and HTS technology, the most effective approach would be to control access to specialized hardware and software. This measure might involve voluntary self-regulation on the part of the major suppliers, perhaps through a set of best practices as the gene synthesis industry has done. (See Chapter 10.) To help identify customers involved in illicit procurement activities, a "tripwire" mechanism could be established. The U.S. government would seek the voluntary cooperation of the leading equipment vendors in the combi-chem field and ask them to report whenever a customer or start-up with whom they are not familiar orders a significant quantity of hardware or a turnkey system. Proliferant states might also use outsourcing contracts with foreign research laboratories to acquire sensitive technology. Suppliers should therefore treat orders from unfamiliar customers and contract labs as potential "red flags" warranting greater scrutiny.

Under a voluntary governance system, suppliers would be asked to perform due diligence on suspect customers and to notify customs or law-enforcement authorities before a sale is allowed to proceed. Alternatively, companies seeking to import combi-chem and HTS equipment might be asked to demonstrate their *bona fides* to authorities in the exporting country before the sale could be approved. To ensure a level playing field for competition, it would be desirable for all major suppliers of combi-chem and HTS systems to harmonize their policies in this area.

Conclusions

The dual-use potential of combinatorial chemistry and high-throughput screening for the discovery of novel CW agents has been recognized since at least 2002. Although this technology is probably too complex and costly to be exploited by terrorist organizations, it poses a significant risk of misuse by proliferant states with advanced CW programs. Proposed governance options include monitoring sales of combi-chem and HTS equipment and software to countries or front companies of CW proliferation concern.

[34] Verdugo, personal communication to author.

Chapter 7: Chemical Micro Production Devices

Amy E. Smithson

Changes are afoot in the chemical and related industries. In addition to their typical business drive for efficiency, simplicity, flexibility, and cost-effectiveness, chemical companies have more recently sought to reduce the industry's environmental footprint and to achieve greater personnel, process, and environmental safety. Chemical micro process technology, which was initially developed in the 1980s, is proving that it can respond to the industry's needs. Compared to standard chemical reactors, these miniaturized devices are safer, faster, more selective, and more energy-efficient. Moreover, micro process devices produce higher and more uniform product yields, have greatly reduced waste streams, and are more cost-effective. These advantages explain why the chemical industry has investigated multiple applications of this technology and begun to adopt it for research and development (R&D), process development, product scale-up, and actual commercial production. Although legitimate businesses are embracing micro processing technology, there is a risk that state and sub-national actors might divert it for military purposes, as is the case with any dual-use technology.

The hijacking of a civilian technology for military purposes is hardly a new phenomenon. World War I ushered in the militarization of chemistry and the use of poison gas was a hallmark of that conflict. Although 70 years later some 25 states were assessed to have chemical warfare (CW) programs, the entry into force of the Chemical Weapons Convention in 1997 eased concerns about the state-level pursuit of these arms. Even as the number of chemical weapons possessors dwindled to a few nations, however, terrorist interest in this type of weaponry became apparent. Aum Shinrikyo's infamous March 1995 attack on the Tokyo subway with the nerve agent sarin, and the use of chlorine-spiked explosive attacks by Islamic fundamentalists in Iraq in 2007, proved that crude forms of chemical warfare are within the reach of terrorists.

Amidst this mixture of positive and negative proliferation trends, the coming of age of chemical micro process technology portends additional uncertainty. Chemical micro process devices handle the sustained processing of corrosive chemicals very well, a factor critical to poison gas production. A chemical micro plant could manufacture substantial quantities of CW agents with few of the telltale indicators commonly associated with chemical weapons factories, such as pollution abatement equipment. Thus, the handful of states with ongoing CW programs

might exploit micro production devices to advance and conceal these activities. Some states might even consider reentering the chemical weapons business, particularly if they are confident that an illicit weapons program will go undetected. For terrorists, micro process devices could ease the technical challenges of scaling up to make large amounts of CW agents. The challenge for the international community is to find a means that permits micro process technology to flourish for legitimate commercial and scientific purposes, while preventing its acquisition by those with hostile intent.

Overview of the Technology

Chemical micro process devices can be strikingly compact, with some as small as credit cards, dice, or coins. With inner channel(s) ranging from sub-micrometer to sub-millimeter in size, chemical micro devices have a high ratio of reactor surface to reactant volume that promotes efficient surface catalysis and enables highly efficient heat exchange. These characteristics in turn allow more precise regulation of the energy in the reaction mass, reducing the formation of unwanted byproducts. Chemical micro devices also operate continuously, utilizing miniature sensors and computers to achieve tight control over mixing, temperature, pH, flow rate, and other reaction conditions. Made of materials such as ceramic, stainless steel, glass, silicon, and the metal alloy combination known as Hastelloy, chemical micro devices are well suited for highly exothermic, potentially explosive reactions and the long-term processing of highly corrosive chemicals.[1]

Precision injection of chemicals into the channels of a micro device allows tiny drops to merge and react, often within seconds. To enhance reaction efficiency further, the channel walls of microreactors can be seeded with catalysts. The channels can also be constructed in shapes such as a herringbone pattern, and internally structured with etched patterns (e.g., diamond shapes) to enhance mixing. A variety of chemical micro process devices have been developed, including several types of reactors, heat exchangers, and mixers.[2] (For simplicity's sake, unless otherwise specified, this chapter refers to all three types of equipment as microreactors.)

[1] J. Yoshida , A. Nagaki, T. Iwasaki, and S. Suga, "Enhancement of Chemical Selectivity by Microreactors," *Chemical & Engineering News*, vol. 83, no. 22 (May 30, 2005), pp. 43–52; C. Wille and R. Pfirmann, "Pharmaceutical Synthesis via Microreactor Technology Increasing Options for Safety, Scale-up and Process Control," *Chemistry Today,* vol. 22 (2004), pp. 20–3.

[2] Among the micro devices are falling-film, cyclone, capillary, cartridge, and sandwich reactors; plate-type and coaxial heat exchangers; and microjet, cascade type, split-plate, caterpillar, and comb-type mixers, to name a few.

Because microreactors are capable of highly focused energy control, efficient contact with catalysts, and rapid mixing, they can convert even low-yield batch reactions into high-yield production processes. They have successfully performed inorganic, biochemical, and organic chemical reactions and have been applied to the combinatorial production of molecular structures for high-throughput screening. Microreactors also have the potential to enable production using chemistries that cannot be performed in standard industrial equipment, such as the high-yield production of hydrogen cyanide from formamide.[3]

History of the Technology

Scientists discussed the possibility of nanoprocessing for over 70 years before the emergence of the requisite manufacturing technologies made it possible to begin turning theory into reality. Another significant factor that contributed to the realization of micro process technology was the German government's response to domestic political pressure in the 1980s, when the green movement pushed for policies and technologies to reduce environmental harm. Although Germany's large chemical industry was already subject to environmental regulation, it nonetheless became a focus of efforts to develop more environmentally friendly technologies. The German government called on leading research institutes to work in collaboration with chemical companies to explore the potential of micro process technologies and, if they showed promise, to integrate them into commercial plants to reduce the industry's environmental footprint.[4] Thereafter, Germany became a hub of microreactor research and development.[5] In the

[3] Electrolytic or electrophoretic processes have been demonstrated in microreactors, which have even been used to produce soluble organic macromolecular compounds. In addition to these features, microreactor systems are also defined by their method of manufacture, which includes precision engineering and microtechnology. See Volker Hessel, Patrick Löb, Holger Löwe, "Development of Reactors to Enable Chemistry rather than Subduing Chemistry around the Reactor−Potentials of Microstructured Reactors for Organic Synthesis," *Current Organic Chemistry*, vol. 9, no. 8 (2005), pp. 765–87; Paul Watts and Stephen J. Haswell, "The Application of Microreactors for Small Scale Organic Synthesis," *Chemical & Engineering Technology*, vol.28, no. 3 (2005), pp. 290–301; Patrick Löb, Holger Löwe, Volker Hessel, "Fluorinations, Chlorinations and Brominations of Organic Compounds in Micro Structured Reactors," *Journal of Fluorine Chemistry*, vol. 125, no. 11 (2004), pp. 1677–94. See also, Wolfgang Ehrfeld, Volker Hessel, Holger Löwe, eds., *Microreactors: New Technology for Modern Chemistry* (Weinheim, Germany: Wiley-VCH, 2000), pp. 1–114; Holger Löwe, Volker Hessel, and Andreas Mueller, "Microreactors: Prospects Already Achieved and Possible Misuse," *Pure Applied Chemistry*, vol. 74 (2002), pp. 2271–6; Ian Hoffman, "Scientist: Terrorists Could Use Microreactors," *Oakland Tribune*, August 12, 2005.

[4] This account of the origins of the microreactor industry was provided by several European and U.S. scientists who were engaged in R&D activities in the 1990s. (Author interviews with scientists and senior corporate officials from the chemical micro process technology industry, New Orleans, Louisiana, and Washington, DC, March-April 2008.) According to the German Ministry of Economics and Technology, the German chemical industry accounts for 12 percent of the world's total chemical production, employs over 438,000 workers, and generates revenues in excess

1990s and early 2000s, scientists and companies in the United States, a few other European countries, and Japan also undertook research and development (R&D) on microreactors.[6] Japan later followed in Germany's footsteps by urging its chemical industry and university scientists to jointly develop micro process technology.[7]

Utility of the Technology

Microreactors have several advantages over standard batch reactors. First, because the chemical industry produces and processes highly combustible and toxic materials, safety is always a primary concern. Reactions that involve hazardous reagents or unstable intermediates and generate extreme temperatures can be executed much more safely in microreactors because their high surface area-to-reactant ratio and computerized monitoring enable the continuous adjustment of operational parameters to prevent a reaction from spiraling out of control.[8] Also, rather than buying, transporting, and storing multi-ton quantities of hazardous chemicals on-site, companies can reduce safety risks by employing microreactors to produce the quantity of hazardous chemical(s) needed for a specific manufacturing process on a "just-in-time" basis. To illustrate, had Union Carbide in Bhopal, India, produced methyl isocyanate on demand instead of using standard production and storage methods, it might have prevented the 1984 disaster at the

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of 42 billion Euros per year. More detail on Germany's chemical industry can be found at: <www.german-business-portal.info/GBP/Navigation/en/Business-Location/Industrial-sectors/chemical-industry,did=221220.html>.

[5] Several German entities played leading roles in bringing chemical micro process technology to life, including Mikroglas ChemTech GmbH, the Institute for Mikrotechnik Mainz, the Karlsruhe Research Center, Cellular Process Chemistry Systems GmbH, the Fraunhofer Alliance for Modular Microreaction Systems, and Ehrfeld Mikrotechnik BTS, a company founded by one of the field's pioneers, Wolfgang Ehrfeld.

[6] A sampling of the locations in which early R&D work was performed includes Pacific-Northwest Laboratories, the Massachusetts Institute of Technology, Oregon State University, and Microfluidics in the United States; the University of Hull and University College London in the United Kingdom; the Lund Institute of Technology in Sweden; the University of Twente and TNO Science and Industry in the Netherlands; the National Center for Scientific Research in France; and Tokyo University in Japan, among others. Conference program, 1st International Conference on Microreaction Technology, Frankfurt, February 23–25, 1997; conference program, 3rd International Conference on Microreaction Technology," Frankfurt, April 18–21, 1999.

[7] The Research Association of Micro Chemical Process Technology was founded to facilitate Japanese collaboration to bring about high-efficiency chemical plants. For more, see: < www.mcpt.jp/eindex.html>.

[8] Xini Zhang, Stephen Stefanick, and Frank J. Villani, "Application of Microreactor Technology in Process Development," *Organic Process Research & Development*, vol. 8, no. 3, 2004, pp. 455–60; Kunio Yube and Kazuhiro Mae, "Efficient Oxidation of Aromatics with Peroxides under Severe Conditions Using a Microreaction System," *Chemical & Engineering Technology*, vol. 28, no. 3, 2005, pp. 331–6.

plant, which killed over 3,800 people and injured upwards of 11,000.[9] In short, the wider industrial use of microreactors can provide significant safety benefits.[10]

Other major advantages of micro process technology involve the quality, quantity, and rapidity of reactions. Chemical companies typically discard 10 to 20 percent of the output from standard reactors because it fails to meet product quality standards. Microreactors, in contrast, can produce chemicals with low byproduct contamination. Studies and initial industrial experience have also demonstrated that reactions performed in micro devices have greatly increased product yields. Converting a process from standard batch reactors to microreactors usually results in yields that are at least 20 to 30 percent higher.[11] To illustrate both the safety and yield advantages, the Xi'an Huian Industrial Group in China installed a fully automated microreactor plant to make nitroglycerine, a poisonous and explosive compound, after initial experiments yielded 100 liters per hour of nitroglycerine that was 90 percent pure. The nitration reaction, which requires high temperatures in a standard reactor, occurs at room temperature in the microreactor system.[12]

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[9] On Bhopal, see Robert D. McFadden, "India Disaster: Chronicle of a Nightmare," *New York Times*, December 10, 1984; Jackson B. Browning, "Union Carbide: Disaster at Bhopal," in Jack Gottschalk, ed., *Crisis Management: Inside Stories on Managing Under Siege* (Detroit: Visible Ink Press, 1993)

[10] Eero Kolehmainen et al., "Advantages of On-Site Microreactors from Safety Viewpoint," presentation 198e delivered at the 10th International Conference Microreaction Technology, New Orleans, April 9, 2008; Ralf Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," *Arms Control Today*, vol. 38, no. 2 (March 2008), p. 19; Mahdi Balali-Mood, Pieter S. Steyn, Leiv K. Sydnes, and Ralf Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention: Report of the International Union of Pure and Applied Chemistry" *Pure and Applied Chemistry*, vol. 80, no. 1 (2008), p. 188. Note that companies purchase the chemicals used to manufacture their products in large quantities because bulk purchases are more economical. In addition to on-demand production, the use of microreactors obviates the risks associated with transporting hazardous chemicals from plant to plant via truck, rail, and tanker shipments.

[11] With a bromination reaction, scientists from Hitachi reported an increase in yield of 98 percent. Myake Ryo, Togashi Shigenori, "Innovation of Chemical Process Engineering Based on Micro-Reactor," *Hitachi Hyoron*, vol. 88, no. 1 (2006), pp. 916–21. See also, Keven M. McPeak, Jason B. Baxter, "Microreactor for High-Yield Chemical Bath Disposition of Semiconductor Nanowires: ZnO Nanowire Case Study," *Industrial & Engineering Chemistry Research*, vol. 48, no. 13 (2009), pp. 5954–61; Chanbasha Basheer, Sindhu Swaminathan, Hian Kee Lee, Suresh Valiyaveettil, "Development and Application of a Simple-Capillary Microreactor for Oxidation of Glucose with a Porous Gold Catalyst," *Chemical Communications*, vol. 2, no. 1(January 2005), pp. 409–10; Koichi Mikami, Masahiro Yamanaka, Md. Nazrul Islam, Takayuki Tonoi, Yoshimitsu Itoh, Masaki Shinoda, and Kenichi Kudo, "Nanoflow Microreactor for Dramatic Increase Not Only in Reactivity but Also in Selectivity: Baeyer–Villiger Oxidation by Aqueous Hydrogen Peroxide Using Lowest Concentration of a Fluorous Lanthanide Catalyst," *Journal of Fluorine Chemistry*, vol. 127, no. 4–5 (May 2006), pp. 592–6.

[12] Xi'an Huian produces nitroglycerine using micromixers, micro heat exchangers, and a reactor that was only 0.0021 cubic meters in a $30m^3$ plant. The production rate is 15 kilograms per hour. Ann M. Thayer, *Chemical & Engineering News*, vol. 83, no. 22 (May 30, 2005), p. 43. For other examples, see Volker Hessel, Patrick Löb, Holger Löwe, "Industrial Microreactor Process Development up to Production: Pilot Plants and Production" in Thomas Wirth, ed., *Microreactors in Organic Synthesis and Catalysis* (Weinheim, Germany: Wiley-VCH, 2008), pp. 238–70. On industrial applications in Europe, the United States, and Japan, see Norbert Kockmann, Oliver

Because of the higher yields of microreactors, companies can increase their profit margins because smaller quantities of feedstock chemicals are required. In some processes, chemical catalysts can be reused thousands of times.[13] Additional cost saving results because companies do not have to buy and operate expensive temperature-control equipment, which is often used with standard reactors to moderate reaction temperatures. Cost-efficiency also occurs because reactions in microreactors are so speedy: a reaction that would require an hour in a batch reactor typically takes less than 10 seconds in a microreactor. A further advantage is the ability to scale-up a process rapidly. Once a process has been proven and optimized in a single-channel device, it can be scaled up to industrial production simply by "numbering up" to tens or even hundreds of identical micro process systems, operating in parallel arrays, to achieve the desired output.[14] In contrast, the physics and kinetics of reactions in standard batch equipment may vary considerably as volumes are increased, complicating the scale-up process.

Lower energy consumption is just one of the reasons that chemical micro devices are considered a green technology. Switching a process from standard reactors to microreactors often allows the use of different solvents, reduced volumes, and even solvent-free reactions, radically reducing the waste streams from a chemical manufacturing process. Once transitioned

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Brand, Gary K. Fedder, Christofer Hierold, Jan G. Korvink, and Osamu Tabata, eds., *Micro Process Engineering−Fundamentals, Devices, Fabrication, and Applications* (Weinheim, Germany: Wiley-VCH, 2006), pp. 387–462 . On higher yields, see Wolfgang Ehrfeld, Klaus Golbig, Volker Hessel, Holger Löwe, and Thomas Richter, "Characterization of Mixing in Micromixers by a Test Reaction: Single Mixing Units and Mixer Arrays," *Industrial & Engineering Chemistry Research*, vol. 38, no. 3 (1999), pp. 1075–82; Chanbasha Basheer et al., "Design of a Capillary-Microreactor for Efficient Suzuki Coupling Reactions," *Tetrahedron Letters*, vol. 45, no. 39 (September 2004), pp. 7297–7300.

[13] Other advantages of micro process devices over conventional equipment include improved kinetic data to guide the optimization of the reaction, short retention time of the reactants in the device, higher selectivity of the reactions, and a reduced quantity of reaction by-products. Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 188. Regarding the economical reuse of catalysts, Velocys has patented a technology for liquid phase reactions wherein the catalyst is tethered inside the microchannel, allowing for continuing processing and eliminating the traditional step of recovering the catalysts and its associated costs. For more information, go to: <www.velocys.com>.

[14] Note that rapid scale-up ability is very attractive to the pharmaceutical industry, where product specifications are particularly demanding and regulatory approval of a scaled-up process in standard reactors can be very time consuming. Ehrfeld, Hessel, and Löwe, *Microreactors: New Technology for Modern Chemistry*, pp. 6–12; Anna Lee, Y. Tonkovich, and Eric A. Daymo, "Microreaction Systems for Large-Scale Production," in Thomas R. Dietrich, ed., *Microchemical Engineering in Practice* (Hoboken, NJ: Wiley, John & Sons, 2009), pp. 299–324.Volker Hessel, Patrick Löb, Holger Löwe, "Industrial Microreactor Process Development up to Production," in Wirth, ed., *Microreactors in Organic Synthesis and Catalysis*, pp. 211–70.

into microreactors, some chemical processes do not require traditional pollution abatement systems, such as air filter stacks or "scrubbers."[15]

Standard batch reactors are flexible in that they can be used to synthesize different chemicals. Increasingly, this characteristic is also true of microreactors. Several companies offer modular micro systems that can switch from one process to another within hours.[16] Most applications of microreactors currently involve liquid and gaseous input chemicals, intermediates, and products.[17] To prevent solid precipitants from clogging and fouling the ultra-tiny channels of the devices, microreactor manufacturers routinely coat the channels with special materials and make other adjustments to enable the processing of solids. Micro devices are often packed with solid catalysts, and some solid products are already being commercially

[15] For articles on solvent-free, alternate solvent, and environmentally friendly processing in microreactors, P. Löb , H. Löwe , and V. Hessel, "Fluorinations, Chlorinations and Brominations of Organic Compounds in Micro Reactors," *Journal of Fluorine Chemistry* vol. 125, no. 11 (November 2004), pp. 1677-94.; H. Löwe , V. Hessel, S. Hubbard, P. Löb , "Addition of secondary amines to a,b-unsaturated carbonyl compounds and nitriles by using microstructured reactors," *Organic Process Research & Development*, vol. 10, no. 6 (2006), pp. 1144-1152; G. Socher, R. Nussbaum, K. Rissler, and E. Lankmayr, "Transesterification of fatty acid ethoxylates in supercritical Methanol, then Gas Spectrometry-Mass Spectrometric Determination of the Derived Methyl Esters, for Identification of the Initiators," *Fresenius' Journal of Analytical Chemistry*, vol. 371, no. 3 (October 2001), pp. 369-375; T. Razzaq, T. N. Glasnov, C. O. Kappe, "Continuous-Flow Microreactor Chemistry Under High-Temperature/Pressure Conditions," *European Journal of Organic Chemistry*, vol. 2009, no. 9 (March 2009), pp. 1321-1325; V. Hessel, D. Kralisch, U. Kritschil, "Sustainability through Green Processing – Novel Process Windows Intensity Micro and Milli Process Technologies," *Energy & Environmental Science*, vol. 1, no. 4 (2008), pp. 467-78; Stephen J. Haswell and Paul Watts, "Green Chemistry: Synthesis with Micro Reactors," *Green Chemistry* vol. 5 (2003), pp. 240–9; Lingjie Kong, Qi Lin, Xiaoming Lv, Yongtai Yang, Yu Jia, and Yaming Zhou, "Efficient Claisen Rearrangement of Allyl para-Substituted Phenyl Ethers Using Microreactors," *Green Chemistry* 11, 2009, pp. 1108–11; Andrezej I. Stankiewicz and Jacob A. Moulijn, "Process Intensification: Transforming Chemical Engineering," *Chemical Engineering Progress* vol. 96 (January 2000), pp. 22–34.

[16] The modules perform different functions required for a chemical reaction (e.g., pumps and sensors, mixers, heat exchangers, reactors, filters and separators, valves), allowing for the plant configuration to be changed as needed. Daniel A. Snyder, Christian Noti, Peter H. Seeberger, Frank Schael, Thomas Bieber, Guido Rimmel, and Wolfgang Ehrfeld, "Modular Microreaction Systems for Homogeneously and Heterogeneously Catalyzed Chemical Synthesis," *Helvetica Chimica Acta* 88, no. 1, January 24, 2005, pp. 1–9; Tassilo Moritz, Reinhard Lenk, Jorg Adler, and Michael Zins, "Modular Micro Reaction System Including Ceramic Components," *International Journal of Applied Ceramic Technology* 2, no. 6, November 21, 2005, pp. 521–8. Companies offering modular systems include the Institute fur Mikrotechnik Mainz and Ehrfeld Mikrotechnik, a division of Bayer Technology Services.

[17] Madhvanand N. Kashid and Lioubov Kiwi-Minsker, "Microstructured Reactors for Multiphase Reactions: State of the Art," *Industrial & Engineering Chemistry Research*, vol. 48, no. 14 (2009), pp. 6465–85; Berengere Chevalier, Elena Daniela Lavric, Carine Cerato-Noyerie, Clemens R. Horn, Pierre Woehl, "Microreactions for Industrial Multi-phase Applications: Test Reactions to Develop Innovative Glass Microstructure Designs," *Chemistry Today*, vol. 26, no. 2 (March/April 2008), pp. 38–42; Lingling Shui, Jan C.T. Eijkel, Albert van den Berg, "Multiphase Flow in Microfluidic Systems─Control and Applications of Droplets and Interfaces," *Advances in Colloid and Interface Science*, vol. 133, no. 1 (May 31, 2007), pp. 35–49; George N. Doku, Willem Verboom, David N. Reinhoudt, and Albert van den Berg, "On-microchip Multiphase Chemistry—A Review of Microreactor Design Principles and Reagent Contacting Modes," *Tetrahedron*, vol. 61 no. 11 (March 14, 2005), pp. 2273–45.

manufactured in micro pilot plants.[18] Like standard reactors, chemical micro devices can be applied in many ways in all sectors of the chemical industry, from bulk chemical processing to cosmetics.

Potential for Misuse

The formulas for the classic chemical warfare agents (e.g., mustard, sarin, VX) and certain details of their manufacturing processes have long been available in the patent and professional literature.[19] While such information makes it possible for relative novices to synthesize beaker-sized quantities of these agents, it does not include the operational details of scaling-up the synthesis process to very large quantities. As a result, any individual or group that attempts the large-scale manufacture of blister or nerve agents for the first time may be surprised by the reactivity and volatility of the chemicals used in these processes.[20] When demonstrations proved that numbered-up microreactor arrays could produce tons of chemicals per day, however,

[18] See, for example, the case of Clariant International Ltd., which opened a plant in 2004 that makes over 80 tons per year of di-keto-pyrrolo-pyrrole pigments. Ch. Wille, H.-P. Gabski, Th. Haller, H. Kim, L. Unverdortben, and R. Winter, "Synthesis of Pigments in a Three-State Microreactor Pilot Plant: An Experimental Technical Report," *Chemical Engineering Journal*, vol.101, no. 1–3 (August 2004), pp. 179–85; Rainer Weihonen, "A Mighty Mini: Improved Process Control—Thanks to Microreaction Technology (MRT)," *Clariant Factbook: 2006* (Muttenz/Schweiz, Switzerland: 2006), pp. 21–7. See also, S. Duraiswamy and S.A. Khan, "Continuous-flow Synthesis of Metallodielectric Core-Shell Nanoparticles using Three-phase Microfluidics," *11th International Conference on Microreaction Technology: Book of Abstracts* (Kyoto, Japan: 8-10 March 2010), pp. 78–79. Klavs F. Jensen, "Microreaction Engineering–Is Smaller Better?" *Chemical Engineering Science*, vol. 56, no. 2 (January 2001), pp. 297–9; Mathew W. Losey, Martin A. Schmidt, and Klavs F. Jensen, "Microfabricated Multiphase Packed-bed Reactors: Characterization of Mass Transfer and Reactions," *Industrial & Engineering Chemistry Research*, vol. 40, no. 12 (2001), pp. 2555–62.

[19] Thousands of citations describe the synthesis of choking, blister, and nerve agents, including the operating parameters, catalysts, and the chemical reactions. To make warfare agents, particular attention must be paid to temperature control during certain reaction processes. Some of the technically demanding steps are not often used in industry, and the distillation process to obtain pure agent can be very hazardous. U.S. Congress, Office of Technology Assessment, *Technologies Underlying Weapons of Mass Destruction*, OTA-BP-ISC-115 (Washington, DC: U.S. Government Printing Office, 1993), p. 18; Central Intelligence Agency, *The Chemical and Biological Warfare Threat* (Washington, DC: Central Intelligence Agency, 1995), p. 15; Robert K. Mullen, "Mass Destruction and Terrorism," *Journal of International Affairs*, vol. 32, no. 1 (Spring/Summer 1978), pp. 67–8; Stockholm International Peace Research Institute, *The Rise of CB Weapons: The Problem of Chemical and Biological Warfare*, vol. 1 (Stockholm: Almqvist & Wiksell, 1971), p. 76.

[20] While terrorists may not take the step of distilling a warfare agent, a state-level proliferator that seeks a long shelf life for the agent is likely to do so. For more detail on some of the technical production challenges, see U.S. Congress, Office of Technology Assessment, *Technologies Underlying Weapons of Mass Destruction*, pp. 16, 26–7, 133. On the specialized scale-up knowledge not found in the open literature, author's interview with PhD chemist and chemical weapons expert, Washington, DC, July 14, 2000; Raymond A. Zilinskas, "Aum Shinrikyo's Chemical/Biological Terrorism as a Paradigm?" *Politics and the Life Sciences*, vol.15, no. 2 (September 1996), p. 238.

technical specialists began to express concern that the technology could be misused as a proliferation breakout tool.

Chemical micro process devices can perform the sustained processing of corrosive chemicals, a characteristic of the production of chemical warfare agents. Moreover, whereas chemical plants with standard reactors sprawl across many acres, a chemical micro plant is closet-sized and fully automated, avoiding the need for a large staff to monitor operations closely to prevent an accident. As noted earlier, towering exhaust stacks and scrubbers are not present because chemical micro plants do not generate significant hazardous waste streams, nor do they have a high energy consumption rate resulting from the use of industrial-scale chillers to control exothermic reactions.[21] As the commercial chemical industry converts to micro plants, virtually all of the intelligence signatures associated with chemical weapons production will vanish, leaving intelligence agencies hard-pressed to locate clandestine CW facilities. If utilized to make warfare agents, micro process devices could create an international security paradigm shift by enabling states and sub-national actors to amass significant stocks of poison gas covertly, setting the stage for surprise attacks.

Two case studies exemplify why state and non-state proliferators may turn to micro devices to overcome some of the technical challenges involved in making chemical warfare agents. At the terrorist level, the most instructive case concerns Aum Shinrikyo, the Japanese cult that released the nerve agent sarin in the Tokyo subway on March 20, 1995. Aum's attack killed 13 people, seriously injured several dozen, and so badly frightened over 5,000 that they inundated Tokyo hospitals. The cult's use of a crude dispersal method—using sharpened umbrellas to puncture plastic bags filled with a dilute solution of sarin—averted a much larger casualty toll. Other factors that prevented the cult from killing more subway commuters were Aum's inability to scale up the production of sarin at its dedicated $10 million plant, called Satyan 7, and the low purity (roughly 30 percent) of the sarin released that fateful morning.[22]

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[21] Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," p. 19; Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 188; John Gee, "Advances in Science and Technology: Maintaining the Effectiveness of the Convention," *Pure and Applied Chemistry* vol. 74, no. 12 (2002), p. 2233; George W. Parshall, "Trends in Processing and Manufacturing that Will Affect Implementation of the Chemical Weapons Convention," *Pure and Applied Chemistry* vol.74, no. 12 (2002), pp. 2261, 2263; M.M. Sharma, "Strategies of Conducting Reactions on a Small Scale: Selectivity Engineering and Process Intensification," *Pure and Applied Chemistry* vol. 74, no. 12 (2002), pp. 2265–8; Löwe, Hessel, and Mueller, "Microreactors: Prospects Already Achieved and Possible Misuse," 2274–5.

[22] For more on Aum's chemical weapons program, see Chapter 3 of Amy E. Smithson with Leslie-Anne Levy, *Ataxia: The Chemical and Biological Terrorism Threat and the US Response*, Report No. 35 (Washington, DC:

Aum Shinrikyo's scientists cut their teeth by synthesizing small amounts of the agents VX, sarin, tabun, soman, mustard, and sodium cyanide, but the cult's goal was to produce 70 tons of sarin, a militarily significant quantity, in 40 days.[23] Aum Shinrikyo acquired top-of-the-line equipment for the task, including items made of corrosion-resistant Hastelloy and a $200,000 Swiss-built, computerized pilot plant with automatic temperature and injection controls, plus analytical and record-keeping features. Recurring leaks at Satyan 7 reflected the cult's technical difficulties in scaling up the process. Several technicians inhaled fumes on repeated occasions and exhibited symptoms ranging from nosebleeds to convulsions. Citizens living near the cult's compound in the Mount Fuji foothills lodged numerous complaints with the police in July 1994 about noxious fumes emanating from the site. In November 1994, an accident at Satyan 7 forced the cult to suspend sarin production operations.[24]

The state-level case involves Libya, which dramatically reversed course and relinquished its weapons of mass destruction programs on December 19, 2003. Libya had topped the U.S. chemical weapons proliferation watch list since September 1998, when the State Department charged that Tripoli was producing poison gas at a plant called Rabta. Although U.S. and other Western intelligence agencies charged Libya with making large quantities of both blister and nerve agents, this estimate later proved incorrect.[25] When Libya opened its facilities to international inspectors in 2004, it became clear that Libya possessed about 23 metric tons of

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Henry L. Stimson Center, October 2000), pp. 80–111; Anthony T. Tu, *Chemical Terrorism: Horrors in Tokyo Subway and Matsumoto City* (Fort Collins, CO: Alaken, Inc., 2002).

[23] Anthony T. Tu, "Aum Shinrikyo's Chemical and Biological Weapons," *Archives of Toxicology, Kinetics and Xenobiotic Metabolism*, vol. 7, no. 3 (Autumn 1999), pp. 75, 79; Kaplan and Marshall, *Cult at the End of the World* (New York: Crown Publishers, Inc., 1996), pp. 150, 211; U.S. Congress, Senate Committee on Governmental Affairs, Permanent Subcommittee on Investigations, Staff statement and testimony of John F. Sopko, *Global Proliferation of Weapons of Mass Destruction*, 104th Cong., 1st sess. (Washington, DC: U.S. Government Printing Office, 1996), pp, 21–2, 61–2, 87–8; D.W. Brackett, *Holy Terror: Armageddon in Tokyo* (New York: Weatherhill, 1996), pp. 110, 113–4, 118, 146, 157, 175,

[24] Anthony T. Tu, "Overview of Sarin Terrorist Incidents in Japan in 1994 and 1995," *Proceedings from the 6th CBW Protection Symposium* (Stockholm: May 10-15, 1995), pp. 14–5; Brackett, *Holy Terror*, pp. 116–7.

[25] Similar to Aum Shinrikyo, a production accident at Rabta released highly toxic fumes and killed a bunch of wild dogs near the plant, tipping off intelligence officials to the site's probable illicit activity. The Rabta plant was officially known as Pharma-150, ostensibly a pharmaceutical production facility. Libya planned two more chemical weapons plants at Sebha and Tarhuna, but did not complete construction on either facility. For an assessment of Libya's chemical weapons program, see Gordon M. Burk and Charles C. Flowerree, *International Handbook on Chemical Weapons Proliferation* (New York: Greenwood Press, 1991), pp. 267–326; Thomas C. Wiegele, *The Clandestine Building of Libya's Chemical Weapons Factory: A Study in International Collusion* (Cardondale, IL: Southern Illinois Univ. Press, 1992); Department of Defense, *Proliferation Threat and Response* (Washington, DC: Office of the Secretary of Defense, 1996 and 1997 editions); U.S. Congress, Office of Technology Assessment, *Technologies Underlying Weapons of Mass Destruction*, pp. 42–3; Bill Gertz, "Chinese Move Seen as Aiding Libya in Making Poison Gas," *Washington Times*, July 12, 1990.

sulfur mustard agent and 1,300 metric tons of precursor chemicals.[26] Libya had not produced and stockpiled nerve agents because Libyan technicians had failed to overcome the same technical obstacle that had stymied Aum Shinrikyo, namely the scale-up of a key production process.[27]

Had microreactors been available to the chemical weapons programs of Libya or Aum Shinrikyo, both might have succeeded at the industrial-scale production of nerve agents. Anyone scaling-up a chemical manufacturing process in standard reactors must contend with the vagaries of controlling reaction temperatures and other key operational parameters, but once a method has been developed for synthesizing chemical(s) in a single-channel microreactor, scale-up can be achieved far more easily than with conventional reactors simply by adding parallel arrays.[28] Several micro devices and pilot plants available for purchase are capable of producing tons of chemicals per hour.[29] By employing microreactors, Aum Shinrikyo would probably have averted the safety problems and leaks that alerted law enforcement authorities to the cult's nefarious activities and forced Aum to abort its production operations. Finally, the cult could have used microreactors to synthesize a higher, more uniform quality of sarin. With tons of high-grade

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[26] To comply with the terms of the Chemical Weapons Convention, Libya destroyed 3,563 unfilled chemical bombs under the oversight of international inspectors. "Libya Submits Initial Chemical Weapons Declaration," press release (The Hague: Organization for the Prohibition of Chemical Weapons, March 5, 2004); "Initial Inspection in Libya Completed," press release (The Hague: Organization for the Prohibition of Chemical Weapons, March 22, 2004).

[27] Libyan technicians were not able to scale up the production of a key precursor for the sarin family of nerve agents known as DF, short for methylphosphonyl diflouride. Author's interview with senior U.S. government official and chemical weapons expert, Washington, DC, November 17, 2003.

[28] Parshall, Pearson, Inch, and Baker, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 2333; Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 188; Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," p. 19; *Report of the Scientific Advisory Board on Developments in Science and Technology*, doc. RC-2/DG.1 (The Hague: February 28, 2008), p. 11.

[29] Hitachi offers a mini-plant with 20 microreactors that can produce 72 tons per year. S. Togashi, T. Miyamoto, T. Sano, and M. Suzuki, "Micoreactor Systems Using the Concept of Numbering Up," in F.G. Zhuang and J.C. Li, eds., *New Trends in Fluid Mechanics Research* (New York: Springer, 2009), pp. 678–81. Microinnova offers a microreactor that can produce three tons of chemicals per hour. For more information, go to: <www.microinnova.com/index_e.html>. In another example, DSM operated a Corning microreactor that yielded 25 tons of nitrate over four weeks. With 8,000 hours of operation, Corning's glass microreactor can process 800 metric tons a year. Patricia L. Short, "Microreactors Hit the Major Leagues," *Chemical & Engineering News*, vol. 86, no. 42 (October 20, 2008), pp. 37–8. See also, Ann M. Thayer, "Handle with Care," *Chemical & Engineering News*, vol.87, no. 11 (March 16, 2009), pp. 17–9; Derek Atkinson and Jeff McDaniel, "Honey, I Shrunk the Hardware," *The Chemical Engineer*, vol. 86, no. 809 (November 8, 2008), pp. 42–3. The German Institute for Micro Process Engineering makes a device with 4,000 internal channels that churns out seven tons of chemicals per hour. Juergen Brandner, "Fouling and Long Term Stability in Micro Heat Exchangers," presentation at the 10th International Conference on Microreaction Technology, New Orleans, April 7, 2008). More information about this institute, founded in July 2001 as part of the Karlsruhe Research Center in Eggenstein-Leopoldshafen, Germany, can be found at: <www.fzk.de/fzk/idcplg?IdcService=FZK&node=0047&lang=en>. Note that the numbering up of channels can be accomplished externally with separate devices or internally with additional channels inside a single device.

sarin in its possession, Aum's attacks would have been of a scale more consistent with the apocalyptic vision of its founder, Shoko Asahara. In short, terrorists or states armed with militarily significant quantities of chemical warfare agents could inflict tremendous harm.[30]

Ease of Misuse (Explicit and Tacit Knowledge)

The main hurdle to the misuse of micro process technology by state proliferators, terrorists, or criminals appears to be adapting the synthesis of CW agents to microreactors. Relevant knowledge on the development, capabilities, operation, and applications of chemical micro devices is accessible from more than 1,500 articles in professional and trade journals[31] as well as textbooks.[32] Operational know-how can also be gleaned from professional conferences, such as the International Microreaction Technology Conference or the World Congress of Chemical Engineers, where attendees can meet and query top microreactor developers and scientists from companies that work with this equipment.

In addition to a PhD in chemistry or chemical engineering, however, practical hands-on experience with the technology is needed to transpose the synthesis of chemical warfare agents from standard-sized to miniaturized equipment.[33] To acquire this tacit knowledge, anyone intent on proliferation could enroll in university courses on microreactors or get a job at a company that uses micro process technology in its R&D laboratories and production plants. With such

[30] Mass casualties can be achieved without use of military dispersal systems (e.g., bombs, missiles, rockets) by releasing a super-toxic chemical into the ventilation systems of densely populated buildings or the synchronized use of sprayers at congested transit points or at major public gatherings. Commercially available sprayers for pesticides and fertilizers could be used in this fashion.

[31] For a summary of recent developments, Volker Hessel, Christoph Knobloch, and Holger Löwe, "Review on Patents in Microreactor and Micro Process Engineering," *Recent Patents in Chemical Engineering* 1, no. 1, 2008, pp. 1–16. Trade news coverage can be found in publications such as *Chemical & Engineering News* and *The Chemical Engineer*, peer reviewed articles in the journals *Industrial & Engineering Chemistry Research*, *Journal of Fluorine Chemistry*, *Tetrahedron Letters*, *Chemical Engineering Journal*, among others.

[32] See, for example, Ehrfeld, Hessel, and Löwe, eds., *Microreactors: New Technology for Modern Chemistry*; Volker Hessel, Steffen Hardt, Holger Löwe, eds., *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions* (Weinheim, Germany: Wiley-VCH, 2004); Volker Hessel, Holger Löwe, Andreas Muller, Gunther Kolb, eds., *Chemical Micro Process Engineering: Processing and Plants* (Weinheim, Germany: Wiley-VCH, 2004); Wirth, ed., *Microreactors in Organic Synthesis and Catalysis*; Dietrich, ed., *Microchemical Engineering in Practice*; Volker Hessel, Jaap C. Schouten, Albert Renken, and Jun-Ichi Yoshida, eds., *Micro Process Engineering*: *A Comprehensive Handbook* (Weinheim, Germany: Wiley-VCH, 2009).

[33] Scientists and senior corporate officials from the chemical micro process technology industry, interviews with author, March-April 2008 and August 2009. Note that the techniques for constructing these devices, for packing channel beds with solid catalysts, and for cleaning the tiny micro channels also require similar experiential know-how. Terry Mazanec, PhD, chief scientist at Velocys, presentation titled "Microchannel Reactor for the Production of Vinyl Acetate Monomer," at the Symposium on Micro Process Technology of the 8th World Congress of Chemical Engineers, Montreal, August 27, 2009.

experience, states, terrorist groups, or individuals could more readily overcome the most challenging aspect of exploiting this technology for malevolent purposes.

Accessibility of the Technology

In 2009, roughly 20 companies were selling chemical micro devices. Most manufacturers market their products over the Web, so would-be proliferators may be able to purchase micro process equipment without ever coming in direct contact with company officials.[34] The accessibility of the technology must therefore be considered high because these devices are available in the marketplace without restrictions.

Imminence and Magnitude of Risk

Since microreactors are potentially capable of producing large volumes of CW agents, the imminence and magnitude of the dual-use risk are both high. Even a half-wily proliferator could recognize that microreactors offer other advantages aside from enhanced safety and ease of scale-up. To put it bluntly, proliferators will have high confidence that they can operate a covert CW program because microreactors will deprive intelligence agencies of the key indicators of warfare agent production.[35] The significant safety margins of microreactors would also allow an aspiring proliferator to experiment more aggressively with highly toxic and volatile compounds in order to discover, test, and develop novel CW agents.[36]

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[34] Law enforcement and intelligence agencies apparently have no particular window into microreactor sales other than stories in trade journals and press releases from the companies themselves, which combined cover a fraction of the sales activity taking place.

[35] Löwe, Hessel, and Mueller, "Microreactors: Prospects Already Achieved and Possible Misuse," p. 2274; Parshall, Pearson, Inch, and Baker, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 2333; Parshall, "Trends in Processing and Manufacturing that Will Affect Implementation of the Chemical Weapons Convention," p. 2261; Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 188; *Report of the Scientific Advisory Board on Developments in Science and Technology*, doc. RC-2/DG.1 (The Hague: February 28, 2008), p. 11; Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," p. 19.

[36] Such aggressive experiments often carry a risk of explosions. A senior scientist observed that for this reason it was "possible to work with compounds in microreactors that one would never dream of working with in standard equipment." Senior pharmaceutical industry scientist, "Panel Discussion: Progress in the Commercialization of Micro Process Technology," 10th International Conference Microreaction Technology, New Orleans, April 9, 2008 Trapp, "Advances in Science and Technology and the Chemical Weapons Convention," p. 19; Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," pp. 183–6, 188; Parshall, Pearson, Inch, and Baker, "Impact of Scientific Developments on the Chemical Weapons Convention," p. 2233; *Report of the Scientific Advisory Board on Developments in Science and Technology*, p. 11.

Awareness of Dual-Use Potential

Since the turn of the 21st century, relatively little has been written on the security implications of microreactor technology—a paragraph here, a few paragraphs there. Experts have stated that highly toxic chemicals, including CW agents, can be made in micro devices. Reportedly, chemicals that have already been synthesized in microreactors include hydrogen cyanide and phosgene, which were both used as weapons during World War I, and methyl isocyanate, the toxic industrial chemical that was released in the Bhopal tragedy.[37]

Characteristics of the Technology Relevant to Governance

Embodiment. Chemical micro process technology consists of hardware, but computer software controls the devices and their accompanying sensors. According to leading scientists in the micro process industry, reactors, heat exchangers, mixers, and their associated control equipment are merely the first items of chemical production equipment to be miniaturized. Scientists are also working on shrinking components for chemical separation, reforming, and distillation.[38]

Maturity. Chemists and chemical engineers working at the cutting edge of green chemistry and process intensification are exploring the potential of micro process technology. Refinements in the technology are ongoing, such as new device configurations and channel coatings to improve throughput and other performance parameters. Recent years have seen a shift from employing microreactors as a laboratory R&D tool to their increasing use in pilot- and industrial-scale production.

Convergence. For many decades, industrial chemists have utilized reactors, mixers, and heat exchangers to synthesize chemicals from two or more liquids, gases, and/or solids. By miniaturizing this equipment, micro chemical process technology involves the convergence of

[37] Technical experts stated that methyl isocyanate could be produced in a microreactor with "catalytic dehydrogenation of *N*-methylformamide, a common and less-toxic solvent." Löwe, Hessel, and Mueller, "Microreactors: Prospects Already Achieved and Possible Misuse," p. 2274. Also on this point, Agnes Shanley, Nicholas P. Chopey with Gerald Ondrey and Gerald Parkinson, "Microreactors Find New Niches," *Chemical Engineering* 104, no. 3, March 1997, pp. 30–3; George W. Parshall, Graham S. Pearson, Thomas D. Inch, and Edwin D. Baker, "Impact of Scientific Developments on the Chemical Weapons Convention," *Pure and Applied Chemistry* vol. 74, no. 12 (2002), p. 2333; Tuan H. Nguyen, "Microchallenges of Chemical Weapons Proliferation," *Science* 309, August 12, 2005, p. 1021.

[38] Author interviews with scientists and senior corporate officials from the chemical micro process technology industry, New Orleans, Louisiana, Washington, DC, Montreal, Canada, and Kyoto, Japan, March-April 2008, August 2009, and March 2010.

standard chemical processing with the manufacturing technologies used to make modern microelectronic devices, such as laser micromachining and microlamination.

Rate of advance. Early studies demonstrated the utility of microreactors as tools for laboratory R&D because these devices can generate copious data on kinetics, residence time, and other reaction parameters, in contrast to the "black box" character of standard reactors. The resulting increase in understanding of chemical reactions enabled scientists to tinker with reaction parameters and improve performance. By the mid-1990s, developers of chemical micro process technology were exploring multiple commercial applications and demonstrating scale-up potential. Top chemical manufacturing companies around the world—including Dow, Sigma Aldrich, DuPont, BASF, Pfizer, and Johnson & Johnson—are working with this technology in their R&D departments, at pilot scale, and for full-scale commercial production.

International diffusion. The diffusion of chemical micro process technology can be considered from four different angles. First is the spread of knowledge about how to manufacture and operate these devices. The second aspect of diffusion relates to the acquisition of technologies that enable the manufacture of chemical micro process devices, basically the same fabrication technologies that underpin the microelectronics industry.[39] Though expensive, these advanced machining technologies are increasingly found in all corners of the globe, including rapidly industrializing and developing countries. Any plant or country that produces computer chips has the technological capacity to make microreactors.

The third aspect of technology diffusion concerns the size of the commercial market for chemical micro process technology. The chemical industry, once centered in Europe, North America, Japan, South Korea, and Taiwan, has grown significantly in countries such as India, China, Brazil, Peru, Pakistan, Singapore, South Africa, and Thailand.[40] Chemical micro devices appeal to any companies seeking to improve their competitive edge through enhanced product

[39] These technologies include precision machining (e.g., electrical discharge machining, laser micromachining); etching (e.g., crystallographic dry, isotropic wet); bonding (e.g., anodic, diffusion, silicon fusion); photolithography; LIGA (an acronym for deep x-ray lithography plus electroforming and plastic molding); injection molding; wire-cut erosion and die sinking; and micro-lamination of various coatings to reduce clogging and fouling. For more on micro device manufacture, see Thomas Frank, "Fabrication and Assembling of Microreactors Made from Glass and Silicon," in Wirth, ed., *Microreactors in Organic Synthesis and Catalysis,* 19–42; Ehrfeld, Hessel, and Löwe, *Microreactors,* 15–35.

[40] Data on contemporary market developments can be found in resources such as the Global Production Index of the American Chemistry Council and trade publications such as the ICIS News, which tracks industry activities worldwide. For an account of the rise and diversification of the international chemical industry, Fred Aftalon, *A History of the International Chemical Industry* (Philadelphia: Univ. of Pennsylvania Press, 1991).

quality and profitability. As a matter of national policy, some countries actively encourage the adoption of chemical micro process technology to obtain its environmental benefits and promote economic competitiveness in the age of outsourced production.

The chemical industry consists of different market sectors, and microreactors are already widely used in some of them. Roughly 33 percent of the chemical manufacturing in the pharmaceutical and fine-chemical industries is currently accomplished in microreactors,[41] with projections that the technology will capture those markets within a decade. Industry insiders also predict that in the cosmetics sector, microreactors will increase their current estimated market share from about 10 percent to 33 percent over the next decade, eventually becoming the dominant manufacturing technology in that market because they produce highly uniform emulsions, a key criterion for cosmetics. Other insider projections include a high level of use of micro process technology in the natural gas and biofuels areas, accounting for an estimated 40 percent of that market in a decade. Microreactors are also expected to make inroads into the polymer, petrochemical, food, and commodity chemical markets over the next 10 years.[42] Companies are even exploring the possibility of using micro systems for the bulk manufacture of commodity chemicals such as formaldehyde, methanol, ethylene, and styrene.[43] The cumulative forecast is that within a decade, 30 percent of all chemical processing will be performed in micro devices.

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[41] According to various industry experts, within a decade microreactors could have about 90 percent of these markets, except for processes involving solids. Early market penetration in these two market sectors can be explained by the ability of microreactors to meet the standards for a high level of purity required for pharmaceutical chemicals and the recognition of fine chemical companies that microreactors are well-suited to produce fairly small quantities of a wide array of chemicals. U.S. and European industry experts, interviews with author, New Orleans, Louisiana, and Washington, DC, March-April 2008. Sigma Aldrich, Clariant, Johnson & Johnson, Novartis, AstraZeneca, Sanofi Aventis, Schering-Plough, Roche, and GlaxoSmithKline are among the major companies in these sectors using microreactors. Clay Boswell, "Microreactors Gain Wider Use as Alternative to Batch Production," *Chemical Market Reporter*, no. 266 (October 4, 2004), p. 8. See also, Dominique M. Roberge, Laurent Ducry, Nikolaus Bieler, Phillippe Cretton, and Bertin Zimmerman, "Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries?" *Chemical Engineering Technology*, vol. 28, no. 3 (2005), pp. 318-823.

[42] Among the companies focusing on the energy market are Velocys Inc., which is concentrating on hydrogen production, creating a synthetic liquid diesel fuel from "stranded" natural gas, biofuels, and synthetic fuels, and Chart Energy & Chemicals, with its ShimTec® and FinTecT™ heat exchangers. For more information, go to: <www.velocys.com/market>and <www.chart-ind.com/app_ec_reactortech_dev.cfm>. For patents according to different areas of application, see Hessel, Knobloch, and Löwe, "Review on Patents in Microreactor and Micro Process Engineering," p. 4.

[43] Clay Boswell, "Microreactors Gain in Popularity among Producers: More than Meets the Eye," ICIS News, April 30, 2009. Available at: <www.icis.com/Articles/2009/05/04/9211877/microreactors-gain-popularity-among-producers.html>.

The fourth dimension of technology diffusion concerns the number of companies that are developing, manufacturing, and selling chemical micro production devices. At present, the industry consists of approximately 20 firms concentrated in Europe (especially Germany), with a few in the United States and Asia.[44] But given the intensive R&D activity in Japan, India, and China, all of which have large chemical industries, it is reasonable to expect that additional micro device companies will be launched in Asia the near future. Industry insiders predict that within ten years, there will be 100 manufacturers of chemical micro devices worldwide.[45] As the industry grows in size and competitiveness, the price of microreactors will drop, making them even more accessible.

Susceptibility to Governance

Now is an opportune time to govern micro process technology because of the relatively small number of suppliers. Most countries with a micro process equipment industry have only one or two companies. Nevertheless, the point at which individual governments will start to perceive that the security risks of the technology are great enough to override economic interests and warrant the regulation of their domestic industry remains an open question.[46] Given the safety, environmental, and economic benefits that will accrue from the widespread use of microreactors, the draconian regulation of sales would be ill-advised for any government. The micro process technology industry, for its part, would prefer to avoid regulation entirely. If, however, a regulatory regime is imposed, industry will lobby for a balanced approach that does not hamper sales to legitimate customers or create an onerous implementation burden.

Past and Current Approaches to Governance

[44] Most of the patents filed recently have been in Germany, the United States, China, and Japan. See Hessel, Knobloch, and Löwe, "Review on Patents in Microreactor and Micro Process Engineering," p. 14.
[45] Author's interviews with scientists and senior corporate officials from the chemical micro process technology industry, New Orleans, Louisiana, and Washington, DC, March-April 2008.
[46] The decision to move forward with regulations is no small matter. Ample precedents for regulations governing product sales exist, but the regulatory process is time-consuming and resource-intensive. This process usually includes meetings of interested government agencies (e.g., commerce, defense, intelligence, law enforcement); consultations with the affected industry; the drafting and revision of proposed regulations; public circulation of the draft regulations for comment; the assignment of responsibility for regulatory implementation; the allocation of resources for implementation; and the updating of the regulations, as needed. Parliamentary participation adds another layer of complexity to the regulatory process through hearings, the drafting and passage of legislation, and the routine reporting and oversight of implementation.

Scientists and security analysts focusing on the nonproliferation of chemical weapons have watched, evaluated, and discussed micro process technology as it became more common for companies to employ such plants for commercial production.[47] To date, however, national policymakers have not intervened, and no barriers exist to the commercial sale of microreactors. For this reason, any sub-national or state-level actor with malign intent would logically purchase the devices on the open market rather than investing the time and resources needed to develop and produce their own.

Both domestic and international measures are needed to safeguard against the diversion and misuse of chemical micro devices. Since the entry into force of the Chemical Weapons Convention (CWC) in 1997, the Organization for the Prohibition of Chemical Weapons (OPCW) in The Hague has overseen its implementation. The architects of the CWC included procedures in Article XV for making technical amendments to ensure the treaty's continued "viability and effectiveness." Scientists have also advised the member states and the OPCW Executive Council to update the verification provisions in response to technical developments (such as microreactors) lest the Convention become "frozen in time."[48] Like the CWC's vaunted challenge inspection provisions, however, the process for modernizing the verification regime has remained dormant.

Because CWC verification focuses on the illicit production of warfare agents and the diversion of chemicals for military purposes, dual-use chemicals—not processing equipment—are the items of accountability for inspectors. Thus, a major shift in verification philosophy would be required to make microreactors accountable under the treaty's declaration and inspection procedures. Given the major political efforts that would be necessary to bring about such a change, the CWC is an unlikely vehicle for addressing the proliferation potential of micro process devices. In 2008, however, the OPCW's Scientific Advisory Board broached the issue of

[47] The CWC prohibits offensive chemical weapons activities but permits defensive research. The Australia Group is an export control cooperative, which began in 1985 with a handful of nations that agreed to harmonize voluntarily their export control policies on chemicals that were at high risk for diversion to chemical weapons programs in Iran and Iraq. The Australia Group now has forty-one members and control lists for sixty-three chemicals; dual-use chemical equipment; biological agents, plant and animal pathogens; and dual-use biological equipment. See the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction, April 29, 1997. Also, go to: <www.australiagroup.net/en/index.html>.

[48] Quote from Balali-Mood, Steyn, Sydnes, and Trapp, "Impact of Scientific Developments on the Chemical Weapons Convention," para. 13, p. 179. See also pages 188–189.

microreactors, opting to reassess periodically the implications of this technology for the verifiability of the Convention.[49]

The Australia Group (AG) is an export-control cooperative of more than 40 countries that harmonize their national export controls on dual-use materials and manufacturing equipment related to the production of chemical and biological weapons.[50] Although the group's control list includes reactors, heat exchangers, and other vessels, the specified internal capacities are orders of magnitude larger than those of chemical micro devices. AG members have discussed chemical micro production equipment but have so far declined to add them to the control list, which was updated in January 2009.[51] In the fall of 2009, however, the AG established a dedicated working group on chemical micro process technology. Although adding chemical micro devices to the control list in the future would be a positive step, it would not be sufficient to curb the potential misuse of these devices because manufacturers would be required to obtain export licenses only for sales to individuals or entities known or suspected to abet countries with CW programs, such as North Korea. The overwhelming majority of sales to "friendly" nations and domestic customers would remain unregulated, an unsatisfactory situation in an era when it is increasingly difficult to tell friend from foe.[52] Purported friendly states might view microreactors as an opportunity to establish or upgrade a covert CW program, and jihadist groups and assorted domestic terrorists operate in far too many countries.

Options for Future Governance

Although no formal steps toward governance have been taken under the auspices of the CWC or the Australia Group, micro process technology—like any other commercial product—is susceptible to control and regulation by individual governments. Any governance scheme should

[49] *Report of the Scientific Advisory Board on Developments in Science and Technology*, p. 11. On the increasing use of microreactors in the commercial sector, see *Report of the Scientific Advisory Board on Developments in Science and Technology*, doc. RC-1/DG.2 (The Hague: April 23, 2003).

[50] On the history and internal workings of this export control cooperative, see Amy E. Smithson, *Separating Fact from Fiction: The Australia Group and the Chemical Weapons Convention*, Occasional Paper no. 34 (Washington, DC: Henry L. Stimson Center, March 1997).

[51] The specified total internal volume for reactors is greater than 100 liters and less than 2,000 liters. The European Union is also an Australia Group member. For the updated chemical equipment control list, go to: <www.australiagroup.net/en/dual_chemicals.html>.

[52] Pakistani nuclear weapons scientist A.Q. Khan was not the only individual to orchestrate the proliferation of weapons of mass destruction. For a case study on how state-level proliferators have utilized front companies, middle men, and supply networks to acquire materials to feed chemical weapons programs, Jonathan B. Tucker, *Trafficking Networks for Chemical Weapons Precursors: Lessons from the Iran-Iraq War of the 1980s* (Washington, DC: Center for Nonproliferation Studies, November 2008).

aim at the most useful points of intervention and be structured so that legitimate users retain access to beneficial dual-use items while those with malicious intent are denied. Control measures for micro process devices would not usefully be targeted at the underlying know-how, which has been in the public domain for over a decade, or the manufacturing technology, which is used to produce a vast array of consumer electronics. Rather, a governance strategy would be targeted most effectively at preventing sales of microreactors to suspected or known proliferators and those that assist them, such as freight forwarders and front companies.

Notional government regulations might include declaration and reporting requirements, mandatory screening of customers against lists of entities or individuals engaged in illicit activities (or against "red flags" that alert sellers to potential misbehavior), and training of company export managers. A hotline to government authorities might also be created for reporting suspicious activities in a timely fashion. Some governments are funding critical developmental work on microreactors and could therefore place conditions on research funding to prod manufacturers to adopt specific policies and procedures. The most expeditious and comprehensive route to preventing misuse would be a self-governance initiative on the part of micro device manufacturers, possibly patterned on the efforts of gene-synthesis companies to screen DNA orders in order to prevent bioterrorists from assembling dangerous pathogens from scratch. Two gene-synthesis industry associations organized this initiative, in part because of pressure from end-users.[53] To date, however, a dedicated global trade association has not yet been formed to represent chemical micro process technology manufacturers.

Conclusions

A multidimensional chemical weapons proliferation quandary is materializing. Chemical micro process devices can significantly enhance safety, increase efficiency, and reduce the environmental footprint of commercial chemical plants, but these devices could also advance the

[53] See Hubert Bernauer et al., "Technical Solutions for Biosecurity in Synthetic Biology," Workshop Report (Munich: Industry Association of Synthetic Biology, April 3, 2008). Available at: <www.synbiosafe.eu/uploads///pdf/iasb_report_biosecurity_syntheticbiology.pdf>. Participating companies have agreed to screen DNA synthesis orders against a database containing genetic sequences of pathogens of concern (e.g., Marburg virus, variola virus). The International Association of Synthetic Biology's code of conduct is available at: <www.ia-sb.eu/tasks/sites/synthetic-biology/assets/File/pdf/iasb_code_of_conduct_final.pdf>. For the code of the International Gene Synthesis Consortium, see: <www.genesynthesisconsortium.org/Harmonized_Screening_Protocol.html>. On other measures that could prevent the misuse of synthetic biology, see Michelle S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, *Synthetic Genomics: Options for Governance* (Rockville, MD: J. Craig Venter Institute, October 2007).

CW programs of states such as North Korea, cause other nations to reconsider their decision to renounce chemical weapons, and accelerate terrorist efforts to acquire them. Chemical micro plants lack nearly all the identifiers that intelligence analysts use to identify suspect poison gas factories, depriving the intelligence community of the ability to provide warning of covert chemical weapons production in time to impede a terrorist attack or a state-level program. The underlying know-how and manufacturing technologies for chemical micro process devices have already diffused so widely that stuffing the genie back in the bottle, so to speak, is impossible; it is also undesirable, given the clear benefits of the technology.

Unfortunately, existing nonproliferation tools are ill-suited to grapple with this proliferation challenge. The CWC does not regulate production equipment, and any new export controls agreed by the Australia Group, should they materialize, will apply only to known states of CW proliferation concern and the entities that abet them. Absent effective policy intervention, aspiring chemical weapons proliferators will, for the foreseeable future, have unfettered access to equipment that could increase their ability to acquire poison gas in an undetectable manner. The most expeditious and perhaps the most effective way to plug this hole in the CW nonproliferation regime may lie in an initiative by the international chemical micro process industry to establish best practices and procedures for responsible sales and customer screening.

Chapter 8: Bioregulators and Peptide Synthesis

Ralf Trapp

Bioregulators are naturally occurring chemicals that help to ensure the proper functioning of vital physiological systems in living organisms, such as respiration, blood pressure, heart rate, body temperature, consciousness, mood, and the immune response.[1] Because these molecules play a key role in life processes in both health and disease, modulating tissue concentrations can have therapeutic effects. In recent years, advances in drug delivery have made bioregulators (and chemical analogues derived from them) more attractive as potential medicines. Excessive doses of these compounds, however, can cause severe physiological imbalances including "heart rhythm disturbances, organ failure, paralysis, coma and death."[2]

This case study assesses the implications of recent scientific and technological developments involving bioregulators and evaluates governance measures to prevent their misuse for hostile purposes. Because many bioregulators are peptides, the chapter also examines technologies to synthesize peptides in large quantities.

Overview of the Technology

Bioregulators have a variety of chemical structures and their action is not associated with any single physiological mechanism. They can be relatively simple molecules in the case of certain hormones or neurotransmitters, or complex macromolecules such as proteins, polypeptides, or nucleic acids. Many bioregulators are peptides, or short chains of amino acids. Examples of the latter include angiotensin (which raises blood pressure), vasopressin (which regulates the body's water balance), Substance P (which transmits pain signals from peripheral receptors to the brain) and bradykinin (with triggers inflammatory responses).[3] Recent research on the types and subtypes of bioregulator receptors has provided insights into how these diverse responses are generated and how they might be manipulated.

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[1] Kathryn Nixdorff and Malcolm R. Dando, "Developments in Science and Technology: Relevance for the BWC," *Biological Weapons Reader* (Geneva: BioWeapons Prevention Project, 2009) p. 39.
[2] The Netherlands, "Scientific and technological developments relevant to the Biological Weapons Convention," paper submitted to the Sixth BWC Review Conference, http://www.unog.ch/80256EDD006B8954/(httpAssets)/018F68EC1656192FC12571FE004982A6/$file/BWC-6RC-S&T-NETHERLANDS.pdf
[3] Jonathan B. Tucker, "The Body's Own Bioweapons," *Bulletin of the Atomic Scientists*, March/April 2008, pp. 16-22.

Bioregulators are involved in regulatory circuits in the nervous, endocrine, and immune systems. A given compound can play different physiological roles in various tissues; indeed, many bioactive peptides in the nervous system were first discovered in the intestine. Not only can a bioregulator have multiple functions depending on its cellular targets, but any important body function is likely to be controlled by more than one bioregulator. A given compound may also have different functions during the development of an organism from embryo to adult.[4] Additional complexity arises from the fact that the physiological systems of the body interact. By affecting the functions of the nervous and the endocrine systems, "even small manipulations to the immune system could be amplified to bring about devastating consequences."[5] Thus, changing one system by modulating the tissue concentration of a bioregulator or interfering with its receptors can affect the function of other systems.

Minor chemical modifications of bioregulators can create analogues with markedly different physiological properties. In this respect, bioregulators differ from toxins—toxic compounds synthesized by living organisms as a defense mechanism or as a weapon to kill prey. Because toxins have evolved to maximize toxicity, it is unlikely that minor chemical modifications will lead to greater lethality. In the case of bioregulators, however, evolutionary pressure has not maximized their toxic potential. Instead, bioregulators modulate cellular activities and do not have a single endpoint of function the way toxins do.[6] The duration of action of a bioregulator can also be extended by structural modifications that slow its rate of degradation in the body. Finally, because bioregulators maintain equilibrium in biological circuits, it is possible (at least in principle) to design molecular analogues that shift this equilibrium to affect body temperature, sleep, and even consciousness in a selective manner.

History of the Technology

Advances in the understanding and use of bioregulators have gone hand-in-hand with developments in peptide synthesis. Peptides can be produced in solution (liquid phase) or on the surface of tiny plastic beads (solid phase). Before 1975, it was not possible to manufacture

[4] Malcolm Dando, *The New Biological Weapons: Threat, Proliferation, and Control* (Boulder, CO: Lynne Rienner, 2001), p. 77.
[5] British Royal Society, "Report of the RS-IAP-ICSU international workshop on science and technology developments relevant to the Biological and Toxin Weapons Convention," RS policy document 38(06), November 2006.
[6] Dando, *The New Biological Weapons*, p. 82.

peptides in large quantities.[7] Since then, however, new methods have transformed the situation. In 1993, the liquid-phase and solid-phase methods were combined to produce complex peptides on a metric-ton scale. Today companies offer peptide-synthesis services ranging from milligrams for laboratory use to hundreds of kilograms for industrial applications. The choice of production method depends largely on the size of a peptide, its amino acid sequence, and the presence of modifications or protective groups.

Overall, the chemical synthesis of peptides remains the most common approach to industrial-scale production.[8] One approach involves synthesizing peptide fragments eight to 14 amino acids long on a solid-phase resin, removing and purifying the fragments, and coupling them together to form longer chains.[9] Fuzeon, a peptide-based anti-HIV drug consisting of 36 amino acids, is currently synthesized in quantities exceeding 3,500 kilograms per year.[10] In the future, microwave synthesis, in which single-frequency microwaves are used to speed up the coupling reactions and achieve better purity and higher yields, may become the method of choice for peptide production.[11] It may also be possible to produce large quantities of peptides in recombinant microorganisms or in transgenic plants and animals.[12]

Peptide synthesis has evolved from a niche market into a mainstream business. As of 2010, more than 40 peptides were marketed worldwide and hundreds more were in some stage of pre-clinical or phased clinical development. In addition, 79 companies were involved in the commercial synthesis of peptides, 13 of them in the multiple-kilogram to multi-ton range.[13] In

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[7] Canada, "Novel Toxins and Bioregulators: The Emerging Scientific and Technological Issues Relating to Verification and the Biological and Toxin Weapons Convention," External Affairs and International Trade, Ottawa, Canada (1991).

[8] Lars Andersson, Lennart Bloomberg, Martin Flegel, Ludek Lepsa, Bo Nilsson, and Michael Verlands, "Large-scale synthesis of peptides," *Biopolymers (Peptide Science)*, vol. 55 (2000), pp. 227–250.

[9] Susan Aldridge, "Peptide boom puts pressure on synthesis—drugs already on the market and in clinical studies drive novel method development," *Genetic Engineering and Biotechnology News*, vol. 28, no. 13 (2008), http://www.genengnews.com/articles/chitem.aspx?aid=2534&chid=3

[10] Brian L. Bray, "Large-scale manufacture of peptide therapeutics by chemical synthesis," *Nature Reviews Drug Discovery*, vol. 2 (July 2003), pp. 587-593; Thomas Bruckdorfer, Oleg Marder, and Fernando Albericio, "From production of peptides in milligram amounts for research to multi-ton quantities for drugs of the future," *Current Pharmaceutical Biotechnology*, vol. 5 (2004), pp. 29-43.

[11] Anonymous**,** "Peptide manufacturers see increased growth—pharma's interest in peptide drugs drives this market" *Genetic Engineering and Biotechnology News*, vol. 25, no. 13 (2005), http://www.genengnews.com/articles/chitem.aspx?aid=1001.

[12] United Kingdom, "Scientific and technological developments relevant to the Biological Weapons Convention," Paper submitted to the 6th BWC Review Conference, paragraph 54, http://www.unog.ch/80256EDD006B8954/(httpAssets)/5B93AF9D015AD633C12571FE0049ADAF/$file/BWC-6RC-S&T-UK.pdf.

[13] Peptide Resource Page, http://www.peptideresource.com/GMP-peptide.html (accessed on 25 May 2010).

some ways, peptide synthesis can be compared to DNA synthesis because specialized companies offer contract manufacturing services to meet customer specifications, and peptide orders can be placed over the Internet. The most significant trend in the evolution of the customer base has been an increase in pharmaceutical industry clients caused by progress in novel peptide formulations and innovative delivery systems.[14]

Utility of the Technology

Scientists are studying bioregulators and their synthetic analogues to obtain a deeper understanding of the physiology of organisms in health and disease. In addition to the quest for new knowledge, important economic and social pressures are driving research and development on bioregulators and the regulatory circuits in which they play a central role. Such research is expected to lead to safer and more specific medicines, including treatments for diseases that affect homeostatic systems in the central nervous system, the endocrine system, and the immune system.

Peptide bioregulators and their synthetic derivatives are attractive drug candidates for treating a variety of ailments, including asthma, arthritis, cancer, diabetes, growth impairment, cardiovascular disease, inflammation, pain, epilepsy, gastrointestinal diseases, and obesity.[15] The advantages of peptides include high activity and specificity, a lack of persistent accumulation in organs, low toxicity, and less immunogenicity than monoclonal antibodies. Bioregulators also have potential applications in agriculture, including growth hormones for animal husbandry, regulation of growth and development in food crops and fruit, and compounds with insecticidal or fungicidal properties for crop protection and pest control. For all these reasons, the diffusion of knowledge about bioregulators, their applications, and production technologies is bound to continue.

Compared with small-molecule drugs, however, peptides have a number of drawbacks: they are less stable in bodily fluids, more expensive to manufacture, and rapidly degraded by enzymes, requiring continuous administration that greatly increases the cost of drug therapy. Bioregulators also tend to be fairly large molecules with an electrical charge and an affinity for

[14] Ibid.
[15] Anil Seghal, "Peptides 2006 -- new applications in discovery, manufacturing, and therapeutics," *D&MD Report*, no. 9214 (June 2006), p.3, available online at: http://www.bioportfolio.com/cgi-bin/acatalog/9214_peptides.pdf

water, which hampers their transport across cell membranes.[16] For these reasons, the therapeutic use of bioregulators depends on the ability to manufacture these substances at acceptable cost and in the required purity, store them as needed, and deliver them to the right targets in the human body. The chemical modification of peptides, for example, can dramatically increase their persistence in the bloodstream. It is also difficult to deliver peptide bioregulators in the form of an inhalable aerosol because they are sensitive to acidic conditions and are rapidly broken down by enzymes in the lungs. One technique used to facilitate the aerosol delivery of bioregulators is microencapsulation, in which solid particles or liquid droplets are coated with a substance that protects them from evaporation, contamination, oxidation, and other forms of chemical degradation.[17] Another approach is to create porous particles that can deliver drugs into the deep regions of the lungs.[18] An international workshop found that "the spray-drying equipment needed to create such particles is relatively cheap and widely available—yet the optimization of a well-engineered particle requires considerable time and skill."[19]

Potential for Misuse

Bioregulators could potentially be developed into biochemical weapons that damage the nervous system, alter moods, trigger psychological changes, and even kill.[20] Studies have found that bioactive peptides can induce profound physiological effects within minutes of exposure.[21] Other advantages of bioregulators as weapons include a highly specific mechanism of action, the ability to elicit a variety of physiological effects, and a lack of susceptibility to existing defensive measures. According to a paper prepared by the U.S. government, "While naturally-occurring threat agents, such as anthrax, and 'conventionally' genetically engineered pathogenic organisms

[16] Dando, *The New Biological Weapons*, p. 109.
[17] UN Secretariat, "Background information document on new scientific and technological developments relevant to the Convention," BWC/CONF.VI/INF.4, September 28, 2006, http://daccessdds.un.org/doc/UNDOC/GEN/G06/643/31/PDF/G0664331.pdf?OpenElement
[18] Jennifer Fiegel, "Advances in aerosol drug delivery," presentation at the IUPAC workshop *Impact of Scientific Developments on the CWC*, Zagreb, Croatia, April 22-25, 2007.
[19] Mahdi Balali-Mood, Pieter S. Steyn, Leiv K. Sydnes, and Ralf Trapp, "Impact of scientific developments on the Chemical Weapons Convention (IUPAC Technical Report)," *Pure and Applied Chemistry*, vol. 80, no. 1(2008), pp. 175–200
[20] Elliot Kagan, "Bioregulators as instruments of terror," *Clinics in Laboratory Medicine*, vol. 21, no. 3 (2001), pp. 607-618.
[21] Elliot Kagan, "Bioregulators as prototypic nontraditional threat agents," *Clinics in Laboratory Medicine*, vol. 26, no. 2 (2006), pp. 421-444.

are the near-term threats we must confront today, the emerging threat spectrum will become much wider and will include biologically active agents such as bioregulators."[22]

Until recently, the hostile use of bioregulators was considered unlikely for a number of reasons, including their limited persistence after being dispersed as an aerosol. Protein bioregulators are also expensive to produce and are rapidly inactivated by high or low temperatures. According to a paper prepared by the British government, "delivery of sufficient quantities to the appropriate target cells or tissues is a significant challenge to the development of therapeutic peptides, with delivery across the blood/brain barrier, for example, remaining a significant problem. Difficulties in delivering bioactive molecules would also affect the utility of such compounds as BW agents."[23] Nevertheless, new technologies have improved the ability to deliver bioregulators effectively, changing the assessment of their dual-use risk.[24]

The potential misuse of bioregulators has historical precedents. Neil Davison,[25] Martin Furmanski,[26] Alan Pearson,[27] and others have described the past interest of several countries in using bioregulators as incapacitating agents. During the Cold War, difficulties with the manufacture, stability, and dissemination of peptide bioregulators meant that smaller psychoactive molecules were generally favored, such as BZ and certain benzilates and glycolates. Nevertheless, former Soviet bioweaponeer Ken Alibek wrote in his memoir that the Soviet Union launched a top-secret project, code-named "Bonfire," to develop bioregulators as biochemical weapons.[28] Another research program under the Soviet Ministry of Health, code-

[22] United States of America, "Scientific and technological developments relevant to the Biological Weapons Convention," Paper submitted to the Sixth BTWC Review Conference, http://www.unog.ch/80256EDD006B8954/(httpAssets)/51A586B1E2205BACC12571FE0049B682/$file/BWC-6RC-S&T-USA.pdf.

[23] United Kingdom "Scientific and technological developments relevant to the Biological Weapons Convention" Paper submitted to the 6th BTWC Review Conference, http://www.unog.ch/80256EDD006B8954/(httpAssets)/5B93AF9D015AD633C12571FE0049ADAF/$file/BWC-6RC-S&T-UK.pdf.

[24] National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006), p. 180.

[25] Neil Davison "'Off the rocker' and 'on the floor': The continued development of biochemical incapacitating agents," *Bradford Science and Technology Report No. 8*, University of Bradford, August 2007.

[26] Martin Furmanski, "Historical military interest in low-lethality biochemical agents," in Alan M. Pearson, Marie Isabelle Chevrier, and Mark Wheelis, eds., *Incapacitating Biochemical Weapon*s (Lantham, MD: Lexington Books, 2007), pp. 35-66.

[27] Alan Pearson, "Late and post-Cold War research and development of incapacitating biochemical weapons," in Pearson, Chevrier, and Wheelis, eds., *Incapacitating Biochemical Weapons*, pp. 67-101.

[28] Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999), pp. 154-155.

named "Flute," sought to develop lethal and non-lethal psychotropic and neurotropic agents for use in KGB operations and included research on bioregulatory peptides.[29]

More recently, several countries have shown a renewed interest in incapacitants for law enforcement use, including China, the Czech Republic, France, Russia, the United Kingdom, and the United States.[30] In 1997, the U.S. Department of Defense established the Joint Non-Lethal Weapons Directorate to coordinate the development of a variety of "non-lethal" weapons technologies and systems. This effort includes certain chemical incapacitating agents, which can legally be employed for law-enforcement purposes under a provision of the 1993 Chemical Weapons Convention (CWC).[31] In 2000, for example, the Applied Research Laboratory of Pennsylvania State University examined several compounds that might provide the basis for developing "calmative" agents. The list included two peptide bioregulators: corticotrophin-releasing factor (CRF) and cholecystokinin (CKK).[32]

In the future, bioregulators might be misused for warfare purposes or employed in a non-consensual manner to manipulate human behavior. Slavko Bokan and his colleagues have prepared a list of bioregulators that might be suited for military or terrorist use, including Substance P, endorphins, endothelins, sarafotoxins, bradykinin, vasopressin, angiotensins, enkephalins, somatostatin, bombesin, neurotensin, oxytocin, thyoliberins, and histamine-releasing factors.[33] The potential emergence of bioregulator-based weapons would add a new and frightening dimension to modern warfare, not only threatening the lives of enemy troops but potentially altering their perception of the world around them, provoking severe bodily malfunctions, and altering emotional state and behavior. Bioregulators might also be employed in conjunction with other weapons to enhance their lethality. The acceptance by some states of this new type of warfare would tend to legitimate it for others.[34]

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[29] Alibek with Handelman, *Biohazard*, pp. 171-172.
[30] Michael Crowley, *Dangerous Ambiguities: Regulation of Riot Control Agents and Incapacitants under the Chemical Weapons Convention*, Bradford Non-lethal Weapons Research Project, University of Bradford, 2009.
[31] Pearson, "Late and post-Cold War research and development," p. 75.
[32] Joan M. Lakoski, W. Bosseau Murray, and John M. Kenny, *The Advantages and Limitations of Calmatives for Use as a "Non-lethal" Technique* (State College, PA: Pennsylvania State University, 2000).
[33] Slavko Bokan, John G. Breen, and Zvonko Orehovec, "An evaluation of bioregulators as terrorism and warfare agents," *ASA Newsletter*, No. 02-3(90), 2002, p. 1.
[34] Although the case study focuses on the potential misuse of bioregulators as antipersonnel weapons, plant regulators such as Agent Orange have been used in the past for deforestation or to destroy crops. See Jeanne Mager Stellman, Steven D. Stellman, Richard Christian, Tracy Weber, and Carrie Tomasalle, "The extent and patterns of usage of Agent Orange and other herbicides in Vietnam," *Nature*, vol. 422 (April 17, 2000), pp. 681-687.

Ease of Misuse (Explicit and Tacit Knowledge)

At least at the state level, access to information on bioregulators is not a limiting factor. Basic knowledge about these compounds and their properties has been published in the scientific literature, presented at conferences, and distributed through other channels. For proprietary reasons, fewer data are available from the early (preclinical) phases of drug development, and information on compounds that pharmaceutical companies have screened but not selected for clinical testing is generally not publicly available. For non-state actors, reliable information on the design of biochemical weapons is hard to come by because it is generally classified. In particular, devising an effective method for disseminating peptide bioregulators is a hurdle that terrorists would have difficulty overcoming. To employ bioregulators for purposes of interrogation or abduction, terrorists would need to know how to administer an agent to achieve the desired effect without killing the victim.

Overall, the dual-use potential of bioregulators is likely to grow in the coming years as the functional understanding of these natural body chemicals increases, along with advances in related areas such as bioinformatics, systems biology, receptor research, and neuroscience. Although progress in these various fields tends to be incremental, what really counts is the cross-fertilization and synergies among them. The effect of these interactions is hard to predict, but one cannot rule out unexpected discoveries that would transform the dual-use potential of bioregulators.

Accessibility of the Technology

As far as peptide bioregulators are concerned, state actors would have no difficulty setting up programs to manufacture them should they decide to do so. For non-state actors, the challenges are somewhat greater. In principle, a terrorist or criminal organization could purchase a peptide synthesizer or order customized peptides from a commercial supplier, although both of these options might require the use of front companies or access to proliferation networks. A decision by law-enforcement agencies to adopt incapacitating agents based on bioregulators, however, would significantly increase the risk of theft or diversion.

Imminence and Magnitude of Risk

The possibility that states might adopt bioregulators and their analogues as biochemical weapons designed to incapacitate rather than kill, albeit for purportedly legitimate purposes such as law enforcement, remains significant. Given the changing nature of war, with urban-warfare scenarios becoming ever more prevalent, some countries are interested in developing incapacitating agents for counterterrorism and counterinsurgency operations. Exploratory research programs exist and there have been a few isolated cases of actual use. At the same time, the likelihood of developing a *truly* non-lethal weapon based on bioregulators is remote for several reasons. Not only would the margin of safety between the incapacitating and lethal doses have to be very large, but getting the agent across the blood-brain barrier remains a formidable challenge. Finally, the ability to control dose under field conditions would have to far exceed what is technically feasible today.[35]

In addition to the possibility that bioregulators might be developed for warfare purposes, one can contemplate their use by occupying forces to repress the local population under the guise of law enforcement and riot control. Employing bioregulators that affect perception, cognition, mood, or trust to render angry civilians more docile might well be tempting. Such use would, of course, raise a host of legal and ethical issues. There is also the possibility that military, intelligence, or police forces could use bioregulators in domestic situations to control crowds, render prisoners more compliant and trusting, or induce acute depression, pain, or panic attacks as an instrument for influencing behavior and enforcing compliance. Although any nonconsensual use of biochemical agents would be illegal, the perception that the use of certain chemicals for law enforcement was "legitimate" could weaken such legal protections, not just with regard to despotic regimes but in democratic societies as well.

The risk that non-state actors, such as terrorist or criminal organizations, could exploit bioregulators for hostile purposes currently appears low because of the limited availability of these agents and the unpredictability of their effects on a target group. It seems unlikely that terrorists would go to considerable effort and expense to develop a bioregulator-based agent unless it offered a clear advantage over weapons they already possess. Nevertheless, should bioregulator-based drugs become widely available for therapeutic purposes, or if they are employed as "non-lethal weapons" by law enforcement agencies, terrorists or criminals might start using them to facilitate hostage-taking, incapacitate security guards, render hostages docile,

[35] British Medical Association, "The Use of Drugs as Weapons," Executive Summary, 2007

extract information during interrogations, or control a group of people in a confined space such as an aircraft.

Awareness of Dual-Use Potential

The 2002 incident at the Dubrovka Theater in Moscow, in which the Russian security forces used a potent incapacitating agent against a group of Chechen rebels holding some 800 theater-goers, causing the collateral deaths of 129 hostages, has raised concern about the future role of incapacitating agents. At the international diplomatic level, awareness of the potential misuse of bioregulators has increased in recent years, and several parties to the Biological Weapons Convention (BWC) made reference to the issue in papers prepared for the Sixth Review Conference in 2006. Bioregulators have not been discussed directly in the CWC context, but several member states and the Director-General of the Organization for the Prohibition of Chemical Weapons have proposed holding informal discussions about the use of incapacitants for law-enforcement purposes under Article II.9(d) of the treaty.[36,37]

A few non-governmental organizations, such as the International Committee of the Red Cross (ICRC), have called attention to the potential misuse of bioregulators, but the wider scientific, medical, academic, and industry communities appear to be largely unaware of the issue. This lack of awareness is not specific to bioregulators but reflects a more general ignorance about the potential for misuse inherent in certain advances in the life sciences. Despite modest attempts to introduce educational materials on dual-use issues into university curricula, and the availability of a few related modules on the Internet, it remains to be seen to what extent this topic will be integrated into mainstream science education.

Characteristics of the Technology Relevant to Governance

Embodiment. Peptide bioregulators can be thought of as a hybrid technology. Although applications of these compounds are based largely on intangible knowledge, the production of peptides requires automated synthesizers and other sophisticated hardware.

[36] Switzerland, "Riot control and incapacitating agents under the Chemical Weapons Convention," OPCW document RC-2/NAT/12 dated April 9, 2008, http://www.opcw.org/documents-reports/conference-of-the-states-parties/second-review-conference/.
[37] OPCW Director-General, "Report of the Scientific Advisory Board on developments in science and technology," OPCW document RC-2/DG.1 and Corr. 1, dated February 28, 2008 and March 5, 2008, http://www.opcw.org/documents-reports/conference-of-the-states-parties/second-review-conference/.

Maturity. Drugs based on bioregulators are in advanced development and automated peptide synthesizers are commercially available. Peptide synthesis on an industrial scale is mature and widely used in many parts of the world.

Convergence. Advances in systems biology, receptor research, brain research, computational biology, and synthetic biology are being integrated with new knowledge about bioregulators. These convergent developments are likely to bring about revolutionary changes in biology and medicine by increasing the ability to intervene *selectively* in fundamental biological processes. Advances in delivery technologies, such as microencapsulation and aerosolization, may also play an important role in the practical application of synthetic bioregulators.

Rate of advance. Significant progress has been made in the large-scale synthesis and purification of peptides, including peptide bioregulators. Most therapeutic peptides in use today are from 10 to 50 amino acids long, but improvements in peptide chemistry have pushed the maximum length that can be produced in large quantities to as many as 80 to 100 amino acids.

International diffusion. According to a paper prepared by The Netherlands, the biotechnology industry was once concentrated in Western countries, but "nowadays Brazil, China, Cuba, India, Singapore and South Korea are all host to high-quality biotechnology firms. . . . Although a great deal of innovative research is still being done by the large companies, part of it has been outsourced to manage risks and cut costs. Innovative research is also being done by universities, government laboratories and small firms established as spin-offs of university research."[38] These observations also hold true with respect to research on peptide bioregulators and the manufacture of these compounds and their synthetic derivatives.

Susceptibility to Governance

Overall, bioregulator research and development appears fairly susceptible to governance because it is still at an early phase. Many of the governance measures proposed for synthetic genomics are also relevant to bioregulators because of the similarities between the scientific, technological, and industrial aspects of the two fields.[39] The main costs of poorly designed governance measures would be to obstruct progress in a field of research that offers many

[38] The Netherlands, "Scientific and technological developments relevant to the Biological Weapons Convention," paragraph 10.

[39] Michele Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, *Synthetic Genomics: Options for Governance* (J. Craig Venter Institute, Center for Strategic and International Studies, Massachusetts Institute of Technology, October 2007).

benefits for medicine, agriculture, and biotechnology, and to impede international scientific cooperation. Because bioregulator research has such a wide range of potential beneficial applications, exchanges of basic scientific information among states must remain unhindered.

Past and Current Approaches to Governance

The development, production, and retention of bioregulators for hostile purposes are banned by both the BWC and the CWC. Nevertheless, although the CWC is designed to prevent the emergence of new forms of chemical warfare, the debate over how the law-enforcement exemption in Article II.9(d) should be interpreted with respect to incapacitating agents has yet to be resolved.[40] At present, no institutional process exists to clarify what—if anything—constitutes a legal use of incapacitating biochemicals as weapons. Accepting the use of these agents for law enforcement would open the door to the introduction of a new category of biochemical weapons. Associated risks include providing a cover for illicit intent, diminishing national control over weaponized chemicals, requiring the use of personal protective equipment during combat operations, and potentially expanding the scope of "law enforcement" to include counterinsurgency, counterterrorism, and special-forces operations. It would be only a small step from there to accepting biochemical weapons back into national force postures for a range of military applications—with the potential to move down a "slippery slope" toward the remilitarization of chemistry.[41] Given these risks, the states parties to the CWC should strive to reach consensus on acceptable ways to reexamine Article II.9(d) in an effort to clarify and delimit its scope.

Options for Future Governance

Other possible governance measures for bioregulators, with an emphasis on peptides, include establishing legal norms through regulations (licensing, guidelines, and export controls) self-regulation by the user community, and the involvement of civic society in monitoring compliance with the applicable norms. If one employs a similar approach to that proposed for synthetic genomics, the various intervention points could target firms that manufacture peptides

[40] Alan Pearson, Marie Isabelle Chevrier, and Mark Wheelis, eds., *Incapacitating Biochemical Weapons*: *Promise or Peril?* (Lanham, MD: Lexington Books, 2007).
[41] Julia Perry Robinson, "Non lethal warfare and the Chemical Weapons Convention," Harvard-Sussex Program, submission to the OPCW Open-ended Working Group on Preparation for the Second CWC Review Conference, October 24, 2007

to order, in particular at the multiple-kilogram and larger scale; firms that sell peptide synthesizers; and scientists who work with bioregulators in the research, medical, and pharmaceutical communities. Other possible targets for governance measures include manufacturers of delivery systems (aerosol generators) and organizations that specialize in particle engineering for biomedical purposes. Although no single measure can prevent the misuse of bioregulators, a combination of measures may be effective at reducing the risk.

Conclusions

Bioregulators are an important element of the revolution in the life sciences and are expected to yield beneficial applications in medicine, agriculture, and other fields. At the same time, bioregulators have a potential for misuse as biochemical weapons, both on the battlefield (directly or to enhance the effects of other weapons) and as a means to manipulate and coerce human behavior. For governance to be effective, it will be essential to reach a broad international agreement on which uses of these chemicals are acceptable and which constitute a violation of existing norms, including the CWC. Overall, managing the risk of misuse of bioregulators will require a multi-stakeholder, multi-disciplinary, and multi-dimensional approach.[42]

[42] Nayef R.F. Al-Rhodan, Lyubov Nazaruk, Marc Finaud, and Jenifer Mackby, *Global Biosecurity – Towards a New Governance Paradigm* (Geneva: Editions Slatkine, 2008), pp. 200-201

Chapter 9: Protein Engineering

Catherine Jefferson

Proteins, which consist of long folded chains of amino acids, play vital roles in the body as structural components and catalysts in biochemical reactions. To serve these functions, each protein molecule folds up spontaneously into a unique three-dimensional shape that constitutes its active form. Protein engineering involves the design and synthesis of tailor-made proteins—either modified from nature or created from scratch—for a variety of applications in industry, agriculture, and medicine. The same methods could potentially be exploited to increase the toxicity of natural proteins for hostile purposes, such as warfare or terrorism.[1] Accordingly, governance measures are needed to prevent the misuse of protein engineering while preserving its beneficial applications.

Overview of the Technology

There are three basic approaches to protein engineering. The first, called "rational design," involves modifying the sequence of amino acids in a protein to alter its 3-D shape and functional properties. (There are 20 different amino acid building blocks, each of which has a distinct molecular structure and electrical charge.) Even when the precise folding pattern of a protein is known, however, predicting the effect of one or more changes in amino acid sequence is a difficult task. As a result, rational design usually requires several cycles of modification and testing before it yields a protein with the desired activity.[2]

The second approach to protein engineering, called "directed evolution," was developed in the early to mid-1990s.[3] This technique employs the shuffling of DNA segments to create thousands of mutant proteins with slightly altered structures, which are then subjected to high-throughput screening to identify those that exhibit a desired function or activity. (See Chapter 13.) Compared to rational design, directed evolution is a semi-automated, randomized process that requires much less expertise, although it involves

[1] Tamas Bartfai, S. J. Lundin and Bo Rybeck, "Benefits and threats of developments in biotechnology and genetic engineering," in SIPRI, Stockholm International Peace Research Institute, *SIPRI Yearbook 1993: World Armaments and Disarmament* (Oxford: Oxford University Press, 1993), p. 297; Charles B. Millard, "Medical Defense Against Protein Toxin Weapons," in Luther E. Lindler, Frank J. Lebeda and George W. Korch, eds., *Biological Weapons Defense: Infectious Diseases and Counterbioterrorism* (New Jersey: Humana Press, 2005).
[2] Jonathan B. Tucker and Craig Hooper, "Protein Engineering: Security Implications," *EMBO Reports*, vol. 7, no. S1 (July 2006), pp. 14-17.
[3] Willem P. C. Stemmer, "Rapid evolution of a protein *in vitro* by DNA shuffling," *Nature*, vol. 370 (August 1994), pp. 389-391. See also: Cara A. Tracewell and Frances H. Arnold, "Directed enzyme evolution: climbing fitness peaks one amino acid at a time," *Current Opinion in Chemical Biology*, vol. 13 (2009), pp. 3-9.

specialized screening techniques.[4] Some analysts have raised concerns that directed evolution could generate mutant proteins that are toxic to human cells.[5]

The third approach to protein engineering is the synthesis of artificial proteins. This method expands on the set of 20 natural amino acids by adding unnatural amino acids with novel properties. Because of the difficulty of predicting the folding patterns associated with unnatural amino acids, however, synthesizing fully functional proteins that do not exist in nature is currently beyond the state of the art.[6] Nevertheless, incremental progress is being made towards the synthesis of artificial proteins—a capability that, when realized, could have important dual-use implications.[7]

The three approaches to protein engineering are not mutually exclusive, and some investigators have successfully combined elements of rational design and directed evolution.[8] This paper focuses primarily on rational design and describes specific areas of research with a potential for misuse.

History of the Technology

Protein engineering first emerged in the early 1980s, made possible by advances in X-ray crystallography, which can determine the 3-D structure of a protein from the diffraction pattern that results when x-rays pass through a crystallized protein, and by advances in chemical DNA synthesis.[9] Since then, the technology has been gradually refined.

Utility of the Technology

Engineered proteins have multiple uses in industry, agriculture, and medicine. One well-known application is for the development of heat-resistant proteases (enzymes that break down proteins), which are added to laundry detergent formulations to remove protein-rich stains.[10] Protein engineering has also been used to endow existing proteins with new biological functions. For example, modifying the amino acid sequence of an antibody molecule can change its folding pattern so that it behaves like an enzyme to catalyze a

[4] Author's interview with Dr. Neil Crickmore, Department of Biochemistry, University of Sussex, June 16, 2009.
[5] Ibid.
[6] Steven A. Benner and Michael Sismour, "Synthetic Biology," *Nature Reviews: Genetics*, vol. 6 (July 2005), pp. 533-543.
[7] Charles B. Millard, "Medical Defense against Protein Toxin Weapons," p. 274.
[8] Tucker and Hooper, "Protein Engineering: Security Implications," p. 15.
[9] Kevin M. Ulmer, "Protein Engineering," *Science*, vol. 219 (February 1983), pp. 666-671.
[10] David A. Estell, "Engineering enzymes for improved performance in industrial applications," *Journal of Biotechnology*, vol. 28 (1993), pp. 25-30; C. von der Osten, S. Branner, et al., "Protein engineering of subtilisins to improve stability in detergent formulations," *Journal of Biotechnology*, vol. 28 (1993), pp. 55-68.

specific biochemical reaction. Such catalytic antibodies have been created for reactions that have no naturally occurring enzymes.[11]

The pharmaceutical industry has also promoted the field of protein engineering. One important medical application involves the development of "fusion toxins" for advanced therapeutics.[12] Protein toxins are non-living poisons of biological origin: examples include snake, insect, and spider venoms; plant toxins such as ricin, and bacterial toxins such as botulinum toxin and diphtheria toxin. Because of the highly specific manner in which protein toxins interfere with cellular metabolism, they can kill or incapacitate at very low doses. Many protein toxins consist of two functional components: a binding domain that recognizes and binds specifically to a receptor on the surface of a target cell, and a catalytic domain that enters the cell and exerts a toxic effect, such as blocking protein synthesis.[13] With protein engineering, it is possible to create hybrid molecules consisting of the binding and catalytic portions of two different toxins. For example, combining the catalytic domain of diphtheria toxin or ricin with the binding domain of interleukin-2, an immune-system signaling protein, produces a fusion toxin that can selectively kill cancer cells while sparing healthy ones.[14] Because of its enhanced affinity for interleukin-2 receptors on the surface of cancer cells, this fusion toxin provides a 17-fold increase in cell-killing activity.[15] One such fusion toxin has been marketed commercially for the treatment of cutaneous T cell lymphoma.[16] In 2006, the market for engineered proteins was worth almost $67 billion, and in 2011 it is expected to rise to $118 billion, or 12 percent of pharmaceutical sales.[17]

Potential for Misuse

Protein engineering research could lead to new security challenges, both in terms of harmful physical products and the creation of knowledge that could be misused for nefarious

[11] James A. Branningan and Anthony J. Wilkinson, "Protein Engineering 20 Years On," *Nature Reviews Molecular Cell Biology*, vol. 3 (December 2002), pp. 964-970.
[12] Tucker and Hooper, "Protein Engineering: Security Implications," p. 14.
[13] Charles B. Millard, "Medical Defense against Protein Toxin Weapons," p. 273.
[14] D. P. Williams, K. Parker, et al., "Diphtheria toxin receptor binding domain substitution with interleukin-2: genetic construction and properties of a diphtheria toxin-related interleukin-2 fusion protein," *Protein Engineering*, vol. 1 (1987), pp. 493-498; Arthur E. Frankel, Chris Burbage, et al., "Characterization of a ricin fusion toxin targeted to the interleukin-2 receptor," *Protein Engineering*, vol. 9 (1996), pp. 913-919.
[15] Tetsuyuki Kiyokawa, Diane P. Williams, et al., "Protein engineering of diphtheria-toxin-related interleukin-2 fusion toxins to increase cytotoxic potency for high-affinity IL-2-receptor-bearing target cells,' *Protein Engineering*, vol. 4 (1991), pp. 463-468.
[16] Francine M. Foss, "Interleukin-2 Fusion Toxin: Targeted Therapy for Cutaneous T Cell Lymphoma," *Annals of the New York Academy of Science*, vol. 941 (2006), pp. 166-176.
[17] Business Insight Report, *Next Generation Protein Engineering and Drug Design: Strategies to improve drug efficacy and improve drug delivery*, London, 2007, online at: http://www.globalbusinessinsights.com/content/rbdd0013m.pdf

purposes.[18] One dual-use application of protein engineering is to increase the toxicity of protein toxins, such as ricin and botulinum, which have been acquired in the past by state biological warfare programs and by terrorist groups.[19] In principle, protein engineering could create protein toxins with enhanced lethality, target range, and resistance to detection, diagnosis, and treatment.

Bacillus thuringiensis (Bt), for example, is a soil bacterium that is commonly used as a biological pesticide.[20] It produces a variety of crystalline protein toxins with insecticidal activity (termed Cry or Cyt toxins) that offer an environmentally-friendly means of pest control.[21] Because insects can become resistant to Bt toxins, scientists have used both rational-design and directed-evolution methods of protein engineering to increase the ability of Bt toxins to kill the target pests.[22] This research is controversial, however, because Bt is closely related to the bacterium *Bacillus anthracis*, which produces protein toxins that cause the lethal disease anthrax. At least in principle, the same protein-engineering methods that make Bt toxins more effective could also enhance the lethality of anthrax toxin.[23]

Fusion toxins may also have a potential for misuse.[24] In general, the systemic toxicity of fusion toxins produced for medical applications is less than that of either parent toxin because the hybrid molecules are narrowly targeted against malignant or otherwise abnormal cells.[25] It is theoretically possible, however, to increase the lethality of fusion toxins against normal cells for weapons purposes. Tucker and Hooper speculate that the extreme toxicity of botulinum toxin might be combined with the stability and persistence of staphylococcal enterotoxin B (SEB) to create a highly lethal fusion toxin that could withstand heat and

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[18] Caitríona McLeish, "Reflecting on the Problem of Dual-use," in Brian Rappert and Caitríona McLeish, *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007), pp. 189-203.
[19] Mark Wheelis, Lajos Rózsa and Malcolm Dando, eds., *Deadly Cultures: Biological Weapons since 1945* (Cambridge, MA: Harvard University Press, 2006).
[20] Author's interview with Crickmore.
[21] Donald H. Dean, "Biochemical Genetics of the Bacterial Insect-Control Agent *Bacillus thuringiensis*: Basic Principles and Prospects for Genetic Engineering," *Biotechnology and Genetic Engineering Reviews*, vol. 2 (October 1984), pp. 341-363.
[22] E. Schnepf, N. Crickmore, et al., "*Bacillus thuringiensis* and its pesticidal crystal proteins," *Microbiology and Molecular Biology Reviews*, vol. 62 (September 1998), pp. 775-806; Chandi C. Mandal, Srimonta Gayen, et al., "Prediction-based protein engineering of domain I of Cry2A entomocidal toxin of *Bacillus thuringiensis* for the enhancement of toxicity against lepidopteran insects," *PEDS*, vol. 20 (November 2007), pp. 599-606; Xinyan S. Liu and Donald H. Dean, "Redesigning *Bacillus thuringiensis* Cry1Aa toxin into a mosquito toxin," *PEDS*, vol. 19 (January 2006), pp. 107-111; Hiroshi Ishikawa, Yasushi Hoshino, et al., "A system for the directed evolution of the insecticidal protein from *Bacillus thuringiensis*," *Molecular Biotechnology*, vol. 36 (June 2007), pp. 90-101.
[23] Author's interview with Crickmore.
[24] Tucker and Hooper, "Protein Engineering: Security Implications," pp. 14-15.
[25] Author's e-mail correspondence with Dr. Benjamin E. Rich, researcher, Department of Dermatology, Brigham and Women's Hospital, Boston, USA, July 29, 2009.

environmental stresses.[26] Fusion toxins may also have other properties that increase their potential for misuse. For example, when the catalytic domain of tetanus toxin or Shiga toxin is combined with the binding domain of anthrax toxin, the resulting fusion toxin can target a broader range of mammalian cell types than either parent toxin.[27] Scientists have also developed a method to produce fusion toxins rapidly and efficiently by engineering mammalian cells to secrete them as properly folded protein molecules.[28] Also of concern is the diagnostic challenge presented by the hostile use of fusion toxins.[29] Because a fusion toxin may have different physiological effects than either parent toxin, it could elicit confusing medical signs or symptoms, making detection, diagnosis, and treatment more difficult.[30]

Another potential misuse of protein engineering involves protein-based infectious agents called prions, which are known to cause transmissible spongiform encephalopathies, diseases of animals and humans characterized by a spongy degeneration of the brain that result in severe neurological symptoms and death.[31] Although prion diseases resemble genetic or infectious disorders, the transmissible particles lack DNA or other genetic material and instead consist exclusively of a modified protein.[32] Prion replication involves the conversion of the normal protein into a misfolded conformation.[33] A prion disease that affects cattle, bovine spongiform encephalopathy (BSE), first appeared in the United Kingdom in November 1986 and became popularly known as "mad cow disease." In March 1996, a new variant form of Creutzfeldt-Jakob disease, a prion infection that affects humans, was reported in Britain and linked to the consumption of food contaminated by BSE, demonstrating the transmission of prions from one species to another.[34]

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[26] Tucker and Hooper, "Protein Engineering: Security Implications," pp. 15-16.
[27] Naveen Arora, Lura C. Williamson, et al., "Cytotoxic Effects of a Chimeric Protein Consisting of Tetanus Toxin Light Chain and Anthrax Toxin Lethal Factor in Non-neuronal Cells," *Journal of Biological Chemistry*, vol. 269 (October 1994), pp. 26165-26171; Naveen Arora and Stephen H. Leppla, "Fusions of Anthrax Toxin Lethal Factor with Shiga Toxin and Diphtheria Toxin Enzymatic Domains Are Toxic to Mammalian Cells," *Infection and Immunity*, vol. 62 (November 1994), pp. 4955-4961.
[28] S. Shulga-Morskoy and Benjamin E. Rich, "Bioactive IL7-diphtheria fusion toxin secreted by mammalian cells," *PEDS*, vol. 18 (March 2005), pp. 25-31.
[29] Janet R. Gilsdorf and Ramond A. Zilinskas, "New Considerations in Infectious Disease Outbreaks: The Threat of Genetically Modified Microbes," *Clinical Infectious Diseases*, vol. 40 (April 2005), pp. 1160-1165.
[30] Bartfai, Lundin, and Rybeck, "Benefits and threats of developments in biotechnology and genetic engineering," p. 297.
[31] Charles Weissman, "The State of the Prion," *Nature Reviews: Microbiology*, vol. 2 (2004), pp. 861-871.
[32] See Stanley B. Prusiner, "Prions," *Proceedings of the National Academy of Sciences*, vol. 95 (November 1998), pp. 13363-13383, for more on the prion concept and the now largely discredited alternative viral hypothesis.
[33] Ibid.
[34] Patrick van Zwanenberg and Erik Millstone, *BSE: Risk, Science and Governance* (Oxford: Oxford University Press, 2005)

According to two experts, prions "are lethal pathogens par excellence—indeed, it is hard to think of other examples of infectious diseases with 100 percent mortality once the earliest clinical signs have developed."[35] The feasibility of weaponizing prions is doubtful, however, for several reasons. First, prions do not infect reliably. Second, the incubation period of prion diseases is exceptionally long, with a delay of several months to years between infection and the appearance of clinical illness and death, thus severely reducing the potential utility of prions as biological warfare agents.[36] Finally, the delivery of prions would be problematic because the normal routes of infection are the ingestion of contaminated meat or the intravenous administration of contaminated blood products. Nevertheless, attempts by scientists to design artificial prions have raised dual-use concerns.[37] Although the search for curative treatments drives prion research, it is conceivable that protein engineering could be misapplied to develop prions with more rapid harmful effects. In addition, the recent development of technologies for the large-scale synthesis of proteins might be misused to mass-produce infectious prions.[38]

Ease of Misuse (Explicit and Tacit Knowledge)

The need for both explicit and tacit knowledge to conduct protein engineering limits the ability of terrorist groups to exploit this technology for harmful purposes.[39] Rational-design approaches to protein engineering are hypothesis-driven, conducted at the molecular level, based on a large body of knowledge and expertise, and require extensive tacit knowledge derived from hands-on experience and trial-and-error methods.[40] Typically, the level of expertise required to produce fusion toxins is that of an advanced graduate student in molecular biology.[41]

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[35] John Collinge and Anthony R. Clarke, "A General Model of Prion Strains and their Pathogenicity," *Science*, vol. 318 (November 2007), p. 935

[36] Congressional Research Service, *Agroterrorism: Threats and Preparedness*, CRS Report to Congress, August 13, 2004.

[37] Giuseppe Legname, Ilia V. Baskakov, et al., "Synthetic Mammalian Prions," *Science*, vol. 305 (July 2004), pp. 673-676; Lev Z. Oscherovich, Brian S. Cox, et al., "Dissection and Design of Yeast Prions," *PLOS Biology*, vol. 2 (April 2004), pp. 442-451.

[38] Gabriela P. Saborio, Bruno Permanne and Claudio Soto, "Sensitive detection of pathological prion protein cyclic amplification of protein misfolding," *Nature*, vol. 411 (June 2001), pp. 810-813; Claudio Soto, Gabriela P. Saborio and Laurence Anderes, "Cyclic amplification of protein misfolding: application to prion-related disorders and beyond," *TRENDS in Neurosciences*, vol. 25 (August 2002), pp. 390-394; Nathan R. Deleault, Brent T. Harris, et al., "Formation of native prions from minimal components *in vitro*," *Proceedings of the National Academy of Sciences*, vol. 104 (June 2007), pp. 9741-9746.

[39] Caitríona McLeish and Paul Nightingale, "Biosecurity, Bioterrorism and the Governance of Science: The Increasing Convergence of Science and Security Policy," *Research Policy*, vol. 36 (December 2007), pp 1635-1654, see especially p. 1645.

[40] Author's interview with Crickmore.

[41] Author's e-mail correspondence with Rich.

Accessibility of the Technology

Rational-design approaches to protein engineering are largely hypothesis-driven and the research outputs are unlikely to result in unexpected harmful applications.[42] The directed-evolution approach to protein engineering, however, has a much greater potential to result in the inadvertent creation of a novel protein toxin with greater potency or stability. Although considerable resources are needed to perform directed evolution, the technology is semi-automated and demands a much less expertise than rational design—probably the equivalent to an undergraduate degree in biology.[43] Thus, the growing popularity of directed-evolution techniques has increased the risk that individuals with relatively little specialized knowledge could create a library of novel protein toxins that are harmful to humans.

Imminence and Magnitude of Risk

Even if a more lethal fusion toxin can be developed, the effective weaponization and delivery of the agent would pose additional technical hurdles, particularly for bioterrorists. In addition, because toxins are generally less effective biological weapons than microbial agents, the imminence and magnitude of the risk of misuse associated with protein engineering appears to be moderate.

Awareness of Dual-Use Potential

The risks of misuse of protein engineering were first noted in the 1993 edition of the *World Armaments and Disarmament Yearbook*, published by the Stockholm International Peace Research Institute (SIPRI). According to this source, "The ease with which novel engineered bacterial toxins, bacterial-viral toxins and the like can be produced by protein engineering is of military interest, as is the way in which protein engineering enables the changing of the site on a toxin against which antidotes normally are developed."[44] The danger of engineered prions was mentioned in the 2001 briefing book prepared for the Fifth Review Conference of the BWC by the Department of Peace Studies at the University of Bradford: "In view of the growing knowledge of the dangers of prion diseases, the increasing capabilities for manipulation of receptors and ligands in the nervous, endocrine and immune systems, and the growing understanding of how proteins may be designed for particular

[42] Ibid.
[43] Ibid.
[44] Bartfai, Lundin, and Rybeck, "Benefits and threats of developments in biotechnology and genetic engineering," p. 297.

purposes . . . it is recommended that an explanatory sentence should be added at this Review Conference on prions, bioregulators and proteins."[45] Since these publications, however, only a few commentators have focused on the security implications of protein engineering.[46] Instead, most attention has focused on synthetic biology and more specifically on genome synthesis.[47] As the preceding discussion suggests, however, the dual-use risks associated with protein engineering warrant further characterization.

In general, the scientific community has tended to overlook or minimize the risks of protein engineering. Although the scientists who enhanced the potency of Bt toxin were aware that the same technique might be applied to the anthrax toxin, they did not address this concern directly.[48] As a result, the research went ahead with no consideration of how to manage its dual-use risks. Another scientist involved in the development of fusion toxins downplayed the risk of misuse. "While the prospect of weaponized toxic proteins is worrisome," he wrote, "I think it is more likely to come in the form of enhanced delivery of readily available, robust toxins like ricin or saporin rather than from engineered proteins. I feel that the risk of my work contributing to weapons technology is minimal."[49] In practice, accurate risk assessments are difficult to make, in part because scientists are generally reluctant to view their research as potentially dangerous.

Characteristics of the Technology Relevant to Governance

Embodiment. Protein engineering is based primarily on intangible information and does not require specialized hardware beyond that available in a standard molecular biology laboratory.

Maturity. Most applications of protein engineering are in advanced development, although a few engineered enzymes and fusion toxins are commercially available.

Convergence. Protein engineering is a convergent technology that draws on advances in several scientific fields, including X-ray crystallography, recombinant DNA technology,

[45] Malcolm R. Dando and Simon M. Whitby, "Article 1 – Scope," in Graham S. Pearson, Malcolm R. Dando, and Nicholas A. Sims, eds., *Key Points for the Fifth Review Conference*, University of Bradford, Department of Peace Studies, November 2001. Available at http://www.brad.ac.uk/acad/sbtwc.
[46] Millard, "Medical Defense Against Protein Toxin Weapons," pp. 255-283; Tucker and Hooper, "Protein Engineering: Security Implications," pp. 14-17.
[47] Author's e-mail correspondence with Dr. Neil Davison, senior policy advisor, The Royal Society, London, UK, June 19, 2009.
[48] Author's interview with Crickmore.
[49] Author's e-mail correspondence with Rich.

bioinformatics, and chemical DNA synthesis. Protein engineering also involves scientists from multiple disciplines, such as chemistry, biochemistry, biology, and engineering.[50]

Rate of advance. Although rational-design methods of protein engineering are advancing slowly, directed-evolution techniques have grown rapidly in recent years. Because the latter approach demands less explicit and tacit knowledge, it is potentially more accessible to actors who might exploit the technology for harmful purposes.

International diffusion. As the enabling technologies for protein engineering—bioinformatics, DNA synthesis, and genetic engineering—diffuse worldwide, the development and production of engineered proteins is becoming increasingly common in advanced industrialized states. Nevertheless, protein-engineering techniques are still beyond the capabilities of most developing countries and terrorist organizations.[51]

Susceptibility to Governance

The governability of protein engineering is limited because the technology is based largely on intangible information and draws on techniques and equipment that are widely available in molecular biology laboratories around the world.

Past and Current Approaches to Governance

Some governance measures already apply to protein engineering research involving dangerous toxins. Because toxins are non-living chemicals produced by living organisms, they are covered by the 1972 Biological Weapons Convention (BWC) as well as the 1993 Chemical Weapons Convention (CWC). Although both treaties prohibit the development and production of toxins for hostile purposes, only the CWC includes verification mechanisms for saxitoxin and ricin, which are listed on Schedule 1 in the treaty's Annex on Chemicals. National export controls, such as those harmonized by the Australia Group, provide another mechanism for managing dual-use risk by ensuring that exports of dangerous toxins, as well as dual-use production equipment, do not fall into the hands of proliferators.[52] In the United States, the Select Agent Rules require all institutions to register with the federal government if they possess, transfer, or use listed microbial agents and toxins of bioterrorism concern. The current list of Select Agents includes several protein toxins used in fusion-toxin research,

[50] Stefan Lutz and Uwe Théo Bornscheuer, eds., *Protein Engineering Handbook* (Weinheim: Wiley-VCH, 2008), p. xxvii.
[51] Author's e-mail correspondence with Rich.
[52] See Robert J. Mathews, "Chemical and Biological Weapons Export Controls and the 'Web of Prevention': A Practitioner's Perspective," in Brian Rappert and Caitríona McLeish, *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007), pp. 163-169.

such as botulinum toxin, ricin, shiga toxin, and staphylococcal enterotoxin B, as well as the prion responsible for BSE because of its potential use as an agent of agroterrorism.[53] But specific governance strategies for protein engineering *per se* are not yet in place.

Options for Future Governance

The problem of dual-use technology is inherently multifaceted, and attempts to mitigate the risk of misuse reflect this complexity. A number of commentators and organizations have proposed the need for a "web of prevention" to contain the risk of biological warfare with a variety of mutually reinforcing governance measures.[54] In the early 1990s, Graham Pearson, then director-general of the Chemical and Biological Defence Establishment at Porton Down, first introduced the concept of a "web of deterrence" comprising four key elements: verifiable biological arms control, export monitoring and control, defensive and protective measures, and national and international responses to the acquisition or use of biological weapons.[55] As security challenges shifted from the Cold War confrontation to the threat of rogue states and non-state actors, the "web of deterrence" was reconceptualized as a "web of reassurance," involving a greater emphasis on international and national controls on the handling, storage, transfer, and use of potentially dangerous pathogens.[56] Given the impossibility of a "silver-bullet" solution to the problem of biological weapons, the concept of a "web" of governance measures continues to hold considerable currency in policy debates. Subsumed under this approach are initiatives, measures, and activities ranging from awareness-raising and scientific codes of conduct to export controls and the oversight of dual-use technologies.

A drawback of the "web of prevention" concept is that it obscures the prioritization of issues and the need to identify key actors and intervention points.[57] The hardware, people, and processes involved in dual-use research are often conflated into the term "technology." Unpacking this concept makes clear that makes clear that distinct but complementary measures are needed to govern the different aspects. Hardware (equipment and material) can

[53] U.S. Department of Health and Human Services and U.S. Department of Agriculture, "Select Agents and Toxins," available online at: http://www.selectagents.gov
[54] Daniel Feakes, Brian Rappert, and Caitríona McLeish, "Introduction: A Web of Prevention?" in Brian Rappert and Caitríona McLeish, *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007), pp. 1-13.
[55] Ibid.
[56] Ibid.
[57] Corneliussen has argued that too much focus on one aspect of the web of prevention (such as codes of conduct for scientists) may divert attention from more serious problems. See Filippa Corneliussen, "Adequate regulation, a stop-gap measure, or part of a package?" *EMBO Reports*, vol. 7 (2006), pp. 50-54.

be governed through export controls, the screening of DNA synthesis orders, and the licensing of dual-use equipment, while people can be governed through systems of vetting, education, awareness-raising, and codes of conduct. It is also useful to distinguish among different intervention points, which may be upstream or downstream.

Governing upstream inputs. To reduce the risk that upstream components of protein-engineering research will be diverted to hostile purposes, governance measures should be in place to regulate the transfer and use of dangerous toxins or prions. Recipients of these items should be vetted and registered to confirm their scientific *bona fides*, as is currently the case with items on the U.S. Select Agent List. Governments should also adopt legislation requiring academic institutions or private companies to be licensed if they conduct research with dual-use equipment and materials. Finally, authorized users of such equipment should be held responsible for restricting access to legitimate scientists.[58] Although these measures would go some way toward mitigating the risk of misuse of protein engineering, other problems remain: ensuring that legitimate users of the technology do not permit its diversion to hostile purposes, and managing potentially sensitive research results. These challenges require a concept of technology that goes beyond hardware.

Governing downstream outputs. Oversight of research should make it possible to identify potentially high-risk outputs at a stage when governance measures are still feasible and effective. Such an oversight mechanism should have the legal authority to review and oversee all protein-engineering research involving toxins. As Tucker and Hooper argue, "Every country that is engaged in the engineering of protein toxins or the development of fusion toxins should establish a national biosecurity board to review and oversee the proposed experiments. This board should have the legal authority to block funding of specific projects, or to constrain the publication of sensitive scientific results, whenever the dangers to society clearly outweigh the benefits."[59] Such a board might be modeled on the oversight procedure developed by the U.S. Department of Homeland Security's Compliance Review Group, which reviews the department's biodefense projects to ensure that they are in compliance with the BWC and monitors projects as they evolve.[60] In addition to top-down

[58] Ronald M. Atlas and Malcolm Dando, "The Dual-Use Dilemma for the Life Sciences: Perspectives, Conundrums, and Global Solutions," *Biosecurity and Bioterrorism*, vol. 4 (2006), p. 281.
[59] Tucker and Hooper, "Protein Engineering: Security Implications," p. 17.
[60] Matthew Meselson, "Your Inbox, Mr President," *Nature*, vol. 457 (January 2009), pp. 259-260.

oversight mechanisms, scientists should consult online portals that enable them to discuss the dual-use implications of planned research projects with biosecurity experts.[61]

Governing dual-use knowledge. Governing the dual-use potential of knowledge is a more difficult challenge than governing the transfer and use of hardware. Nevertheless, one approach is to introduce a system for vetting scientific personnel who work with toxins. For example, the United Kingdom recently introduced the Academic Technology Approval Scheme (ATAS), which requires postgraduate students from outside the European Economic Area who are interested in security-sensitive fields to obtain "clearance" before they can apply for a visa to study in Britain.[62] Similar vetting schemes should be adopted by academic institutions and private companies in all countries that work with toxins. The scientific community, aided by civil society, also has an important role to play in managing dual-use risk. Promotion of professional codes of conduct and other forms of self-regulation are important to raise awareness of dual-use issues and to support laboratory biosafety and biosecurity measures.[63] Universities should also encourage scientific responsibility through the inclusion of ethical and security issues in the life-sciences curriculum.[64]

Strengthening the international norm. At the root of all governance measures lies the fundamental ethical norm that poison and disease should not be used as weapons. This norm codifies an ancient, cross-cultural taboo against poison weapons and is the cornerstone of the biological disarmament regime.[65] Despite its lack of formal verification measures, the BWC urges all member states to enact national legislation to prohibit and prevent activities that violate the Convention. A number of states have done so, but the full implementation of such measures and their harmonization among BWC member states remain major challenges. One response to these shortcomings is a proposal to negotiate an international convention that would criminalize the development and use of biological and chemical weapons.[66] This treaty would give the national courts jurisdiction over individuals present on a country's territory,

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[61] Barry Bergman, "Goldman School portal takes the worry out of 'experiments of concern,'" University of California Berkeley News, April 2, 2009.

[62] The scheme is operated by the Foreign and Commonwealth Office. See House of Commons, Foreign Affairs Committee, Fourth Report of Session 2008-09, *Global Security: Non-Proliferation*, June 14, 2009, Evidence, pp. 261-263.

[63] Brian Rappert, "Responsibility in the Life Sciences: Assessing the Role of Professional Codes," *Biosecurity and Bioterrorism*, vol. 2 (2004), pp. 164-174; James Revill and Malcolm Dando, "A Hippocratic Oath for life scientists," *EMBO Reports*, vol. 7 (2006), pp 55-60.

[64] Brian Rappert, "Education for the Life Sciences: Choices and Challenges," in Brian Rappert and Caitríona McLeish, *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007), pp. 51-65.

[65] Catherine Jefferson, "The Chemical and Biological Weapons Taboo: Nature, Norms and International Law," DPhil dissertation, University of Sussex, 2009.

[66] Matthew Meselson and Julian Perry Robinson, "A draft convention to prohibit biological and chemical weapons under international criminal law," *Fletcher Forum of World Affairs*, vol. 28 (Winter 2004), pp. 57-71.

regardless of their nationality or official position, who order, direct, or knowingly render substantial assistance to the use of biological and chemical weapons anywhere in the world. Such a treaty would help to minimize the jurisdictional inconsistencies among states, and the concept of individual criminal responsibility would support the initiatives considered here.

Conclusions

Protein engineering offers many potential benefits, particularly in the field of advanced therapeutics. Nevertheless, the prospect that rogue states or technologically sophisticated terrorist groups could misuse this technology to create enhanced biological weapons is not outside the bounds of possibility. Potential consequences of the misuse of protein engineering include the creation of protein toxins with increased toxicity, potency, stability, and effects that defy diagnosis and treatment. In an effort to balance the risks of misuse against the potential costs of excessive regulation to the scientific enterprise, possible governance measures focus on three dimensions: hardware, people, and products. Protein-engineering research should be managed through formal oversight mechanisms, as well as informal self-governance measures carried out by the scientific community, creating a “web” of measures to prevent the misuse of life-science research.

Chapter 10: Synthesis of Viral Genomes

Filippa Lentzos and Pamela Silver

The emerging field of synthetic biology seeks to establish a rational framework for manipulating the DNA of living organisms based on the application of engineering principles.[1] (See Chapter 11.) This chapter focuses on a key enabling technology for synthetic biology: the ability to synthesize strands of DNA from off-the-shelf chemicals and assemble them into genes and entire microbial genomes. When combined with improved capabilities for the design and assembly of genetic circuits that can perform specific tasks, synthetic genomics offers the potential for revolutionary advances. At the same time, it could permit the recreation of dangerous viruses from scratch, as well as genetic modifications designed to enhance the virulence and military utility of biological warfare agents.

The misuse of gene synthesis to recreate deadly viruses for biological warfare or terrorism would require the integration of three processes: the automated synthesis of DNA segments, the assembly of those segments into a viral genome, and the production and weaponization of the synthetic virus. Each of these steps differs with respect to the maturity of the technologies involved, the ease of misuse by non-experts, and the associated threat. Although the risk of misuse of DNA synthesis will increase over time, the synthesis and weaponization of a synthetic virus would entail significant technical hurdles. This chapter reviews current initiatives to address the security concerns related to DNA synthesis technology and suggests some additional measures to limit the risk of misuse.

Overview of the Technology

DNA molecules consist of four fundamental building blocks: the nucleotides adenine (A), thymine (T), guanine (G), and cytosine (C), which are linked together in a specific sequence to form a linear chain that encodes genetic information. A DNA molecule may consist of a single strand or two complementary strands that pair up to form a double helix. An infectious virus consists of a long strand of genetic material (DNA or RNA) encased in a protein shell. There are at least three ways to synthesize the viral genome *de novo* (from scratch), each requiring a

[1] Royal Academy of Engineering, *Synthetic Biology: Scope, Applications and Implications* (London: Royal Academy of Engineering, 2009), p. 13.

different amount of explicit and tacit knowledge. The first and most straightforward approach would be to order the entire genome from a commercial gene-synthesis company by submitting the DNA sequence online. This sequence would be synthesized in a specialized facility using proprietary technology that is not available for purchase, "packaged" in a living bacterial cell, and shipped back to the customer. (A leading supplier, Blue Heron Biotechnology in Bothell, WA, has already synthesized DNA molecules 52,000 base pairs long.)

The second option would be to order oligonucleotides (single-stranded DNA molecules less than 100 nucleotides in length) from one or more providers and then stitch them together in the correct sequence to create the entire viral genome. The advantage of this approach is that one can obtain more accurate DNA sequences, avoid purchasing expensive equipment, and outsource the necessary technical expertise.

The third option would be to synthesize oligonucleotides with a standard desktop DNA synthesizer and then assemble the short fragments into a genome. At a minimum, this approach would require the acquisition of a DNA synthesizer (purchased or built) and a relatively small set of chemicals. For most viruses, however, *de novo* synthesis is still more difficult than stealing a sample from a laboratory or isolating it from nature.[2]

History of the Technology

The field of synthetic genomics originated in 1979, when the first gene was synthesized by chemical means.[3] Indian-American chemist Har Gobind Khorana and his 17 co-workers at the Massachusetts Institute of Technology took several years to assemble a small gene consisting of 207 DNA nucleotide base pairs. In the early 1980s, two developments facilitated the synthesis of DNA constructs: the invention of the automated DNA synthesizer and the polymerase chain reaction (PCR), which made it possible to copy any given DNA sequence many million-fold. By the end of the 1980s, a DNA sequence measuring 2,100 base pairs had been synthesized chemically.[4]

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[2] Gerald Epstein, "The challenges of developing synthetic pathogens,' *Bulletin of the Atomic Scientists* website, May 19, 2008, http://www.thebulletin.org/web-edition/features/the-challenges-of-developing-synthetic-pathogens.
[3] Har Ghobind Khorana, "Total Synthesis of a Gene," *Science*, vol. 203, no. 4381 (February16, 1979), pp. 614-25.
[4] Wlodek Mandecki, M.A. Hayden, M.A. Shallcross, and Elizabth Stotland, "A Totally Synthetic Plasmid for General Cloning, Gene Expression and Mutagenesis in *Escherichia coli*," *Gene*, vol. 94, no. 1 (September 28, 1990), pp. 103-107.

In 2002 the first functional virus was synthesized from scratch: poliovirus, about 7,500 nucleotide base pairs long.[5] Over a period of several months, Eckard Wimmer and his coworkers at the State University of New York at Stony Brook assembled live, infectious poliovirus from customized oligonucleotides, which they had ordered from a commercial supplier. The following year, Hamilton Smith and his colleagues at the J. Craig Venter Institute published a description of the synthesis of a bacteriophage (virus that infects bacteria) called φX174. Although this virus contains only 5,386 DNA base pairs, or fewer than poliovirus, the new technique greatly improved the speed of DNA synthesis. Compared with more than a year that it took Wimmer's group to synthesize poliovirus, Smith and his colleagues made a precise, fully functional copy of φX174 bacteriophage in only two weeks.[6]

Since then, several other functional viral genomes have been synthesized, including the reconstruction of extinct viruses to gain insights into why they were particularly virulent.[7] In 2005, scientists at the U.S. Centers for Disease Control and Prevention synthesized the genome of the "Spanish" influenza virus strain responsible for the 1918-19 flu pandemic, which killed tens of millions of people worldwide, using sequence data derived from frozen or paraffin-fixed cells recovered from victims of the pandemic. In late 2006, scientists also resurrected a "viral fossil," a human retrovirus that had been incorporated into the human genome around 5 million years ago.[8] In 2008, the SARS virus was synthesized in the laboratory.[9]

Utility of the Technology

The total synthesis of a bacterial genome from chemical building blocks represents a landmark achievement in the use of DNA synthesis techniques to create more complex and functional products. Synthesizing a microbial genome from scratch is a significant methodological shift from recombinant DNA technology, which involves the cutting and splicing of pre-existing genetic material. Because any DNA conceivable sequence can be created by

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[5] Jeronimo Cello, Aniko V. Paul, and Eckard Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template," *Science*, vol. 297, no. 5583 (August 9, 2002), pp. 1016-1018.
[6] Hamilton O. Smith, C. A. Hutchinson III, C. Pfannkoch, and J. Craig Venter, "Generating a Synthetic Genome by Whole Genome Assembly: φX174 Bacteriophage from Synthetic Oligonucleotides," *Proceedings of the National Academy of Sciences*, vol. 100 (November 3, 2003), pp. 15440-15445.
[7] Michele S. Garfinkel, D. Endy, G.L. Epstein, and Robert M. Friedman, *Synthetic Genomics: Options for Governance* (Rockville, MD: J Craig Venter Institute, 2007), available at http://www.jcvi.org/.
[8] Martin Enserink, "Viral Fossil Brought Back to Life," *Science Now*, November 1, 2006, http://news.sciencemag.org/sciencenow/2006/11/01-04.html.
[9] Nyssa Skilton, "Man-made SARS virus spreads fear," *Canberra Times*, December 24, 2008.

chemical synthesis, it allows for greater efficiency and versatility in existing fields of research, while opening up new paths of inquiry and innovation that were previously constrained. Although the chemical synthesis of oligonucleotides up to 120 base pairs is now routine, accurately synthesizing DNA sequences greater than 180 base pairs remains somewhat of an art. It is just a matter of time, however, before technological advances further reduce costs and the frequency of errors, making genome synthesis readily affordable and accessible.[10] According to one estimate, the cost per base pair has already fallen 50-fold and is continuing to halve every 32 months.[11]

Potential for Misuse

These dramatic developments have raised concern that the increased accessibility and affordability of DNA synthesis techniques could make it easier for would-be bioterrorists to acquire dangerous viral pathogens—particularly those that are currently restricted to a few high-security labs, such as variola (smallpox) virus; are difficult to isolate from nature, such as Ebola and Marburg viruses, or have become extinct, such as the 1918 pandemic strain of influenza virus. Although in theory DNA synthesis techniques might permit the creation of bioengineered agents more deadly and communicable than those that exist in nature, this scenario appears unlikely. As Tucker and Zilinskas note, "To create such an artificial pathogen, a capable synthetic biologist would need to assemble complexes of genes that, working in union, enable a microbe to infect a human host and cause illness and death. Designing the organism to be contagious, or capable of spreading from person to person, would be even more difficult. A synthetic pathogen would also have to be equipped with mechanisms to block the immunological defenses of the host, characteristics that natural pathogens have acquired over eons of evolution. Given these daunting technical obstacles, the threat of a synthetic 'super-pathogen' appears exaggerated, at least for the foreseeable future."[12]

For this reason, the recreation from scratch of known viral pathogens, rather than the creation of entirely new ones, is the most immediate risk associated with DNA synthesis technology. (Because bacterial genomes are generally far larger than viral genomes, synthesizing

[10] National Academies of Sciences, *Globalization, Biosecurity, and the Future of the Life Sciences*. (Washington: National Academies of Sciences, 2006).
[11] Garfinkel, Endy, Epstein, and Friedman, *Synthetic Genomics: Options for Governance*, p. 10.
[12] Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," *The New Atlantis*, vol. 25 (Spring 2006), p. 38.

them is a more difficult and time-consuming process.) Although the primary threat of misuse of synthetic genomics appears to come from state-level biological warfare programs, two possible scenarios involving individuals also provide cause for concern. The first scenario involves a "lone operator," such as a highly trained molecular biologist who is motivated to do harm by ideology or personal grievance. For example, the Federal Bureau of Investigation has concluded that Dr. Bruce Ivins, an anthrax expert working in the U.S. Army's premier biodefense laboratory at Fort Detrick in Maryland, was the perpetrator of the 2001 anthrax letter attacks.

The second scenario of concern involves a "biohacker," an individual who does not necessarily have malicious intent but seeks to create bioengineered organisms out of curiosity or to demonstrate technical prowess, a common motivation of many designers of computer viruses. The reagents and tools used in synthetic biology will eventually be converted into commercial kits, making it easier for individuals to acquire them. Moreover, as synthetic biology training becomes increasingly available to students at the college and even high-school levels, a "hacker culture" may emerge, increasing the risk of reckless or malevolent experimentation.[13]

Ease of Misuse (Explicit and Tacit Knowledge)

The construction of a pathogenic virus by assembling pieces of synthetic DNA requires substantial hands-on laboratory experience. As Kathleen Vogel has observed, certain aspects of viral genome synthesis rely on tacit knowledge that is "not merely reducible to recipes, equipment, and infrastructure."[14] Tacit knowledge is also what the National Science Advisory Board for Biosecurity (NSABB) meant when it noted, "The technology for synthesizing DNA is readily accessible, straightforward and a fundamental tool used in current biological research. In contrast, the science of constructing and expressing viruses in the laboratory is more complex and somewhat of an art. It is the laboratory procedures downstream from the actual synthesis of DNA that are the limiting steps in recovering viruses from genetic material."[15]

In assessing the potential of DNA synthesis techniques for misuse, it is important to examine the role of tacit knowledge in synthesizing a pathogen at the laboratory bench. The *World at Risk* report, released in December 2008 by the U.S. Commission on the Prevention of

[13] Ibid., pp. 40-42.
[14] Kathleen Vogel, "Bioweapons Proliferation: Where Science Studies and Public Policy Collide," *Social Studies of Science*, vol. 36, no. 5 (2006), p. 676.
[15] National Science Advisory Board for Biosecurity (NSABB), *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* (Bethesda, MD: National Institutes of Health, 2006), p. 4.

WMD Proliferation and Terrorism, recommended that counterterrorism efforts focus less on the risk of terrorists becoming biologists and more on the risk of biologists becoming terrorists.[16] The report failed to emphasize, however, that not *all* biologists are of concern. Instead, the onus falls on those who have expertise and experience in weaponizing pathogens—namely those who have worked in the past on state-sponsored biological weapons programs.

Accessibility of the Technology

Synthesizing a virus and converting it into an effective biological weapon would involve overcoming several technical hurdles. First, the *de novo* synthesis of an infectious viral genome requires an accurate genetic sequence. Although DNA sequences are available for many pathogenic viruses, the quality of the sequence data varies. Genomes published in publicly available databases often contain errors, some of which may be completely disabling while others would attenuate the virulence of the resulting virus. In addition, some published sequences are not derived from virulent "wild type" viruses but rather from cultures that have spent many generations in the lab and have therefore lost their virulence through attenuating mutations.

A second difficulty with the synthesis of a highly pathogenic virus is ensuring infectivity. For some viruses, such as poliovirus, the genetic material is directly infectious, so that introducing it into a susceptible cell will result in the production of complete virus particles. But for other viruses, such as causative agents of influenza and smallpox, the viral genome itself is not infectious and requires additional components (such as enzymes involved in replication of the genetic material) whose function must be replaced.

A third technical hurdle relates to the characteristics of the viral genome. Viruses with large genomes are harder to synthesize than those with smaller genomes. In addition, positive-stranded RNA viruses are easier to construct than negative-stranded RNA viruses, which in turn are easier to synthesize than double-stranded DNA viruses. For this reason, poliovirus is relatively easy to synthesize because it has a small genome made of positive-stranded RNA, whereas variola virus is hard to synthesize because it has a very large genome made up of double-stranded DNA.

[16] Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, *World at Risk* (New York: Vintage Books, 2008), p. 11.

Imminence and Magnitude of Risk

Rapid improvements in the cost, speed, and accuracy of DNA synthesis mean that although the *de novo* synthesis of viral pathogens is relatively difficult today, the risk of misuse of the technology will increase over time—although by how much remains a matter of debate. For the next five years, the greatest risk will involve the synthesis of a small number of highly pathogenic viruses that are currently extinct or otherwise difficult to obtain. Access to stocks of variola virus and 1918 influenza virus is tightly controlled: samples of the former are stored in two authorized repositories in the United States and Russia, while samples of the latter exist only in a few laboratories. Synthesizing variola virus would be difficult because its genome is one of the largest of any virus and is not directly infectious. Although the genome of the 1918 influenza virus is relatively small and has been reconstructed and published, constructing the virus from scratch would be moderately difficult because the genome is not directly infectious.[17]

Of the pathogenic viruses that can be found in nature, some are easier to isolate than others. Filoviruses, such as Marburg and Ebola, have animal reservoirs that are unknown, poorly understood, or only accessible during active outbreaks. As a result, isolating these viruses from a natural source would require skill, some luck, good timing, and the ability to transport the virus safely from the site of an outbreak. At present, synthesizing Marburg and Ebola viruses would be moderately difficult: although their genomes are relatively small, they are not directly infectious and producing infectious virus particles would be challenging.[18]

Despite these hurdles, the risk of misuse of DNA synthesis techniques will increase over time. One analyst has claimed that ten years from now, it may be easier to synthesize almost any pathogenic virus than to obtain it by other means.[19] Nevertheless, even the successful synthesis of a highly virulent virus would not, in itself, create an effective biological weapon.[20] Although in theory any disease-causing biological agent could be used as weapon, only some pathogens have real military utility. Traditional effectiveness criteria for antipersonnel agents are infectivity (the ability to infect humans reliably and cause disease), virulence (the severity of the resulting

[17] Garfinkel, Endy, Epstein, and Friedman, *Synthetic Genomics: Options for Governance*, p. 13-14.
[18] Ibid.
[19] Ibid., p. 15.
[20] Rebecca L. Frerichs, et al., *Historical Precedence and Technical Requirements of Biological Weapons Use: A Threat Assessment*, SAND2004-1854 (Albuquerque, NM: Sandia National Laboratories, 2004). See also, Raymond A. Zilinskas, "Technical Barriers to Successful Biological Attacks with Synthetic Organisms," in Stephen M. Mauer, Keith V. Lucas, and Starr Terrell, *From Understanding to Action: Community-based Option for Improving Safety and Security in Synthetic Biology* (Berkeley, CA: University of California, 2006).

illness), persistence (the length of time the pathogen remains infectious after being released into the environment), stability, and the ability to disperse the agent over a wide area. Early U.S. developers of biological weapons preferred to use veterinary diseases such as anthrax and tularaemia, which are not contagious in humans, because they would make a biological attack more controllable. The Soviet Union, in contrast, weaponized highly contagious diseases such as pneumonic plague and smallpox for strategic attacks against distant targets, in the belief that the resulting epidemic would not boomerang against the Soviet population. The choice of pathogen also depends on the intended use, such as whether the intent is to kill or incapacitate, to contaminate terrain for long periods, or to trigger an epidemic. Because obtaining strains with the desired characteristics from natural sources is not easy, most of the pathogens developed in the past as biological weapons have been deliberately bred or genetically modified.

Once an appropriate viral pathogen has been synthesized, it would have to be cultivated. Viruses are significantly harder to mass-produce than bacteria because they can only replicate in living cells. One low-tech option would be to grow the virus in fertilized eggs. To avoid contamination, however, the eggs would have to be specially ordered—not an easy task without attracting attention. Cultivating infectious viruses is also extremely hazardous to the perpetrators and those living nearby.

Disseminating biological agents effectively involves even greater technical hurdles. Whereas persistent chemical warfare agents such as sulfur mustard and VX nerve gas are readily absorbed through intact skin, bacteria and viruses cannot enter the body via that route unless the skin has been broken. Thus, biological agents must usually be ingested or inhaled to cause infection. To expose large numbers of people through the gastrointestinal tract, a possible means of delivery is the contamination of food or drinking water, yet neither of these scenarios would be easy to accomplish. Large urban reservoirs are usually unguarded, but unless the terrorists dumped in a massive quantity of biological agent, the dilution factor would be so great that no healthy person drinking the water would receive an infectious dose.[21] Moreover, modern sanitary techniques such as chlorination and filtration are designed to kill pathogens from natural sources and would probably be equally effective against a deliberately released agent.

[21] Jonathan B. Tucker, "Introduction," in Jonathan B. Tucker (ed.), *Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons* (Cambridge, MA: MIT Press, 2000), p. 7.

The only potential way to inflict mass casualties with a biological agent is by disseminating it as an aerosol: an invisible cloud of infectious droplets or particles so tiny that they remain suspended in the air for long periods and can be inhaled by large numbers of people. A concentrated aerosol, released into the air in a densely populated urban area, could potentially infect thousands of victims simultaneously. After an incubation period of a few days (depending on the type of agent and the inhaled dose), the exposed population would experience an outbreak of incapacitating or fatal illness. Although aerosol delivery is potentially the most lethal way to deliver a biological attack, it entails major technical hurdles. To infect through the lungs, the infectious particles must be between one and five microns (millionths of a meter) in diameter. Generating an aerosol cloud with the particle size and concentration needed to cover a large area would require the acquisition or development of a sophisticated delivery system. There is also a trade-off between the ease of production and the effectiveness of dissemination. The easiest way to produce microbial agents is in liquid form, yet when a slurry is sprayed into the air, it forms heavy droplets that fall to the ground so that only a small percentage of the agent is aerosolized. In contrast, if the microbes are dried to a solid cake and milled into a fine powder, they become far easier to aerosolize, but the drying and milling process is technically difficult.

Even if aerosolization can be achieved, the effective delivery of biological agents in the open air is dependent on atmospheric and wind conditions, creating additional uncertainties. Only under highly stable atmospheric conditions will an aerosol cloud remain close to the ground where it can be inhaled, rather than being rapidly dispersed. Moreover, most microorganisms are sensitive to ultraviolet radiation and cannot survive more than 30 minutes in bright sunlight, limiting effective military use to nighttime attacks. The one major exception to this rule is anthrax bacteria, which can form spores with a tough protective coating that enables them to survive for several hours in sunlight. Terrorists could, of course, stage a biological attack inside an enclosed space such as a building, a subway station, a shopping mall, or a sports arena, but even here the technical hurdles would be by no means trivial. The Aum Shinrikyo cult, which was responsible for the March 1995 sarin attack on the Tokyo subway, failed in several attempts to carry out biological attacks. Despite the group’s extensive scientific and financial resources, it

could not overcome some or all of the technical hurdles associated with the acquisition of a virulent strain, cultivation of the agent, and efficient delivery.[22]

Finally, even if a synthetic virus was disseminated successfully in aerosol form, the outcome of the attack would depend on factors such as the basic health of the people who were exposed and the speed with which the public health authorities and medical professionals detected the outbreak and moved to contain it. A prompt response with effective medical countermeasures, such as the administration of antiviral drugs combined with vaccination, might significantly blunt the impact of an attack. In addition, simple, proven methods such as the isolation and home care of infected individuals, the wearing of face masks, frequent hand washing, and the avoidance of hospitals where transmission rates are high, have also been effective at slowing the spread of epidemics.

In summary, the technical challenges involved in carrying out a mass-casualty biological attack are formidable. Contrary to worst-case planning scenarios, in which the aerosol dispersal of military-grade agents causes hundreds of thousands of deaths, only two bioterrorist attacks in the United States are known to have caused actual casualties. Both incidents involved the use of crude delivery methods: the deliberate contamination of food with *Salmonella* bacteria by the Rajneeshee cult in Oregon in 1984, and the mailing of powdered anthrax spores through the postal system in 2001. Such low-tech attacks are likely to remain the most common form of bioterrorism. They are potentially capable of inflicting at most tens to hundreds of fatalities—within the destructive range of high-explosive bombs, but not the mass death predicted by many worst-case scenarios.[23]

Awareness of Dual-Use Potential

In response to media and public interest in synthetic genomics, European countries and the United States have assessed the dual-use risks of this emerging technology. In August 2006, after journalists reported how easy it was to order pathogenic DNA sequences over the Internet, the British government convened a cross-departmental meeting to consider the feasibility and

[22] Milton Leitenberg, "Aum Shinrikyo's Efforts to Produce Biological Weapons: A Case Study in the Serial Propagation of Misinformation," *Terrorism and Political Violence*, vol. 11, no. 4 (1999), pp. 149-158.
[23] Tucker, "Introduction," in Tucker, ed., *Toxic Terror*, pp. 6-9.

potential risks of *de novo* virus synthesis.[24] This meeting concluded that "although there is a theoretical risk, the likelihood of misuse of this kind at the moment, and in the foreseeable future, is very low." It was therefore judged that the existing legislation was adequate and that "additional regulation would be inappropriate at the present time." The British government acknowledged, however, that DNA synthesis techniques "will advance such that pathogenic organisms could be constructed or (more likely) modified more easily" and that the issue should therefore be kept under review. To that end, the government requested key organizations to sound an alert if they became aware of significant advances that could lead to an increased risk. Along similar lines, a December 2006 workshop on synthetic biology conducted by the British Ministry of Defence concluded that the field did not pose immediate threats or opportunities for the United Kingdom, but that it might do so over the longer term.[25]

Also in 2006, the Dutch government asked the Commission on Genetic Modification (COGEM) to assess whether existing risk-management and security measures under the regulatory framework for genetically modified organisms (GMOs) were suitable to cover developments in synthetic biology. COGEM concluded that the existing measures were adequate but that it would continue to monitor advances in the field.[26]

In the United States, gene-synthesis technology is viewed quite differently. In a 2006 report, a federal advisory committee, the National Science Advisory Board for Biosecurity (NSABB), highlighted the potential misuse of DNA synthesis to recreate Select Agent viruses in the laboratory. The NSABB noted that although synthetic DNA was addressed in the U.S. legal framework, the U.S. government should develop a biosecurity system for providers of synthetic

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[24] United Kingdom, Department for Business, Enterprise and Regulatory Reform, *The Potential for Misuse of DNA Sequences (Oligonucleotides) and the Implications for Regulation* (2006), http://www.dius.gov.uk/partner_organisations/office_for_science/science_in_government/key_issues/DNA_sequences.

[25] For a similar assessment, see United Kingdom, Ministry of Defence, *Defence Technology Strategy for the Demands of the 21st Century* (October 2006), p. 152, http://www.mod.uk/NR/rdonlyres/27787990-42BD-4883-95C0-B48BB72BC982/0/dts_complete.pdf

[26] Commission on Genetic Modification (COGEM), *Biological Machines? Anticipating Developments in Synthetic Biology*, CGM/080925-01 (September 2008), http://www.cogem.net/ContentFiles/CGM080925-01-Biological%20machines1.pdf. See also, Rinie van Est, Huib de Vriend, Bart Walhout, *Constructing Life: The World of Synthetic Biology* (The Hague: Rathenau Institute, 2007). The Rathenau Institute, the national technology assessment organization in the Netherlands, encourages social debate and development of political opinion on technological and scientific advances.

DNA. [27] In particular, the Board urged the development of obligatory standards and practices for screening DNA synthesis orders and interpreting the results, and for retaining records on gene-length orders.

Characteristics of the Technology Relevant to Governance

Embodiment. Much of the technology involved in *de novo* DNA synthesis is intangible, based on specialized knowledge acquired through experimentation. The sequencing of microbial genomes, for example, is a key element of the process. At the same time, a piece of specialized hardware, the automated DNA synthesizer, greatly reduces time and cost requirements.

Maturity. DNA synthesis is a mature technology that is commercially available, but synthesizing accurate DNA sequences greater than 180 base pairs long and stitching them together into genome-length sequences still involves significant technical hurdles. At the same time, the synthesis in 2010 of a bacterial genome comprising more than a million DNA base pairs suggests that it will soon become technically possible to synthesize almost any microbial genome for which an accurate genetic sequence has been determined.

Convergence. Genome synthesis is convergent because it draws on several other technologies. The field of bioinformatics provides the DNA sequence to be synthesized. The DNA fragments (oligonucleotides) making up the desired sequence are usually produced to order by a commercial supplier, using automated synthesizers developed by the engineering community. Finally, the assembly of the oligonucleotides into a functional genome requires extensive training in standard molecular biology techniques such as ligation and cloning.

Rate of advance. DNA synthesis methods have continued to advance at an exponential pace. DNA sequences made up of 14,600[28] and 32,000[29] nucleotides were synthesized in 2004, and 2008 saw the synthesis of an abridged version of the genome of the bacterium *Mycoplasma genitalium*, consisting of 583,000 DNA base pairs.[30] In May 2010, scientists at the J. Craig

[27] National Science Advisory Board for Biosecurity (NSABB), *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* (Bethesda, MD, USA: National Science Advisory Board for Biosecurity, 2006), available at http://www.biosecurityboard.gov

[28] Jingdong Tian, H. Gong, N. Sheng, X. Zhou, E. Gulari, X. Gao, and George Church, "Accurate Multiplex Gene Synthesis from Programmable DNA Microchips," *Nature*, vol. 432 (December 23/30, 2004), pp. 1050-54.

[29] Sarah J. Kodumai, K.G. Patel, R. Reid, H.G. Menzella, M. Welch, and Daniel V. Santi, "Total Synthesis of Long DNA Sequences: Synthesis of a Contagious 32-kb Polyketide Synthase Gene Cluster," *Proceedings of the National Academy of Sciences*, vol. 101, no. 44 (September 17, 2004), pp. 15573-78.

[30] Daniel G. Gibson, G.A. Benders, C. Andrews-Pfannkoch, E.A. Denisova, H. Baden-Tillson, J. Zaveri, T.B. Stockwell, A. Brownley, D.W. Thomas, M.A. Algire, C. Merryman, L. Young, V.N. Noskov, J.I. Glass, C.J. Venter,

Venter Institute announced the synthesis of the entire genome of the bacterium *Mycoplasma mycoides*, consisting of more than 1 million DNA base pairs.[31]

International diffusion. Although DNA synthesis techniques were originally accessible only to a handful of top research groups working at state-of-the-art facilities, these methods have become more widely available as they are refined, simplified, and improved. A 2007 survey estimated that at least 24 firms in the United States and an additional 21 firms worldwide can manufacture genome-length stretches of DNA, and the gene-synthesis industry continues to grow and expand internationally.[32]

Susceptibility to Governance

Much can be done at the national or regional level to manage the risk of misuse of DNA synthesis. The fact that only a limited number of companies worldwide currently possess the advanced know-how and technical infrastructure needed to produce synthetic viral genomes offers a window of opportunity to introduce governance measures.

Past and Current Approaches to Governance

In Europe, concerns about DNA synthesis have tended to focus on issues such as safety, the nature and integrity of life, equity and intellectual property, and public confidence and engagement, but not on security and deliberate misuse.[33] Typical of this approach is the European Commission's assessment that the most pressing need is "to examine whether existing safety regulations for the management of engineered microorganisms provide adequate protection against inadvertent release of 'synthetic' pathogens. In particular, who is responsible for ascertaining and quantifying risks, and for implementing any clean-up measures that might be

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C.A. Hutchison III, and Hamilton O. Smith, "Complete Chemical Synthesis, Assembly, and Cloning of *Mycoplasma genitalium* Genome," *Science*, vol. 319, no. 5867 (February 29, 2008), pp. 1215-20.

[31] Daniel G. Gibson, John I. Glass, Carole Lartique, et al., "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome," *Science Express*, May 20, 2010, p. 1. See also, Elizabeth Pennisi, "Synthetic Genome Brings New Life to Bacterium," *Science*, vol. 328 (May 21, 2010), pp. 958-959,

[32] Garfinkel, Endy, Epstein, and Friedman, *Synthetic Genomics: Options for Governance*, p. 2.

[33] Daniel Feakes, "Synthetic Biology and Security: A European Perspective," *WMD Insights* (December 2008 / January 2009) http://wmdinsights.com/I29/I29_EU1_SynthBioSec.htm; Filippa Lentzos, "Synthetic Biology in the Social Context: The UK Debate to Date," *BioSocieties*, vol. 4, no. 3-4 (2009); Markus Schmidt, "Public Will Fear Biological Accidents, Not Just Attacks," *Nature*, vol. 441 (June 29, 2006), p. 1048.

undertaken?"[34] Two European countries, the United Kingdom and the Netherlands, stand out as having considered biosecurity issues in some detail, but both have concluded that their current regulatory frameworks are adequate to address the risk of misuse.

The United States has been far more aggressive in addressing the security dimensions of gene synthesis. In November 2009, the Department of Health and Human Services published a proposed "Screening framework guidance for synthetic double-stranded DNA providers" in the *Federal Register*.[35] These draft guidelines call for subjecting all requests for synthetic double-stranded DNA greater than 200 base pairs in length to a process of customer and sequence screening. Upon receiving a DNA synthesis order, the provider should review the information provided by the customer to verify its accuracy and check for "red flags" suggestive of illicit activity. If the information provided raises concerns, providers should ask the customer for additional information. Screening of the requested DNA sequence is also recommended to search for any sequences derived from or encoding Select Agents. If the customer or sequence screening raise any concerns, providers should pursue follow-up screening to clarify the end-use of the ordered sequence. In cases where follow-up screening does not resolve concerns about an order, or there is reason to believe that it may intentionally or inadvertently violate U.S. law, providers are encouraged to seek advice from designated government officials. The guidance also recommends that providers retain electronic copies of customer orders for at least eight years, the duration of the statute of limitations for prosecution. Although adherence to the screening framework is considered voluntary, the guidance reminds providers of their legal obligations under existing export control regulations.

Recognizing the security concerns around synthetic DNA, the gene-synthesis industry has already begun screening customers and orders on its own initiative.[36] The International Association Synthetic Biology (IASB), a consortium of mainly German companies, launched its "Code of Conduct for Best Practices in Gene Synthesis" on November 3, 2009.[37] This Code, developed over an 18-month period, reflects for the most part what has become common practice

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[34] European Commission, *Synthetic Biology: Applying Engineering to Biology*, report of a NEST High-Level Expert Group (Brussels: Directorate General Research, 2005), p. 18.
[35] U.S. Department of Health and Human Services, "Screening Framework Guidance for Synthetic Double-Stranded DNA Providers," *Federal Register*, vol. 74, no. 227 (November 27, 2009), pp. 62319-62327.
[36] Industry Association Synthetic Biology (IASB), Report on the Workshop "Technical Solutions for Biosecurity in Synthetic Biology" held on April 3, 2008 in Munich, Germany, p. 8.
[37] Corie Lok, "Gene-makers put forward security standards," *Nature* online, November 4, 2009. See the IASB website for the Code itself: http://www.ia-sb.eu/

in gene-synthesis companies. Like the U.S. government guidance, the Code recommends an initial screen to confirm the customer's *bona fides*, followed by an automated screen of the sequence order using a computer program to search for similarities between gene sequences.[38] Any hits from the automated screen are then assessed by human experts. If the hits are deemed to be real and not false-positives, follow-up screening is done to verify the legitimacy of the customer before the order is filled. Although IASB member companies have received DNA synthesis orders for sequences from pathogenic organisms, none of these orders was identified as malicious. Instead, all were related to basic research on pathogenicity or the development of new vaccines.[39]

Shortly before the IASB Code of Conduct was launched, two companies that had initially been involved in the process dropped out and established their own group, the International Gene Synthesis Consortium (IGSC). This body includes five of the world's leading gene-synthesis companies and claims to represent 80 percent of the industry.[40] Because of its large market share, the IGSC asserts it has the experience to develop workable screening measures and has put forward a "Harmonized Screening Protocol" to rival the IASB Code of Conduct. [41]

Options for Future Governance

The development of three sets of voluntary guidelines to prevent the misuse of gene synthesis has helped to raise awareness about the issue but has also been somewhat confusing. Companies have been left to decide whether to adopt one of the three standards, devise their own by mixing and matching various elements, or ignore them altogether. Previous surveys on the effectiveness of voluntary self-governance regimes in the biotechnology industry have highlighted inconsistencies in the way they are implemented.[42] Research has shown, for instance, that biotechnology companies vary greatly in how they establish Institutional Biosafety Committees (IBCs), the structure of these committees, the frequency of the meetings, the quality

[38] One such screening program is the U.S. National Center for Biotechnology Information's Basic Local Alignment Search Tool (BLAST).
[39] IASB, report on the workshop "Technical Solutions for Biosecurity in Synthetic Biology," p. 4.
[40] Erika Check Hayden, "Gene-makers form security coalition," *Nature* online, November 18, 2009. See the IGSC website for the Harmonized Screening Protocol: http://www.genesynthesisconsortium.org/
[41] Judhijit Bhattacharjee, "Gene Synthesis Companies Pledge to Foil Bioterrorists," *Science* Online, November 19, 2009.
[42] Filippa Lentzos, "Managing Biorisks: Considering Codes of Conduct," *Nonproliferation Review*, vol. 13, no. 2 (2006), p. 211-26.

of minutes produced, and whether or not the committees approve individual projects or groups of projects. IBCs also differ in how they interpret their purpose and responsibilities.[43]

Most providers of synthetic DNA are sensitive to security concerns and would probably agree to implement some sort of screening practices if they are not doing so already. It is unclear, however, what the minimum standards for these practices should be. Who decides if the DNA sequence database that a company decides to screen against is adequate? Is 200 base pairs an appropriate cut-off for deciding whether or not to screen a DNA synthesis order? Is it sufficient to retain order records in the form of broad statistics, or must the details of each individual order be kept? Is five years long enough to retain records, rather than eight? One way to settle questions like this is to establish a set of minimum screening standards through statutory legislation rather than voluntary guidance.

In devising a governance framework for the *de novo* synthesis of viral genomes, it can be useful to think of regulation as a process that operates through a trichotomy of mechanisms to influence both formal and informal behavior.[44] The "coercive" mode regulates companies by *explicitly imposing* certain practices, most often through statutory legislation; the "normative" mode regulates companies by *standardizing* particular practices; while the "mimetic" mode regulates companies by *designating* particular practices as necessary for success. Compliance with the three different forms of regulation confers organizational legitimacy on companies and helps to ensure their survival. The most effective regulatory frameworks include all three modes operating congruently, so that companies are directed coercively, normatively, and mimetically to behave in a similar fashion.

Much of the discussion on the regulation of gene synthesis has focused on ensuring that the burgeoning gene-synthesis industry does not bear an unnecessary burden. Yet regulatory law can provide benefits for suppliers if it increases public confidence in the technology. This advantage is particularly relevant in the biotechnology field because private biotech companies ultimately depend on social support for the creation of new markets. Moreover, a regulatory regime that leads companies to act (and to be seen as acting) in a responsible manner may actually be more profitable than a less restrictive regime that generates constant controversy and

[43] Ibid., p. 220.
[44] Filippa Lentzos, "Countering Misuse of Life Sciences through Regulatory Multiplicity," *Science and Public Policy*, vol. 35, no. 1 (Feb 2008), pp. 55-64; Filippa Corneliussen, "The Legal Trichotomy: Biotech Company Perspectives on Institutional Elements Constraining Research Activities," *Zeitschrift für Rechtssoziologie*, vol. 22, no. 2 (2001), pp. 1-18.

hostile campaigning. Indeed, Michael Porter has argued that strict environmental regulations, instead of shifting external costs back onto companies and burdening them relative to competitors in countries with less strict regulations, can result in a "win-win" situation in which the companies' private costs are reduced, along with the external costs they impose on the environment.[45] "Strict environmental regulations do not inevitably hinder competitive advantage against foreign rivals, indeed, they often enhance it," Porter concludes. Thus, the synthetic DNA industry could potentially benefit from a regulatory regime that carefully balances stringency with legitimacy, although this solution would require companies to accept a certain regulatory burden.

Arguing for statutory legislation is not meant to imply that voluntary measures have no merit. Self-governance may encourage companies to act in a certain way if the guidance is followed by others. The reward for adopting screening practices, for example, is inclusion in the club of companies that are seen as reputable and "doing the right thing," sending a positive signal to customers and investors. In this way, successful companies help to regulate others by designating screening practices as necessary for economic success. If, however, the guidelines are not generally adhered to, then self-governance may discourage other companies from implementing them, especially if there are costs involved—as there are with the gene-synthesis guidelines. This is a situation where the force of law can be particularly persuasive. Indeed, the gene-synthesis industry has recognized the problem of non-compliance with voluntary guidelines, as a workshop report from the IASB indicates: "Ultimately, the definition of standards and the enforcement of compliance with these is a government task."[46]

Statutory legislation is also important for managing rogue companies. Commenting on the IASB's early efforts to develop a code of conduct, a *Nature* editorial argued that they were "laudable first steps" but that synthetic DNA providers "still need independent oversight" in the form of statutory legislation. "There have been, and will probably continue to be, companies that are not interested in cooperating with any industry group, and that are happy to operate in the unregulated grey area. The ultimate hope is that customers will put economic pressure on those non-compliers to fall in line, or else lose all but the most disreputable business. But that is just a

[45] Michael E. Porter and Claas van der Linde, "Green and Competitive: Ending the Stalemate," *Harvard Business Review*, (September-October 1995), pp. 120-34. See also H. Landis Gabel and Bernard Sinclair-Desgagné, "The Firm, its Procedures, and Win-Win Environmental Regulations," INSEAD Working Paper N 99/05/EPS (1999).
[46] IASB, report on the workshop "Technical Solutions for Biosecurity in Synthetic Biology," p. 14.

hope. As the recent meltdowns on Wall Street have indicated, industry self-policing can sometimes fail dramatically. When bad business practices can have grave effects for the public, regulators should be firm and proactive."[47]

Another approach is professionalization, which lies between self-governance and statutory measures. In most jurisdictions, all professional practitioners are licensed and belong to an association, established by law, which sets the standards of practice for its members in order to align them with the public good. The officers of the association are elected by the members and are expected to be advocates for the profession. This combination of a legislated mandate and collegial self-governance provides professional accountability for the profession as a whole and for its individual practitioners. Weir and Selgelid argue that the professionalization of synthetic biology would establish educational standards for its members and define normative standards of practice, with the aim of ensuring competence and preventing misconduct. By combining self-governance and legally-authorized governance, this approach avoids the polarization that has characterized much of the debate over the regulation of synthetic biology.[48]

Conclusions

DNA synthesis is a powerful enabling technology that has many beneficial applications but also entails a significant risk of misuse. An optimal strategy to limit this risk would entail applying the three modes of governance (coercive, normative, and mimetic) to DNA synthesis so that: (1) national governments regulate companies by imposing a baseline of minimum security measures that all synthetic DNA providers must adopt; (2) the synthetic DNA community reinforces the statutory legislation through a professional code of conduct that regulates gene-synthesis companies across borders and encourages universal adherence, despite different national assessments of the risk of misuse; and (3) role-model companies, such as synthetic DNA providers that have adopted the IASB Code of Conduct, regulate other companies by designating screening practices as necessary for economic success—much as ISO accreditation and other non-statutory regimes have become accepted as requirements to operate in other fields.

[47] "Pathways to Security" [editorial], *Nature*, vol. 455 (September 25, 2008), p.432.
[48] Lorna Weir and Michael J. Selgelid, "Professionalization as a Governance Strategy for Synthetic Biology," *Systems and Synthetic Biology*, vol. 3 (2009), pp. 91-97.

Chapter 11: Synthetic Biology with Standardized Parts

Alexander Kelle

Nuclear physics was the leading science of the twentieth century, but biology is poised to dominate the twenty-first, with synthetic biology perhaps its most ambitious manifestation. This emerging discipline involves "the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature."[1] Fields where synthetic biology could have a major impact include biomedicine, chemical industry, environment and energy, and biomaterials. If synthetic biology delivers on the promises of its visionaries, it will turn biology into a mechanistic science, bringing about a paradigm shift comparable to how the invention of the periodic table transformed chemistry.

Although synthetic biology promises beneficial applications in several fields, this new technoscience carries with it a risk of misuse. Accordingly, the governance measures developed recently for synthetic genomics (see Chapter 10) should be broadened to cover all aspects of synthetic biology.

Overview of the Technology

Not surprisingly for a discipline still in its formative stages, synthetic biology has several definitions.[2] This chapter focuses on parts-based synthetic biology, or "the design and construction of new biological parts, devices, and systems, and the re-design of existing, natural biological systems for useful purposes."[3] The goal of this emerging discipline is to build functional genetic circuits out of a set of standardized biological parts, including genetic control elements, all of which are made of pieces of synthetic DNA that have been well characterized in order to minimize unintended interactions.

Parts-based synthetic biology aims to be a transformative technology. Those at the forefront of the effort to develop standardized biological parts conceive of it as providing a

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[1] New and Emerging Science and Technology (NEST), *Synthetic Biology: Applying Engineering to Biology*, Report of a NEST High-Level Expert Group (Brussels: European Commission, 2005), p. 5.

[2] Markus Schmidt, "Do I understand what I can create?" in Markus Schmidt, Alexander Kelle, Agomoni Ganguli-Mitra, and Huib de Vriend, eds., *Synthetic Biology: The Technoscience and Its Societal Consequences* (Dordrecht, Netherlands: Springer, 2009), pp. 81-100. Other typologies have been proposed: Maureen O'Malley, Alexander Powell, Jonathan F. Davies, and Jane Calvert, "Knowledge-making distinctions in synthetic biology," in *BioEssays*, vol. 30, no. 1 (2007), pp. 57-65, and Anna Deplazes, "Piecing together a puzzle: An exposition of synthetic biology," *EMBO Reports*, vol. 10, no. 5 (2009), pp. 428-432.

[3] See http://syntheticbiology.org/Who_we_are.html (accessed on November 6, 2008).

toolbox that will enable users to design and build a multitude of biological systems, much as transistors, capacitors, and other standard electronic components can be assembled into an enormous variety of functional devices. Standardized biological parts that have undergone quality controls will be used to build standard modules, which can then be assembled into novel biological systems. A report by the Royal Academy of Engineering describes the design cycle for synthetic biology.[4] The cycle starts with the specification of biological parts, followed by a design step that involves detailed computer modeling. During the implementation stage, a strand of synthetic DNA corresponding to the genetic circuit is assembled and inserted into bacterial or yeast cells. In the final validation stage, the functionality of the circuit is verified.

A key goal of synthetic biology is to create functional building blocks that have a standard interface and can be assembled like Lego blocks, without needing to understand their internal structure. In other words, the parts will be "black-boxed," meaning that their DNA sequence can be safely ignored by the user, much as one does not have to understand how a microprocessor works to use word-processing software on a personal computer. The creation of standardized genetic parts that can be manipulated at a higher level of abstraction will contribute to the process of de-skilling and ultimately make synthetic biology methods more accessible to non-biologists and amateurs.[5]

History of the Technology

The effort to convert biology into a predictive science by incorporating elements of the engineering design cycle was initially termed "open-source biology" or "intentional biology." Rob Carlson, then a research fellow at the Molecular Sciences Institute of the University of California at Berkeley, developed a vision of open-source biological manufacturing driving future industry. Carlson stated in 2001, "When we can successfully predict the behavior of designed biological systems, then an intentional biology will exist. With an explicit engineering component, intentional biology is the opposite of the current, very nearly random applications of biology as technology." [6]

The Massachusetts Institute of Technology (MIT) was an early hub of synthetic biology. During the 1990s, electrical engineering professor Thomas Knight set up a biology

[4] Royal Academy of Engineering, *Synthetic Biology: Scope, Applications and Implications* (London, 2009), pp. 18-21.
[5] Jeanne Whalen, "In Attics and Closets, 'Biohackers' Discover Their Inner Frankenstein," *Wall Street Journal*, May 12, 1009, online at: http://online.wsj.com/article/SB124207326903607931.html.
[6] Rob Carlson, "Open Source Biology and Its Impact on Industry," *IEEE Spectrum*, May 2001, pp. 15-17.

laboratory within the MIT Laboratory for Computer Science and started to develop standard genetic components called "BioBricks" with funding from the U.S. Defense Advanced Research Projects Agency (DARPA) and the Office of Naval Research.[7] Since then, the BioBricks have been incorporated into a Registry of Standard Biological Parts, an open-source database that is available to all *bona fide* researchers in the field.[8]

The main vehicle for expanding the number of publicly available biological parts is the International Genetically Engineered Machine (iGEM) competition, which is organized annually at MIT by the BioBricks Foundation.[9] The goals of iGEM are "to enable the systematic engineering of biology, to promote the open and transparent development of tools for engineering biology, and to help construct a society that can productively apply biological technology." [10] The annual competition also serves as an indicator of the international diffusion of parts-based synthetic biology.[11] Starting in 2003 with a small group of teams from the United States, iGEM has since become a global event. In 2005, when foreign students began to participate, 13 undergraduate student teams from four countries (Canada, Switzerland, UK, and U.S.) participated.[12] Four years later, in 2009, there were 112 student teams from nearly 20 countries around the globe.[13]

The iGEM teams not only utilize existing biological parts but design and build new ones, which are then incorporated into the Registry. The 2006 competition introduced more than 700 new parts, the 2007 competition about 800 parts, the 2008 competition nearly 1,400 parts, and the 2009 competition 1,348 parts.[14] In this way, the number of publicly available biological parts has grown to more than 3,200. Over the next several years, the number of parts is expected to continue growing exponentially. In February 2010, scientists at Stanford University and the University of California at Berkeley received a $1.4 million grant from the

[7] Thomas F. Knight, *DARPA BioComp Plasmid Distribution 1.00 of Standard Biobrick Components*, 2002, available at http://dspace.mit.edu/handle/1721.1/21167
[8] Registry of Standard Biological Parts, http://partsregistry.org/wiki/index.php/Main_Page
[9] BioBricks Foundation, http://biobricks.org/
[10] http://parts2.mit.edu/wiki/index.php/About_iGEM;
[11] International Genetically Engineered Machines (iGEM) competition, http://2009.igem.org/About
[12] The only non-U.S. teams were from ETH Zurich (Switzerland) and the University of Toronto (Canada). For a complete list see http://parts.mit.edu/wiki/index.php/Igem_2005.
[13] Countries represented in 2009 were Belgium, Canada, China (People's Republic of), Colombia, Denmark, France, Germany, India, Italy, Japan, Korea, Mexico, Netherlands, Poland, Spain, Slovenia, Sweden, Taiwan, United Kingdom, and United States. See the list of teams at http://ung.igem.org/Team_List?year=2009
[14] Previous iGEM competitions, http://2010.igem.org/Previous_iGEM_Competitions

National Science Foundation to establish a laboratory called BIOFAB, which will design, fabricate, and test some 3,000 standardized genetic parts, including DNA control elements.[15]

Utility of the Technology

Optimistic assessments of synthetic biology, such as a 2005 report to the European Commission by the expert group on New and Emerging Science and Technology (NEST), predict that it will "drive industry, research, education and employment in the life sciences in a way that might rival the computer industry's development during the 1970s to the 1990s."[16] The NEST report identified six areas that could benefit from synthetic biology techniques: biomedicine, synthesis of biopharmaceuticals, sustainable chemical industry, environment and energy, production of smart materials and biomaterials, and measures to counter bioterrorism.[17]

The most frequently cited example of a high-value application of synthetic biology is the work by Jay Keasling and his colleagues at the University of California at Berkeley to insert an engineered metabolic pathway into yeast to produce artemisinic acid, the immediate precursor of artimisinin, a key anti-malaria drug.[18] The goal of this project is to reduce the production cost for artimisinin and thereby increase its availability to people in developing countries.[19] Synthetic biologists have also made progress utilizing bioengineered microbes to produce biofuels.[20] Although the main focus of synthetic biology is on the design and engineering of artificial microorganisms that can perform useful tasks, some biologists emphasize the field's contribution to "achieving a better understanding of life processes."[21]

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[15] Robert Sanders, "NSF grant to launch world's first open-source genetic parts production facility," *Genetic Engineering & Biotechnology News*, January 20, 2010, http://www.genengnews.com/news/bnitem.aspx?name=73430839.

[16] New and Emerging Science and Technology (NEST), *Synthetic Biology: Applying Engineering to Biology* (Brussels: European Commission, 2005), p. 13.

[17] Ibid., pp.13-17.

[18] Jay Keasling et al., "Production of the antimalarial drug precursor artemisinic acid in engineered yeast," *Nature*, vol. 440 (April 13, 2006), pp. 940-943.

[19] Michelle C.Y. Chang and Jay D. Keasling, "Production of isopronoid pharmaceuticals by engineered microbes," *Nature Chemical Biology*, November 2006, doi:10.1038/nchembio836.

[20] Shotsa Azumi, Taizo Hanai, and James C. Liao, "Non-fermentative pathways for synthesis of branched-chain higher alcohols as biofuels," *Nature*, vol. 451 (January 3, 2008), pp. 86-90; Jay D. Keasling and Howard Chou, "Metabolic engineering delivers next-generation biofuels," *Nature Biotechnology*, vol. 26, no. 3 (2008), pp. 298-299.

[21] Towards a European Strategy for Synthetic Biology (TESSY), *Synthetic Biology in Europe*, available at http://www.tessy-europe.eu/index.html.

Such improved understanding can better the human condition by leading to the development of new diagnostic tools, therapeutic drugs, and other beneficial applications.

Potential for Misuse

The ability to understand, modify, and ultimately create new life forms represents a scientific paradigm shift with a substantial potential for misuse. Once the standardization of genetic parts and modules has progressed to the point that they function reliably and can be inserted into a simplified bacterial genome for application, the technology will cross a threshold of dual-use potential. Predicting when this threshold will occur depends on the speed at which the field progresses. In principle, malicious actors could exploit synthetic biology to increase the efficiency, stability, or usability of standard biological warfare agents or to create new ones.

To date, however, the primary concern with synthetic biology has been the synthesis of known pathogenic viruses, rather than the use of standardized parts to create entirely novel pathogens. Since parts-based synthetic biology is still a cutting-edge technology, bioterrorists would have to overcome formidable technical challenges to exploit it for harmful purposes.[22] Nevertheless, the increasing speed, accuracy, and accessibility of gene-synthesis technology, and its explicit de-skilling agenda, are likely to lower these barriers over time.[23]

Ease of Misuse (Explicit and Tacit Knowledge)

Because synthetic biology currently requires considerable explicit and tacit knowledge, the greatest risk of misuse probably resides in state-level offensive biological warfare programs. As hands-on experience with synthetic biology continues to spread internationally, however, the nature of the risk will change. In addition to the annual iGEM competition, which has helped to popularize synthetic biology, de-skilling efforts by leading synthetic biologists include the dissemination of do-it-yourself synthetic biology kits and "how-to" protocols. As a result of these efforts, the field of synthetic biology will gradually become accessible to a growing number of people, potentially enabling non-state actors to employ genetic parts and modules for nefarious purposes.

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[22] See Gerald L. Epstein, "The challenges of developing synthetic pathogens," *Bulletin of the Atomic Scientists* website, May 19, 2008.

[23] Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, *Synthetic Genomics: Options for Governance*, October 2007, p. 12, available at: http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf.

Accessibility of the Technology

Access to the Registry of Standard Biological Parts is currently limited to recognized research laboratories, regardless of geographical location, although this rule may change in the future. The registry is "open-source" and no efforts have been made to date to patent the genetic components or to restrict access on the basis of nationality or other criteria. Some laboratory supply companies have also begun to sell synthetic biology reagent kits and "how-to" manuals to interested biologists, both professional and amateur.[24] Examples include the "BioBrick Assembly Kit" and the "BioBrick Assembly Manual" distributed jointly by Ginko BioWorks and New England Biolabs.[25]

Imminence and Magnitude of Risk

Given the early stage of development of parts-based synthetic biology, the risk that a terrorist or criminal group could order standard biological parts and construct an artificial pathogen for harmful purposes must be assessed as extremely long-term. Should the technology proliferate widely, however, the potential consequences of deliberate misuse could be considerable.

Awareness of Dual-Use Potential

In 2006, the National Research Council, a policy analysis unit of the U.S. National Academies, tasked an expert committee chaired by microbiologists Stanley Lemon and David Relman to analyze the security implications of the revolution in the life sciences.[26] The Lemon-Relman committee concluded that the *de novo* synthesis of existing pathogens posed a greater near-term threat than the creation of artificial organisms through the parts-based approach.[27] Similarly, the National Science Advisory Board on Bioscurity (NSABB) and its Synthetic Biology Working Group have focused primarily on the use of DNA synthesis technology to recreate "select agents," defined as biological agents and toxins that can pose a

[24] See Aaron Rowe, "Cloning Kits: More Fun Than a Chemistry Set?" *Wired*, May 2008, available at http://www.wired.com/wiredscience/2008/05/cloning-kits-mo/; See also the presentations on DIYbio by Natalie Kuldell and Reshma Shetty at http://mitworld.mit.edu/video/646

[25] Ginkgo BioWorks, "BioBrick Assembly Kit," http://ginkgobioworks.com/biobrickassemblykit.html.

[26] National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, D.C.: National Academies Press, 2006) www.nap.edu/catalog.php?record_id=11567

[27] Ibid., p.109.

severe threat to public, animal, or plant health, or to animal or plant products.[28] Thus, the primary focus of threat assessment to date has been on the synthesis of select-agent viruses rather than the construction of functional genetic modules from standardized biological parts.

Characteristics of the Technology Relevant to Governance

Embodiment. Parts-based synthetic biology relies both on automated DNA synthesizers (hardware) and on powerful bioinformatics tools (software) that allow the modeling of desired biological functions and the design of genetic circuits. Even so, the dichotomy between hardware and intangible information is not as clear as it is for other emerging dual-use technologies. After all, the basic building blocks of the parts, devices, and systems created by synthetic biology are pieces of DNA, which is sometimes described as computer code for programming living matter.

Maturity. Parts-based synthetic biology is still at an early stage of research and development, although it is emerging from the proof-of-principle phase.

Convergence. Synthetic biology is a convergent technology that draws primarily on two enabling technologies: DNA synthesis, and bioinformatics for the design and redesign of genetic circuits.

Rate of advance. At first glance, the field's rate of progress appears dramatic, with an exponential increase in the number of standardized parts available in the MIT Registry. A few caveats are in order, however. Practitioners have faced several difficulties in "taming the complexity of living systems," such as unintended genetic interactions.[29] According to the Registry's director, Randy Rettberg, "[a]bout 1,500 registry parts have been confirmed as working by someone other than the person who deposited them."[30] More skeptical observers, however, claim that only 5 to 10 percent of the standardized parts function as predicted.[31] According to this estimate, at most 500 of the roughly 5,000 parts in the Registry may actually be usable, reducing the number of possible devices that can be built from them.

Another progress-limiting factor is the issue of standardization, namely defining specific technical parameters for the standardized parts. This issue has been the focus of three workshops held by the BioBricks Foundation, which have included discussions from both the

[28] National Science Advisory Board for Biosecurity (NSABB), *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents* (Washington, D.C.: National Institutes of Health, 2006). http://oba.od.nih.gov/biosecurity/pdf/Final_NSABB_Report_on_Synthetic_Genomics.pdf

[29] Roberta Kwok, "Five Hard Truths for Synthetic Biology," *Nature*, Vol. 463 (January 21, 2010), pp. 288-290, quote on p. 288.

[30] Ibid.

[31] Victor de Lorenzo, "Not really new," interview in *Lab Times*, March 2009, pp.21-23.

technical and the legal standpoints.[32] To date, however, the field has not yet arrived at a generally accepted standard. As Stanford University professor Drew Endy and his colleagues point out, "the design and construction of engineered biological systems remains an ad hoc process for which costs, times to completion, and probabilities of success are difficult to estimate accurately."[33] Adam Arkin, a professor of bioengineering at Berkeley, also points out that one of the issues impeding the formulation of unambiguous technical standards for biological parts is the fact that "unlike many other engineering disciplines, biology does not yet possess a theory of what the minimal information about a biological part should be."[34] Until practitioners of synthetic biology can formulate uniform standards for biological parts and implement them extensively, however, it will not be possible to elevate activities such as the biosynthesis of artemisinin from traditional metabolic engineering into the realm of parts-based synthetic biology.[35]

International diffusion. In parallel with the rapid growth of the iGEM movement, the international Synthetic Biology Conferences held since 2004 have attracted a growing number of participants from a variety of countries. The fact that the second and third conferences were held in Zurich and Hong Kong, respectively, is an indicator of the rapid global diffusion of the discipline. A more recent factor in the spread of synthetic biology is the so-called "do-it-yourself" (DIY) movement. One of the more prominent groups in this area, *DIYbio*, describes itself as an "organization that aims to help make biology a worthwhile pursuit for citizen scientists, amateur biologists, and DIY biological engineers who value openness and safety."[36] Noteworthy from a dual-use perspective is the absence of "security" in the group's list of objectives. Several *DIYbio* groups have emerged, most of them in the United States, but a few in Europe and Asia.[37]

Susceptibility to Governance

The discussion above suggests that certain areas of synthetic biology are susceptible to governance measures. Most proposals have focused on the bottleneck of gene-length DNA synthesis, an enabling technology that is currently the most "mature" part of the supply chain

[32] Open Wetware, http://bbf.openwetware.org/
[33] Barry Canton, Anna Labno, and Drew Endy, "Refinement and standardization of synthetic biological parts and devices," *Nature Biotechnology*, vol. 26, no. 7 (July 2008), pp. 787-793, quote on p. 787.
[34] Adam Arkin, "Setting the Standard in Synthetic Biology," *Nature Biotechnology*, vol. 26, no. 7 (July 2008), pp. 771-774, quote on p. 772.
[35] Quoted in Kwok, "Five Hard Truths for Synthetic Biology," p.289.
[36] DIYbio website, http://diybio.org/about/.
[37] See map at http://diybio.org.

for the synthesis of biological parts. Although some proposals place a greater emphasis on government involvement than others, all try to minimize the negative impact of top-down regulation on scientific progress and technological development. The notion of making the Registry of Standard Biological Parts the object of governance measures has yet to receive much attention. Instead, policy discussion has focused on whether or not to keep the Registry "open-source" or to allow large biotechnology companies to claim intellectual property rights over certain biological parts in order to exploit them for commercial purposes.[38] If the open-source movement prevails, it could unintentionally increase the risk of misuse by making synthetic biology capabilities more widely available.

Past and Current Approaches to Governance

From the formative days of synthetic biology, the question of governance mechanisms and their relative utility has been a feature of the unfolding discourse about the discipline. At least in part, the early engagement of the scientific community with the potential risks of synthetic biology can be traced back to earlier debates about the ethical, legal, and social implications (ESLI) of genetic engineering. One of the first proposals to address the dual-use implications of synthetic biology was made by George Church of Harvard Medical School in 2004. He proposed a system for licensing DNA synthesizers and reagents, as well as screening DNA sequence orders sent to commercial suppliers to determine the extent of homology with Select Agent genes.[39]

Although Church's proposals foresaw some form of government involvement or oversight in both areas, subsequent policy analysts have placed greater emphasis on self-governance by the scientific community. The Second International Conference on Synthetic Biology, held at the University of California at Berkeley in May 2006, devoted a full day to the discussion of societal issues surrounding synthetic biology, including "biosecurity and risk."[40] The discussion during this session was informed by preparatory work by the Berkeley SynBio Policy Group, which submitted a white paper titled "Community-Based Options for

[38] Kenneth A. Oye and Rachel Wellhausen, "The Intellectual Commons and Property in Synthetic Biology," in Schmidt, Kelle, Ganguli Mitra, and de Vriend, eds., *Synthetic Biology*, pp. 121-140.
[39] George Church, "Synthetic Biohazard Nonproliferation Proposal," available online at: http://arep.med.harvard.edu/SBP/Church_Biohazard04c.htm
[40] Synthetic Biology 2.0 conference, http://syntheticbiology.org/SB2.0/Biosecurity_and_Biosafety.html

Improving Safety and Security in Synthetic Biology."[41] Although the white paper was intended to serve as the basis of a code of conduct for the synthetic-biology community, more than three dozen civil-society groups publicly criticized the paper because they had been excluded from its preparation and believed that the proposed measures were inadequate. Synthetic biology practitioners attending the meeting also refused to adopt the proposed code of conduct.[42] Instead, the final conference declaration called for "ongoing and future discussions with all stakeholders for the purpose of developing and analyzing governance options . . . such that the development and application of biological technology remains overwhelmingly constructive."[43]

A subsequent analysis of governance options for synthetic biology, conducted jointly by MIT, the J. Craig Venter Institute, and the Center for Strategic and International Studies (CSIS), followed the trend of focusing on DNA synthesis technology, with a primary emphasis on commercial suppliers of gene-length DNA sequences. This report, released in 2007, concluded that a combination of screening of DNA synthesis orders and the certification of such orders by a laboratory biosafety officer would provide the greatest benefit in preventing the misuse of synthetic DNA.[44] The ideas in the MIT-Venter-CSIS report were subsequently taken up in proposals by two industry associations in the field of synthetic biology and the U.S. government. (For details, see Chapter 10.)

Options for Future Governance

A complete or even partial ban on parts-based synthetic biology is unlikely to find much political support. Unless an accident or a deliberate attack involving an artificial microorganism were to result in serious harm or economic losses, the beneficial applications of synthetic biology will generally be perceived as outweighing the downside risks. Nevertheless, exclusive reliance on self-governance by industry associations and professional societies is unlikely to provide sufficient public reassurance that synthetic biology will not be misused for nefarious purposes.

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[41] Stephen M. Maurer, Keith V. Lucas, and Starr Terrell, *From Understanding to Action: Community-Based Options for Improving Safety and Security in Synthetic Biology* (Berkeley, CA: Goldman School of Public Policy, University of California), Draft 1.1, April 15, 2006, http://gspp.berkeley.edu/iths/UC White Paper.pdf.

[42] "Global Coalition Sounds the Alarm on Synthetic Biology", May 19, 2006, http://www.etcgroup.org/en/node/8

[43] Revised public draft of the SB2.0 declaration, https://dspace.mit.edu/handle/1721.1/18185.

[44] Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, Robert M. Friedman, *Synthetic Genomics. Options for Governance*, October 2007, http://www.csis.org/media/csis/pubs/071017_synthetic_genomics_options.pdf

Governance measures that focus primarily on commercial providers of synthetic DNA are necessary but not sufficient. Instead, what is required is a balanced mix of top-down and bottom-up governance measures. I have termed this approach the "5P" strategy because it includes five policy intervention points: the principal investigator, the project, the premises, the provider, and the purchaser. Governance measures can be applied at each of these intervention points, including awareness-raising, education and training, guidelines, codes of conduct, regulations, national laws, and international agreements.[45]

For bottom-up measures to be effective, however, it will first be necessary to raise the awareness of dual-use issues among practitioners of synthetic biology. In 2007, interviews with 20 leading European synthetic biologists revealed that their awareness of key elements of the biosecurity discourse (such as the Lemon-Relman report) was extremely low.[46] Although several conferences on synthetic biology have provided opportunities to discuss dual-use issues, they have not added up to a systematic effort at raising the awareness of practitioners. Awareness-raising must also include the education of future generations of synthetic biologists about the dual-use implications of the field they are about to enter. As was clearly demonstrated by a survey of 142 courses at 57 universities in 29 countries, only a small minority of life-science courses include a biosecurity component, and in all cases this component is optional and not part of the core curriculum.[47]

It is important to distinguish, however, between academic practitioners of synthetic biology and industrial scientists who work for DNA synthesis companies. The latter are generally more aware of the dual-use potential of their work, as evidenced by the biosecurity measures that the industry has implemented on a voluntary basis. Indeed, DNA synthesis companies have taken the lead in formulating governance proposals of a technical nature. According to an industry official, oversight and regulation offer two advantages: they "reassure the public that biosafety and biosecurity concerns are addressed" and "provide legal security to the industry by defining clear compliance rules."[48]

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[45] Alexander Kelle, "Ensuring the security of synthetic biology – towards a 5P governance strategy," *Systems and Synthetic Biology*, vol.3, nos.1-4, December 2009, pp. 85-90.

[46] Alexander Kelle, *Synthetic Biology and Biosecurity Awareness in Europe* (Vienna, Austria: Organization for International Dialogue and Conflict Management, 2007), http://www.synbiosafe.eu/uploads///pdf/Synbiosafe-Biosecurity_awareness_in_Europe_Kelle.pdf

[47] Giulio Manchini and James Revill, *Fostering the Biosecurity Norm: Biosecurity Education for the Next Generation of Life Scientists*, University of Bradford (UK), Report No.1, November 2008, available at: http://www.brad.ac.uk/acad/sbtwc/dube/publications/index.html

[48] SYNBIOSAFE, *Compilation of all SYNBIOSAFE e-conference contributions* (Vienna: Organization for International Dialogue and Conflict Management, 2008), http://www.synbiosafe.eu/uploads/pdf/Synbiosafe_e-conference_all_contributions.pdf.

Comparable governance measures will have to be formulated for the wider circle of users of standardized biological parts. Such rules could take the form of end-user certificates that researchers would have to submit before being granted access to the Registry of Standard Biological Parts. There might also be a requirement for the formal registration of laboratories or companies involved in assembling biological parts into devices or more complex biological systems. Although such a step would be motivated primarily by public health and biosafety concerns, it would also help to prevent deliberate misuse. Existing domestic legislation and regulations in the area of genetic engineering should also be reviewed to assess their applicability to biological parts and modules.[49]

At the international level, countries participating in the Australia Group have agreed to harmonize their national export controls on genetic material from listed pathogens.[50] It would be desirable to expand this measure to cover standardized biological parts that could be used for harmful purposes. Although the Biological Weapons Convention (BWC) bans the acquisition of genetically modified as well as natural pathogens and toxins for hostile purposes, the treaty does not prohibit research but only development, production, other acquisition, and stockpiling. Creating a comprehensive governance mechanism for parts-based synthetic biology would help to fill this gap in the biological nonproliferation regime. Finally, to achieve the international harmonization of national governance mechanisms, states should consider negotiating a Framework Convention to Prevent the Misuse of Synthetic Biology, which could be easily updated to keep pace with rapid advances in technology.

Conclusions

Synthetic biology is one of the most dynamic new subfields of biotechnology, with the potential to engineer biological parts, devices, and systems for socially useful purposes. By applying the tools of engineering and information technology to biology, it may be possible to realize a wide range of useful applications. Some of the potential benefits could be transformative, such as the development of low-cost drugs or the production of fine chemicals and biofuels by engineered bacteria. At the same time, however, synthetic biology entails significant risks of deliberate or accidental harm and can therefore be described as a prototypical dual-use technoscience.

[49] Michael Rodemeyer, *New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology* (Washington, D.C.: Woodrow Wilson International Center for Scholars, March 2009), available at http://www.synbioproject.org/library/publications/archive/synbio2/

[50] Australia Group homepage, available at: www.australiagroup.net.

Early attempts to formulate governance mechanisms for synthetic biology have focused almost entirely on a key enabling technology: the commercial synthesis of gene-length DNA sequences. In contrast, a governance system for parts-based synthetic biology is still in its infancy. Developing such a system will require awareness-raising efforts that reach all practitioners of synthetic biology, the integration of dual-use education into the life-science and bioengineering curricula, and the formulation of codes of conduct that go well beyond the screening of DNA synthesis orders. Domestic governance measures could include the mandatory registration of all facilities involved in the assembly of standardized biological parts and the requirement for an end-user certificate to obtain access to them.

Chapter 12: RNA Interference

Matthew Metz

RNA interference (RNAi) is a rapidly expanding field of biomedical research that holds great promise for curing and preventing disease. At the same time, RNAi has possibilities for misuse, including the creation of pathogens with enhanced virulence and the targeted disruption of genes that serve vital functions in the human body. Because RNAi is closely linked to several enabling biotechnologies, it is not well suited to formal regulation, but soft-law and normative approaches to governance may be effective.

Overview of the Technology

RNA interference is an innate cellular mechanism for controlling the expression of genes. To date, the best-characterized function of RNAi is to defend against invading viruses, which reproduce inside the cells of the host by commandeering their biochemical machinery. During the life cycle of a virus, the genetic information encoded by the sequence of nucleotide bases in the viral genome is transcribed into complementary molecules of messenger RNA (mRNA), which are then translated into viral proteins. Many viral genomes consist of RNA rather than DNA, so that during the process of transcription, the genomic RNA template and the corresponding mRNA are temporarily paired with each other to form a double-stranded RNA duplex. In addition, many viruses with RNA genomes replicate their entire genomic sequence by creating a complementary strand of RNA, a process that generates double-stranded RNA when the two molecules are paired.

Although double-stranded RNA is part of the life cycle of many viruses, it is foreign to the infected host cell. The cell responds to this anomalous molecular structure by using the viral RNA duplex as a template to generate “small interfering” RNA (siRNA) molecules roughly 22 nucleotide bases long, which are complementary to

particular mRNA sequences. In this way, siRNA can recognize molecules of viral mRNA with high specificity and mark them for destruction by the cellular machinery.

A wide variety of vertebrates, invertebrates, fungi, and plants employ RNAi as a mechanism for innate cellular immunity against viruses. For this reason, it appears that RNAi evolved as a mechanism to protect against viral infection. Strong evidence also suggests that RNAi helps to regulate the expression of the organism's own genes. Many genomes have been found to contain "micro-RNA" sequences that appear to control gene expression using an RNAi-type mechanism.

History of the Technology

The biotechnology research community's first brush with RNAi came in 1990, when Richard Jorgensen and his colleagues, then at DNA Plant Technology, Inc., published the unexpected results of their attempt to increase the intensity of purple color in petunias. The researchers genetically modified the plants by inserting a gene to increase the levels of a key enzyme involved in the synthesis of the purple pigment. Paradoxically, however, many of the genetically modified petunias actually produced little or no purple pigment in their flowers because the expression of the enzyme was actually reduced. Further study showed that transcription of the inserted gene into mRNA had occurred as expected, but that the mRNA transcripts had been destroyed.[1] Jorgensen and his colleagues termed this phenomenon "co-suppression" because the mRNAs from both the endogenous plant gene and the inserted foreign gene had been eliminated.

In the years immediately following this discovery, researchers found that by genetically engineering animal, plant, and fungal cells to express RNA molecules that were complementary ("antisense") to the mRNA for a gene, the expression of the targeted gene could be suppressed. The mechanism behind antisense suppression was a topic of speculation but remained unsolved for many years. Even so, the phenomenon itself was used frequently to disrupt specific genes in order to gain insights into their

[1] Carolyn Napoli, Christine Lemieux, and Richard Jorgensen, "Introduction of a chimeric chalcone synthase gene into petunia results in reversible co-suppression of homologous gene in trans," *Plant Cell*, vol. 2 (April 1990), pp. 279-89.

function. As researchers explored the uses of antisense RNA, they found that sense RNA could also disrupt the expression of a gene with the same sequence.[2] This finding was essentially a rediscovery of the phenomenon reported by Jorgensen, in which an inserted gene designed to increase the expression of a flower pigment had actually blocked it. Antisense technology also became a platform for pharmaceutical development. In 1998, Isis Pharmaceuticals and Novartis marketed a therapeutic based on antisense RNA to treat AIDS-associated retinitis caused by cytomegalovirus infection. It is now known that antisense RNA stimulates the production of siRNA, albeit less effectively than double-stranded RNA. Thus, the treatment for cytomegalovirus retinitis can be considered the first RNAi-based drug.

Meanwhile, Andrew Fire of Stanford University and Craig Mello of the University of Massachusetts Medical School, working with the roundworm *Caenorhabditis elegans*, found that injecting double-stranded RNA into cells had a far more potent gene-silencing effect than either antisense RNA or sense RNA. The effect was so powerful that only a few molecules of double-stranded RNA were required to silence a gene, and the effect was transmitted to the next generation.[3] This observation led Fire and Mello to conclude that something catalyzed by double-stranded RNA was targeting the mRNA for destruction, introducing the concept of "RNA interference." Subsequent research began to elucidate the cellular systems that recognize double-stranded RNA, use it as a template to generate siRNA molecules, and then destroy the mRNA molecules that pair with the siRNAs. As a result of these advances, Fire and Mello were awarded the Nobel Prize in Physiology or Medicine in 2006.

The breadth of potential applications of RNAi quickly led to its recognition as a revolutionary discovery, and intense interest from the scientific community resulted in a flurry of research activity. In 2004, Acuity Pharmaceuticals (a subsidiary of Opko Health, Inc.) began Phase I clinical trials of an RNAi drug for the treatment of age-related

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[2] Su Guo and Kenneth J. Kemphues, "par-1, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed," *Cell*, vol. 81 (May 19, 1995), pp. 611-620.

[3] Andrew Fire, SiQun Xu, Mary K. Montgomery, et al., "Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*," *Nature*, vol. 391 (February 19, 1998), pp. 306-311.

macular degeneration. As of 2010, about a dozen pharmaceutical biotechnology companies were developing drugs based on RNAi. In addition, several biotechnology companies offer contract services for generating RNAi reagents and for testing and optimizing the design of siRNAs.

Utility of the Technology

The powerful biomedical applications of RNAi stem from its highly specific mechanism of action, which can target precise gene sequences. Because RNAi can detect the difference of a single nucleotide base among the thousands of bases making up a gene, it can not only recognize that the genes of an invading virus are distinct from those of the host but can distinguish between two nearly identical host genes. Recent discoveries have shown how to optimize the specificity of siRNA molecules, stabilize them as they travel through the bloodstream, and deliver the molecules to the appropriate target cells.

Because of RNAi's ability to disrupt gene expression in a targeted manner, it provides a valuable tool for basic research aimed at determining the function of unknown genes. Researchers can use RNAi to silence specific genes and infer their function from the effects of the disruption. For example, if silencing a particular gene leads to albinism, then the gene in question probably plays a role in pigmentation. The broad appeal of RNAi for basic research in molecular genetics is unlikely to diminish any time soon.

The use of RNAi to disrupt the life cycle of viruses is also being tested in various experimental systems as a means of combating viral disease. Progress has been made in designing therapeutics against important human pathogens such as HIV[4], herpes viruses[5], and Ebola virus.[6] Antiviral drugs often have side effects because of the unintended

[4] Shuo Gu, Jianfei Ji, James D. Kim, et al., "Inhibition of Infectious Human Immunodeficiency Virus Type 1 Virions via Lentiviral Vector Encoded Short Antisense RNAs," *Oligonucleotides*, vol. 16 (2006), pp. 287–295.
[5] Yichao Wu, Francisco Navarro, Ashish Lal, et al., "Durable Protection from Herpes Simplex Virus-2 Transmission Following Intravaginal Application of siRNAs Targeting Both a Viral and Host Gene," *Cell Host & Microbe* , vol. 5 (January 22, 2009), pp. 84-94.
[6] Kevin B. Spurgers, Lynn S. Silvestri, Kelly L. Warfield, and Sina Bavari, "Toward RNA Interference-Based Therapy for Filovirus Infections," *Drug Development Research*, vol. 70 (2009), pp. 246–254.

interactions of the drug with the host metabolism. In contrast, the sequence-specific nature of RNAi therapy makes it unlikely to interact with metabolic pathways or other drugs, providing a safer and more widely indicated therapy.

Another promising biomedical application of RNAi is for regulating harmful gene expression in genetic disorders. Genes define the inherited characteristics of all organisms, and different versions of each gene, called "alleles," confer specific traits such as eye color. Each individual of a species carries a unique set of alleles. An RNAi-based drug could block the expression of alleles that are responsible for inherited diseases or that have mutated to cause cancer. In experimental systems, for example, RNAi selectively disrupts the expression of an allele that causes the severe neurological disease amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease).[7] Test-tube experiments have also shown that the use of RNAi to silence cancer-associated genes can inhibit several types of human cancer cells or sensitize them to chemotherapy.[8]

Other promising therapeutic uses of RNAi include controlling inflammatory responses to burns, allergens, and autoimmune disorders. Part of the injury caused by burns—ranging from simple sunburn to severe burns caused by heat or radiation exposure—is inflammation and tissue death resulting from the expression of genes activated by the burn. RNAi might help to moderate this gene expression. In addition, drugs have long been used to suppress the immune system's overreaction to allergens in severely allergic individuals, as well as the inappropriate recognition of the body's own tissues as foreign that occurs in autoimmune diseases such as lupus. RNAi offers a new and potentially more specific method for switching off the genes responsible for allergic and autoimmune disorders.

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[7] Dianne S. Schwarz, Hongliu Ding, Lori Kennington, et al., "Designing siRNA that Distinguish between Genes that Differ by a Single Nucleotide," *PLoS Genetics*, vol. 2 (September 2006), pp. 1307-1318.

[8] Wenzhi Tian and Hsiou-Chi Liou, "RNAi-Mediated c-Rel Silencing Leads to Apoptosis of B Cell Tumor Cells and Suppresses Antigenic Immune Response In Vivo," *PLoS ONE* 4 (April 2009), doi:10.1371/journal.pone.0005028; F.X. Chen, Y.R. Qian, Y.H. Duan, et al., "Down-regulation of 67LR reduces the migratory activity of human glioma cells in vitro," *Brain Research Bulletin*, vol. 79 (August 14, 2009), pp. 402-408; Kamal Yavari, Mohammad Taghikhani, Mohammad G. Maragheh, et al., "Downregulation of IGF-IR expression by RNAi inhibits proliferation and enhances chemosensitization of human colon cancer cells," *International Journal of Colorectal Disease*, vol. 25 (August 10, 2009), pp. 9-16.

Because RNAi can be directed specifically against any genetic sequence, its ability to disrupt gene expression in a targeted manner may lead to numerous sought-after applications, such as altering metabolism and cosmetic treatments. Genes associated with obesity, for example, are potential targets for RNAi-based weight-loss therapies, and RNAi might be used to block genes that restrict muscle mass in order to enhance performance in competitive sports. It might even be possible to use RNAi to alter the expression of genes that control hair, eye, and skin color, or play a role in aging. Despite ethical concerns about such applications, strong consumer interest is likely to drive research in these areas.

Using RNAi for therapeutic purposes will involve further innovation because each application is unique and requires its own product development cycle. Current hurdles for the development of RNAi drugs include delivering the double-stranded RNA templates into cells and ensuring that the resulting siRNAs persist long enough to disrupt gene expression. Gene-therapy techniques involving a genetically engineered viral "vector" may be used to deliver siRNA or double-stranded RNA templates into a patient's cells. The alternative approach is to administer bulk quantities of template RNA or siRNA in a formulation that enables the molecules to survive the trip through the patient's bloodstream and reach the target cells. Because this approach does not confer a permanent genetic source of RNAi, however, sustained administration will be required to provide ongoing benefit.

Potential for Misuse

In addition to its many promising medical applications, the ability of RNAi to control gene expression gives it a serious potential for misuse. Just as the mechanism can block the expression of disease-related genes from inherited disorders or invading viral pathogens, it could be manipulated to disrupt healthy metabolism and immunity. In particular, RNAi could be used to cause harm by targeting two different processes. (See Table 12-1.)

Table 12-1: Potential misuses of RNA interference

Manifestation	Target	Application Method		Effect
		Genetic Engineering	Formulation	
RNAi used to disrupt host metabolism or immunity	Metabolism	Toxin-like gene engineered into a virus *(more likely)*	Toxic formulation *(less likely)*	Toxicity
	Immunity	Virulence gene engineered into a virus *(more likely)*	Addition to a pathogen weapon formulation *(less likely)*	Immune suppression
Disruption of host RNAi mechanisms	Defenses against viruses	Virulence gene engineered into a virus *(more likely)*	Addition to a pathogen weapon formulation *(theoretical)*	Immune suppression

The first approach to misuse would involve genetically engineering a viral pathogen to express interfering RNA that disrupts the host's metabolism, with effects similar to those of a toxin. RNAi-inducing formulations against herpes virus have protected laboratory animals from infection,[9] but targeting the RNAi genes of the host could have the opposite effect by increasing susceptibility to disease. A formulation of interfering RNAs or blockers of host RNAi might either be delivered alone or in combination with a weaponized pathogen to enhance its pathogenicity. Nevertheless, such formulations would not be sufficiently attractive weapons to justify the effort needed to develop them. Not only would they have effects similar to toxins and immune suppressants, which are far easier to produce, but they would not spread from person to person along with the pathogen, limiting their effects to the population that was directly exposed. The other means of delivery would be to use genetic engineering methods to insert RNAi into a viral pathogen designed for use as a weapon. In various experimental systems, RNAi generated by a genetically engineered virus has disrupted the function of host genes.[10] Engineering RNAi into a contagious virus that could spread through a

[9] Yichao Wu, Francisco Navarro, Ashish Lal, et al., "Durable Protection from Herpes Simplex Virus-2 Transmission Following Intravaginal Application of siRNAs Targeting both a Viral and Host Gene," *Cell Host & Microbe*, vol. 5 (January 22, 2009), pp. 84-94.

[10] A. Georgiadis, M. Tschernutter, J. W. B. Bainbridge, et al., "AAV-mediated knockdown of Peripherin-2 in vivo using miRNA-based hairpins," *Gene Therapy*, advance online publication (December 10, 2009) doi: 10.1038/gt.2009.162; Yun Dai, Liang Qiao, Kwok Wah Chan, et al., "Adenovirus-mediated down-

population might have the potential to cause mass casualties, possibly from only a small amount of weaponized material.

The second form of misuse would be to block the expression of host RNAi genes that normally fight infection, thereby suppressing immunity. A wide variety of viruses have genes that interfere with RNAi, enhancing their own infectivity and virulence by disrupting the innate cellular defenses of the host.[11] Experiments have shown that the deletion of these RNAi-disrupting genes reduces viral virulence.[12] Through genetic engineering, RNAi-disrupting genes might be inserted into viral pathogens to increase their virulence in humans, as has already been demonstrated in laboratory animals.[13] Another possibility would be the development of new drugs that inhibit the RNAi mechanisms of the host. Although the development of such drugs remains speculative, they would contribute to the spectrum of dual-use RNAi technologies.

Ethnic weapons. If interfering RNAs were developed as a biological weapon, it would be possible to target them precisely—a fact with troubling implications for the possible misuse of this technology. The siRNA molecules that mediate RNA interference do so by matching up with the gene (allele) that has been targeted for silencing: a small stretch of 22 RNA bases defines the target.[14] Numerous experiments have shown that the

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regulation of X-linked inhibitor of apoptosis protein inhibits colon cancer," *Molecular Cancer Therapeutics*, vol. 8 (November 2009), pp. 2762-2770; Lawrence C.S. Tam, Anna-Sophia Kiang, Avril Kennan, et al., "Therapeutic benefit derived from RNAi-mediated ablation of IMPDH1 transcripts in a murine model of autosomal dominant retinitis pigmentosa (RP10)," *Human Molecular Genetics*, vol. 17 (July 15, 2008), pp. 2084-2100.

[11] Hans Hemmes, Lucas Kaaij, Dick Lohuis, et al., "Binding of small interfering RNA molecules is crucial for RNA interference suppressor activity of rice hoja blanca virus NS3 in plants," *Journal of General Virology*, vol. 90 (July 2009), pp. 1762-1766; Bassam Berry, Safia Deddouche, Doris Kirschner, et al.,"Viral Suppressors of RNA Silencing Hinder Exogenous and Endogenous Small RNA Pathways in Drosophila," *PLoS ONE*, vol. 4 (June 2009), e5866. doi:10.1371/journal.pone.0005866; Wan-Xiang Li, Hongwei Li, Rui Lu, et al., "Interferon antagonist proteins of influenza and vaccinia viruses are suppressors of RNA silencing" *Proceedings of the National Academy of Sciences*, vol. 101 (February 3, 2004), pp. 1350-1355.

[12] Ibid.

[13] Chris M Cirimotich, Jaclyn C Scott, Aaron T Phillips, et al., "Suppression of RNA interference increases alphavirus replication and virus-associated mortality in *Aedes aegypti* mosquitoes," *BioMedCentral Microbiology*, vol. 9, online publication (March 5, 2009), doi:10.1186/1471-2180-9-49; Esther Schnettler, Walter de Vries, Hans Hemmes, et al., "The NS3 protein of rice hoja blanca virus complements the RNAi suppressor function of HIV-1 Tat," *EMBO Reports*, vol. 10 (March 2009), pp. 258-263.

[14] Yusuke Ohnishi, Yoshiko Tamura, Mariko Yoshida, et al., " Enhancement of Allele Discrimination by Introduction of Nucleotide Mismatches into siRNA in Allele-Specific Gene Silencing by RNAi," *PLoS*

mismatch of even one base in the genetic sequence dramatically reduces the effectiveness of gene silencing.[15] Because of this principle, anyone with access to human DNA sequence data can identify RNAi targets specific to a particular gene allele, and the ongoing public release of additional genomic information makes possible the development of new RNAi specificities. With the accumulation of publicly available human genomic data, it may eventually be possible to use RNAi as an "ethnic weapon" by targeting an allele for a critical metabolic or immune function that is present at high frequency in a particular human population.[16]

Of course, sequence alone is not sufficient to identify a target gene for RNAi silencing; the function of the gene must also be understood. Today scientists understand the function of a small but significant minority of human genes, and that of a handful of others can be inferred by their relatedness to genes in other organisms whose function is known. The combined knowledge of the sequence and function of a gene presents an opportunity to disrupt it through RNAi. In some cases this disruption would be directly harmful, while in other cases it would interfere indirectly with the host's susceptibility to disease. Given the vast quantity of data generated by the Human Genome Project and other efforts to map human genetic diversity and to understand recent human evolution[17], it may eventually become possible to design RNAi-based weapons that target gene alleles characteristic of certain human populations.

Because of the genetic diversity that exists within ethnic groups, it is rare that all of the individuals within a group have the identical allele for a given gene. (Such a universal allele is said to be "monomorphic.") In some cases, attempts to identify genetic markers for the forensic identification of individuals based on DNA fingerprinting have

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ONE, vol. 3 (May 2008), e2248. doi:10.1371/journal.pone.0002248; Dianne S. Schwarz, Hongliu Ding, Lori Kennington, et al., "Designing siRNA that Distinguish between Genes that Differ by a Single Nucleotide," *PLoS Genetics*, vol. 2 (September 2006), pp. 1307-1318.

[15] Xiuyuan Hu, Sharlene Hipolito, Rebecca Lynn, et al., "Relative gene-silencing efficiencies of small interfering RNAs targeting sense and antisense transcripts from the same genetic locus," *Nucleic Acids Research*, vol. 32 (2004), pp. 4609-4617.

[16] Debra Robertson, "Racially defined haplotype project debated," *Nature Biotechnology*, vol. 19 (2001), p. 795-796.

[17] Examples are the International HapMap Project , <hapmap.ncbi.nlm.nih.gov/>; the Human Genome Diversity Project, < www.stanford.edu/group/morrinst/hgdp.html>; and The 1000 Genomes Project <1000genomes.org/page.php>.

been confounded by the presence of monomorphic alleles.[18] Although monomorphic alleles are rare, there are many instances in which certain alleles are found only in a given ethnic group or lineage. Such "private" alleles are defined as occurring with a prevalence of 5 percent to 20 percent or more in a particular population and less than 0.1 percent to 1 percent in other populations.

Recent efforts to trace the relatedness and ancestry of different ethnicities (African-Americans, Asians, Hispanics, and Europeans) have analyzed large quantities of genomic data for patterns of shared and distinctive genetic markers. These studies have borne out the existence of private alleles within ethnic groups at frequencies of up to 10 percent.[19] For example, the discovery of a private allele in Native Americans supports the hypothesis that a single founding population colonized the Americas.[20] This study examined 1,249 individuals from 21 Native American and Western Beringian populations and 54 other populations worldwide and found that the private allele was present more than 35 percent of the time in Native Americans and Western Beringians but absent from all other subjects. Although a private allele would not provide a genetic target that could be used to attack all members of a particular ethnic group, it might be possible to attack a subset of that group.

Ease of Misuse (Explicit and Tacit Knowledge)

The design of functional siRNA molecules and the double-stranded RNAs that serve as their templates draws on several fields of research, each of which involves a skill

[18] Cintia Alvesa, Leonor Gusmaoa, Joselina Barbosa, et al., "Evaluating the informative power of Y-STRs: a comparative study using European and new African haplotype data," *Forensic Science International*, vol. 134 (2003), pp. 126-133; Neil Leat, Liezle Ehrenreich, Mongi Benjeddou, et al., "Properties of novel and widely studied Y-STR loci in three South African populations," *Forensic Science International*, vol. 168 (2007), pp. 154–161.

[19] Raymond D. Miller, Michael S. Phillips, Inho Jo, et al., "High-density single-nucleotide polymorphism maps of the human genome," *Genomics*, vol. 86 (2005), pp. 117-126; Stephen L. Guthery, Benjamin A. Salisbury, Manish S. Pungliya, et al., "The Structure of Common Genetic Variation in United States Populations," *American Journal of Human Genetics*, vol. 81 (2007), pp. 1211-2131; Jinchuan Xing, W. Scott Watkins, David J. Witherspoon, et al., "Fine-scaled human genetic structure revealed by SNP microarrays," *Genome Research*, vol. 19 (2009), pp. 815-825.

[20] Kari B. Schroeder, Mattias Jakobsson, Michael H. Crawford, et al., "Haplotypic Background of a Private Allele at High Frequency in the Americas," *Molecular Biology and Evolution*, vol. 26 (2009), pp. 995–1016.

set that is not fully codified in the published scientific literature. As a result, RNAi-based applications require tacit knowledge associated with genomics, genetic engineering, cell culture, microbiology, and medicinal chemistry. This requirement for hands-on experience raises the threshold that an offensive biological warfare (BW) program would have to reach in order to succeed, although the skill sets are not so rare as to preclude trained individuals from being recruited or coerced. Some of the required skills could also be outsourced because a wide variety of commercial companies provide DNA and RNA synthesis, gene expression analysis, and DNA sequencing on a fee-for-service basis.

Accessibility of the Technology

Although basic and applied research on RNAi provides a roadmap for the possible development of a biological weapon, only a state actor with an advanced BW program or a technically sophisticated and well-resourced terrorist organization could hope to do so successfully. Publicly available research could help to inform the design of such a weapon, but the development process would require a multi-disciplinary team with knowledge of genomics, molecular biology, cell biology, tissue culture, and formulations. In addition, sophisticated biotechnological capabilities would be needed to generate, test, and optimize the effectiveness of specific siRNA designs. Finally, translating RNAi into pharmacologically active products would require access to medicinal chemistry or gene-therapy techniques, and new methods for stabilizing and delivering siRNA molecules. Even under the best of circumstances, developing an RNAi-based weapon would require a sustained program of development and testing lasting at least several years.

Imminence and Magnitude of Risk

As mentioned above, possible hostile applications of RNAi technology include genetically engineering a virus for enhanced virulence or interfering with the RNAi defenses of the host. There is also the longer-term risk of creating “ethnic weapons” specific to particular races or ethnic groups, where common ancestry has resulted in the inheritance of particular alleles that are the source of distinctive characteristics. Although

the large amount of allelic variation within ethnic groups makes it unlikely that a critical allele will be both private and monomorphic within a population, that scenario is not essential for an ethnic weapon to be effective. A biological weapon capable of causing harm to 20 percent or even 10 percent of people from a specific ethnicity would have devastating social, cultural, and public health consequences, and would certainly suffice for terrorists or dictators who wish to rid society of a "troublesome" minority. Moreover, those diabolical enough to develop and use an ethnic weapon would probably not be deterred by the potential collateral damage caused by the presence of the targeted allele in other populations at frequency of 1 percent or less. Accordingly, the possibility of targeted attacks warrants concern. At the same time, given the extensive and technologically advanced efforts that would be required to develop such a weapon, the risk of misuse remains hypothetical and is therefore not imminent.

Awareness of Dual-Use Potential

National policymakers have not viewed the malicious use of RNAi as an immediate concern but have focused instead on the unintended safety hazards of the technology. For example, the June 2007 oversight framework proposed by the National Science Advisory Board for Biosecurity (NSABB) assessed RNAi as unlikely to pose a risk of misuse.[21] Similarly, although the Federation of American Scientists included a case study of RNAi in its set of online tutorials on dual-use biological research, it characterized the technology mainly as a biosafety concern.[22]

Even so, a few policy analyses concerned with dual-use biotechnologies have recognized the potential offensive applications of RNAi.[23] In November 2006, the United

[21] National Science Advisory Board for Biosecurity, "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information" (June 2007), http://oba.od.nih.gov/biosecurity/pdf/Framework%20for%20transmittal%200807_Sept07.pdf.
[22] Federation of American Scientists, "Case Studies in Dual-use Biological Research," Module 6, http://www.fas.org/biosecurity/education/dualuse/index.html.
[23] Allison Chamberlain and Gigi Kwik Gronvall, "The Science of Biodefense: RNAi," *Biosecurity and Bioterrorism*, vol. 5 (2007), pp. 104-106. Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006), pp. 165-169.

Kingdom presented a report to the Sixth Review Conference of the Biological Weapons Convention (BWC) that discussed RNAi as a potential ethnic weapon, observing that, "Theoretically, the technology now exists for the long-term, efficient silencing of an allele that segregates with ethnicity."[24] The British report did not discuss the implications of this possibility, however, either in terms of the potential harm to society or the attractiveness of such a weapon to malicious actors.

An earlier report by the Sunshine Project provided a more in-depth analysis of the potential misuse of RNAi to create ethnic weapons.[25] This report argued that human genetic variation presents ample opportunity to exploit gene alleles that are found exclusively in specific ethnic groups. To make this point, the report examined a small collection of point mutations, or single nucleotide polymorphisms (SNPs), from two databases. Of the roughly 300 SNPs found within genes, 3.3 percent were absent from one ethnic group but were present in another group at a frequency of greater than 20 percent. The report extrapolated from this finding that a large number of potential targets exist for ethnic weapons. Although questions remain about the sample size and how the SNPs were selected, these results support the possibility that a significant—and insufficiently understood—risk of misuse may exist.

A contrasting assessment was provided in a report from the U.S. National Research Council (NRC), which dismissed the likelihood that ethnic-specific SNPs could serve as a target for RNAi-based weapons. The report argued that "the hugely large number of point mutations and other polymorphisms within the genome are not likely to lead to any selective targeting in the near future. . . . [T]he proportion of such mutations lying in functionally important areas of the genome is small and the technical difficulties

[24] United Kingdom, "Scientific and Technological Developments Relevant to the Biological Weapons Convention," presented to the Sixth Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons (BTWC), Geneva, Switzerland, November 2006.
[25] Sunshine Project, "Emerging Technologies, Genetic Engineering and Biological Weapons," Background Paper No. 12 (November 2003).

associated with exploiting them are real." [26] The NRC report, however, provided no references or analysis to justify its conclusions.

Characteristics of the Technology Relevant to Governance

Embodiment. RNAi technology is not based primarily on novel or specialized hardware, but rather on intangible knowledge about the molecular mechanisms that help to control gene expression. Only a handful of reagents and laboratory resources are specific to the technique, and more common materials can be substituted for them. In addition, the key principles that underlie RNAi research and development can be understood from information published in the scientific literature.

Maturity. RNA interference is a common tool in basic biomedical research and is also being applied in numerous pharmaceutical development programs, with some RNAi-based drugs currently in clinical trials. Research services, including the design, production, and testing of RNAi reagents, are commercially available, greatly reducing the amount of in-house expertise and laboratory capability needed to pursue RNAi research. At the same time, each application is unique and requires substantial technical knowledge and access to laboratory resources in order to develop, test, and produce it.

Convergence. The development of RNAi tools draws on several enabling technologies in the biological and chemical sciences. Bioinformatics provides the sequence data needed to design the siRNAs that silence the target genes. The capability to synthesize short pieces of RNA is required to generate the double-stranded RNA that serves as a template for siRNA. In addition, researchers often employ genetic engineering methods to combine the template molecules with other genetic sequences.

Rate of advance. Few biomedical technologies have progressed as rapidly as RNAi from discovery to applied research and clinical trials. Development of the technology has been fueled by advances in genomic science, formulations for the stabilization and delivery of small-molecule drugs, and gene-therapy techniques and

[26] Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences*, p. 177.

vectors. The selection of appropriate genes as targets of RNAi is limited only by the scientific understanding of gene function and genomic sequences. In addition, the effectiveness of siRNA as a therapeutic depends on the ability to deliver the molecules into cells, where they act to silence genes. Methods for improving the specificity, potency, delivery, and stability of siRNA molecules in drug formulations are advancing rapidly. The genetic engineering techniques needed to incorporate RNAi-generating sequences into gene-therapy vectors are well established, and the vectors themselves are on the verge of broad clinical application. In fact, the development of new RNAi products is constrained less by the existence of effective methods than by patents and trade secrets that limit their availability.

International diffusion. The advantages of RNAi-based pharmaceutical products have contributed to the rapid international diffusion of the technology. Academic or industry laboratories in every industrialized country are conducting research involving the technique, and a review of the scientific literature indicates that RNAi research is also taking place in developing countries such as Pakistan and Iran. Not only is expertise in this field widely distributed, but a large number of companies provide reagents and research services, including the design, production, and testing of RNAi reagents. While many of these companies are based in the United States, several of them have worldwide distribution networks for their products and services.

Susceptibility to Governance

Any attempt to impose legally binding regulations on an enabling technology like RNAi would be confounded by its global diffusion and the fact that it draws on much of the same information, equipment, reagents, and procedures as other areas of molecular biology. The genomic sequences that inform the design of specific RNAi tools, for example, are publicly available and play a pivotal role in biomedical research. Although a few specialized algorithms have been developed for the design of RNAi-activating molecules, standard molecular biology techniques and reagents would be sufficient to produce an RNAi-based weapon.

As a result of these factors, even narrowly focused governance measures for RNAi would be expensive, burdensome to unrelated areas of research, and of little value in deterring those who wish to do harm. Mandatory declarations and inspections, personnel screening or licensing, registration or certification of labs or individuals, and scrutiny of equipment and reagent purchases would all be more disruptive than effective in managing the risk of misuse. Similarly, restricting access to research or to educational settings where RNAi skills could be acquired would have a chilling effect on basic research and could end up slowing pharmaceutical advances, delaying fundamental discoveries that fuel innovation, and impeding international scientific collaboration. Innovation in several non-medical fields, such as agriculture and renewable energy, would also feel the effects of restrictions on access to RNAi materials or training. Nevertheless, while the costs of formal regulation would outweigh the benefits, "soft-law" approaches to governance may still be practicable.

Past and Current Approaches to Governance

To date, the United States has made no attempt to regulate RNAi technology. The NSABB has dismissed the likelihood of RNAi being used as a weapon, and the Recombinant DNA Advisory Committee has addressed the technique only from the standpoint of biosafety.[27] Regulation of RNAi is also absent at the international level. The Australia Group focuses exclusively on harmonizing national export controls on lists of dangerous pathogens and dual-use production equipment, while the Biological Weapons Convention lacks formal verification or enforcement measures, although some parties to the treaty have raised RNAi as a potential security concern.

Options for Future Governance

Because the technical and financial resources of a nation-state would probably be required to develop an RNAi weapon, governance should focus on the state level, including efforts to make scientists involved in legitimate research less vulnerable to

[27] National Institutes of Health Public Consultation, "Synthetic Nucleic Acids and the NIH Guidelines for Research Involving Recombinant DNA Molecules," Arlington, VA, June 23, 2009.

exploitation by those who would misuse their knowledge and skills. Soft-law and normative approaches include training programs to increase scientists' awareness of the dual-use implications of their research, and channels for reporting suspicions or concerns to the proper authorities. Governments, professional societies, and trade associations could help to formalize these steps and provide resources to implement them.

To empower the scientific community to detect and report suspicious research activities both at home and abroad, it will also be essential to expand professional networks. Hosting foreign scientists in U.S. and other Western laboratories and establishing collegial relationships not only yields scientific advances but helps to build a international cohort of researchers who are sympathetic to U.S. security needs and less likely to transfer dual-use expertise to potential adversaries. Such professional collaborations also encourage members of the international scientific community to act as sentinels, providing useful insights into the legitimacy of research being conducted in countries of concern. Given these potential benefits, the U.S. government should roll back post-9/11 policies that have made it more difficult for foreign scientists to obtain visas to work in U.S. research institutions.

Conclusions

The discovery of RNAi, a powerful and precise natural mechanism for disrupting gene expression, has spawned a multitude of basic and applied research activities. Although the development of RNAi-based weapons would be a technically challenging task requiring the resources of a state, the potential ability to target specific ethnic groups could provide a strong incentive for those with malicious or genocidal intent. Attempts at governance should focus on raising the awareness of scientists about dual-use issues and encouraging them to report suspicious activities, so that the international community can take action against proliferant states or sophisticated terrorist organizations seeking to misuse RNAi technology. Enhancing international scientific exchanges to build enduring relationships would help to empower the scientific community in this regard.

Chapter 13: DNA Shuffling and Directed Evolution

Gerald L. Epstein[1]

DNA shuffling seeks to accelerate the evolutionary process by using molecular-biology techniques to manipulate an organism's genome, the genetic blueprint that determines its inherited characteristics, in order to achieve a practical goal such as increasing the expression of a protein or improving enzymatic activity. In principle, actors seeking to create novel pathogens or toxins for harmful purposes could misuse this approach, although they have not yet done so. Because all of the tools, materials, and equipment needed to perform DNA shuffling are available in molecular biology laboratories, this technology is potentially accessible to many thousands of researchers worldwide, although skill and expertise are required to perform it efficiently. No effective options exist to prevent the further spread of DNA shuffling, but a number of governance measures may lessen the risk of malicious use.

Overview of the Technology

The evolution of species, first described by Charles Darwin in 1859, involves a process in which organisms inherit genes from their parents, resulting in offspring with a range of characteristics. Sexual reproduction produces diversity because each descendant inherits a different combination of traits from its two parents.[2] Additional genetic diversity results from mutations, or mistakes in DNA replication that give the offspring traits their parents did not possess. The descendants are then subjected to "natural selection," a test of their ability to survive and reproduce in an environment full of hazards. Organisms that are not well adapted to their environment will either die before

[1] The author would like to thank Drs. Roger Brent, Hal Padgett, Kathleen Vogel, Christopher Locher, and Frances Arnold for their suggestions, comments, or reviews of this paper or portions of it. Any remaining errors are, of course, solely the responsibility of the author.

[2] The relevant aspect of sexual reproduction is not so much that each offspring gets half of its chromosomes from its mother and half from its father, but that each of the parental chromosomes constitutes a random combination of the two versions of that chromosome that each parent inherited from his or her own parents. In other words, the chromosomes in egg and sperm cells are created through a process that randomly intersperses portions copied from the mother's chromosome with portions copied from the father's.

reproducing or will not reproduce as prolifically. The more successful organisms will pass on their traits, again with some variability, to their own descendants, increasing the fraction of offspring in the next generation that possess characteristics adapted to that particular environment. In this way, each successive generation is filtered or selected by external factors.

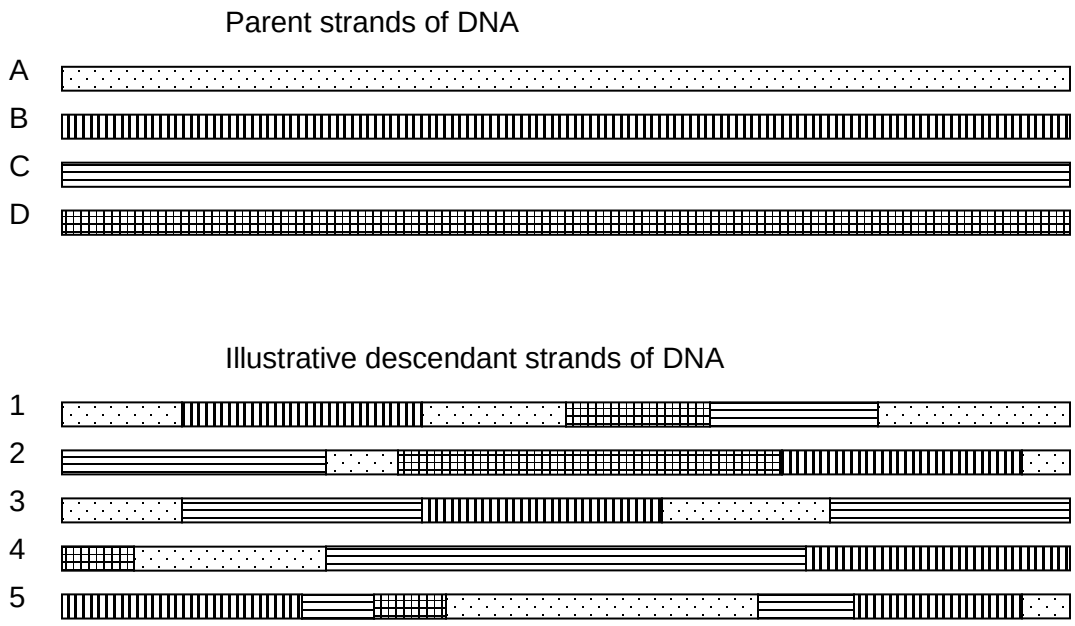
Whereas natural selection pursues no particular goal, *directed* evolution takes place under the control of human beings with specific objectives in mind. In the case of crops or agricultural animals, breeders target attributes such as yield, strength, disease resistance, and tolerance to drought or low temperatures. To enhance these traits, they select parent organisms that perform better than their peers and look for descendants that are better yet. The best-performing members of each generation are then used to sire the next generation. Over the past century, breeders have increased the diversity of the next generation by raising the mutation rate through irradiation or chemicals.

DNA shuffling is a form of directed evolution that, unlike breeding, yields genetic variations that are unlikely to arise in nature. When DNA shuffling is performed on microbes, it vastly increases the diversity of each successive generation beyond what natural processes would create, permitting an investigator to screen for rare genetic variants that have a particular desirable characteristic. In this way, DNA shuffling can generate bacteria with properties that would be unlikely to evolve naturally, such as the enhanced ability to produce a given protein. The technique also provides an effective way to engineer enzymes and other proteins, particularly because it does not require an understanding of the underlying biological mechanisms. In this context, DNA shuffling can be viewed as the biological equivalent of combinatorial chemistry and high-throughput screening. (See Chapter 6.)

When used on microorganisms, DNA shuffling provides a significantly accelerated form of directed evolution. Microbes typically reproduce asexually from a single parent by simple division, resulting in two daughter cells that have genomes

identical to the parent.[3] Normally, errors in the replication of a microbial genome are the only source of diversity in its descendants. DNA shuffling creates far more diversity by starting with several different parent genomes and producing "daughter" genomes that randomly incorporate distinct stretches of DNA from the different parents (Figure 13-1).

Figure 13-1: Construction of diverse descendants from random combinations of parental DNA



Even if the parent genomes differ in only a few places, there are many ways in which those differences can appear in a given descendant. For example, if there are four different parent genomes, each of which differs from the others at any of five places, each descendant genome can have DNA from any of the four parents at those five places, creating a library of up to 4^5 or 1,024 different descendants. Further diversity can be introduced by creating the descendant genomes through a process that deliberately

[3] Less common processes exist, such as "conjugation," through which descendants can acquire genetic material from more than one "parent" microbe; antibiotic resistance is transmitted through this mechanism.

introduces additional mutations, so that not all versions of the DNA sections copied from the same parent are identical. Some of the descendant organisms might not be viable, but the ones that survive will have a wide range of characteristics, and a researcher can test them manually or with high-throughput assays to see how well they perform with respect to the property being optimized, such as the yield of a given protein. Those variants that perform best can then be prepared for another round of shuffling in which *their* genomes are randomly mixed, and the entire process repeated. Selection schemes that do not rely on high-throughput screening may also be used, such as those in which the culture conditions are designed so that the microbial variants of interest are the only ones that can survive and propagate, while all others are inhibited. Those strains best suited to thrive in a stressful environment will reproduce most prolifically and will therefore constitute the bulk of the recovered organisms. Several studies have demonstrated the ability of DNA shuffling to improve an organism's resistance to antibiotics, which can serve as a proxy for optimizing its enzymatic activity or protein production.[4]

The power of DNA shuffling comes from the ability to create a vast number of genetic variants, along with the ability to screen the resulting library with high-throughput methods to identify variants with the desired properties. If a large enough number of variant strains is created, at least one organism will usually satisfy the selection criteria. Repeating the process for multiple generations will further optimize the resulting organisms. As opposed to traditional recombinant DNA methods, which require knowing precisely which molecular changes are needed to achieve a desired improvement, an investigator using DNA shuffling does not have to know, or even guess, which specific molecular changes will accomplish the objective.

History of the Technology

During the early 1990s, researchers at the Affymax Research Institute in Palo Alto, California, pursued directed-evolution studies by using mutation-inducing

[4] Willem P. C. Stemmer, "Rapid evolution of a protein *in vitro* by DNA shuffling," *Nature*, vol. 370 (August 4, 1994), pp. 389-391; Ying-Xin Zhang, Kim Perry, Victor A. Vinci, Keith Powell, Willem P. C. Stemmer, and Stephen B. del Cardayre, "Genome shuffling leads to rapid phenotypic improvement in bacteria," *Nature*, vol. 415 (February 7, 2002), p. 644-646.

chemicals or other means to introduce random errors into the genomes of microorganisms.[5] In 1993, Willem P. C. Stemmer invented a new, combinatorial approach for producing diverse microbial genomes by randomly combining DNA fragments from different sources and screening them for desired properties. This method provided a substantial leap in capability. Stemmer's initial publications demonstrated the ability of DNA shuffling to increase the antibiotic resistance of a bacterium by a factor of 32,000.[6] Other studies created diversity by shuffling analogous genes from different species, such as mouse and human genes coding for the same protein.[7]

In 1997, Stemmer and three colleagues founded a company called Maxygen—an abbreviation of "maximizing genetic diversity"—to commercialize the DNA shuffling technique. At the time of its incorporation, Maxygen had filed 12 patent applications and received one. Different divisions of the company worked on agricultural, chemical, pharmaceutical, and vaccine applications of DNA shuffling.[8] Maxygen researchers investigated the utility of the technique for strain libraries of up to 10,000 genetic variants. Using high-throughput screening, the researchers selected 20 to 40 variants that had the greatest ability to produce a particular enzyme that the original strain manufactured only at low levels; these variants then provided the basis for the next round of shuffling. Seven rounds of selection produced a strain of *E. coli* with enzymatic activity 66 times greater than the original strain, showing that even modestly-sized strain libraries can evolve effectively.[9]

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[5] Jon Cohen, "'Breeding' Antigens for New Vaccines," *Science*, vol. 293 (July 13, 2001), pp. 236-238.
[6] Willem P. C. Stemmer, "Rapid evolution of a protein *in vitro* by DNA shuffling," *Nature*, vol. 370 (August 4, 1994), pp. 389-391; Willem P. C. Stemmer, "DNA shuffling by random fragmentation and reassembly: In vitro recombination for molecular evolution," *Proceedings of the National Academy of Sciences USA*, vol. 91 (October 1994), pp. 10747-10751.
[7] Stemmer, "DNA shuffling by random fragmentation and reassembly," p. 10750.
[8] Maxygen's first patent for this technology was U.S. patent No. 5,605,793, "Methods for In Vitro Recombination" issued on February 25, 1997. "Zaffaroni Announces New Start-Up Company—Maxygen, Inc.," *Maxygen News* (press release), June 2, 1997, http://www.maxygen.com/news-arch.php?y=1997.
[9] Ji-Hu Zhang, Glenn Dawes, and Willem P. C. Stemmer, "Directed evolution of a fucosidase from a galactosidase by DNA shuffling and screening," *Proceedings of the National Academy of Sciences USA*, vol. 94 (April 1997), pp. 4504–4509. The variants of interest were identified because they grew into bacterial colonies that turned blue, with the greatest enzymatic activity resulting in the deepest blue. The bluest colonies were visually identified and harvested.

A 1998 paper demonstrated the power of shuffling a pool of related genes from four bacterial species to evolve an enzyme that could degrade an antibiotic, thereby conferring resistance to it.[10] Each of the bacterial genes was shuffled individually, generating a library of genes that differed only by a few point mutations. In each case, a single round of shuffling led to an eight-fold increase in enzymatic activity. Yet when all four genes were shuffled together, introducing diversity not only through point mutations but by randomly recombining portions of the four original genes, a single round of shuffling yielded as much as a 540-fold increase in enzymatic activity. In addition, a 2002 paper in *Nature* described how two rounds of whole-genome shuffling over the course of a year resulted in a nine-fold increase in the ability of a bacterial strain to produce the antibiotic tylosin. This same level of improvement had taken 20 years to achieve with the conventional technique of successive mutation and screening.[11]

Although the initial applications of DNA shuffling were to optimize protein expression in bacteria, a paper published in 2000 described the use of the technique on viruses. A single round of shuffling six strains of mouse leukemia virus yielded a variant strain that could infect a different organ in a separate species: ovaries in Chinese hamsters.[12] Analysis of the shuffled genome revealed DNA-sequence changes that would not have easily resulted from natural recombination. Another DNA shuffling experiment extended the host range of human immunodeficiency virus (HIV) to infect the cells of pig-tailed macaques.[13] In this way, DNA shuffling was able to extend the range of tissues and species that a virus could infect in a manner unlikely to have occurred naturally.

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[10] Andreas Crameri, Sun-Ai Raillard, Ericka Bermudez, and Willem P. C. Stemmer, "DNA shuffling of a family of genes from diverse species accelerates directed evolution," *Nature*, vol. 391 (15 January 1998), p. 288

11 Ying-Xin Zhang, Kim Perry, Victor A. Vinci, Keith Powell, Willem P. C. Stemmer, and Stephen B. del Cardayre, "Genome shuffling leads to rapid phenotypic improvement in bacteria," *Nature*, vol. 415 (February 7, 2002), p. 644-646.

[12] Nay-Wei Soong, Laurel Nomura, Katja Pekrun, Margaret Reed, Liana Sheppard, Glenn Dawes, and Willem P.C. Stemmer, "Molecular breeding of viruses," *Nature Genetics*, vol. 25 (August 2000), pp. 436-439

[13] Katja Pekrun, Riri Shibata, Tatsuhiko Igarashi, Margaret Reed, Liana Sheppard, Philip A. Patten, Willem P. C. Stemmer, Malcolm A. Martin, and Nay-Wei Soong, "Evolution of a Human Immunodeficiency Virus Type 1 Variant with Enhanced Replication in Pig-Tailed Macaque Cells by DNA Shuffling," *Journal of Virology*, vol. 76 (March 2002), pp. 2924–2935.

These findings demonstrated the remarkable power of the technique—as well as its dual-use potential.

By 2001, the U.S. Defense Advanced Research Projects Agency (DARPA) had invested $20 million in Maxygen for the development of new vaccines. Vaccines work by exposing the body to foreign proteins (antigens) similar to those found on the surface of pathogenic microbes, eliciting an immune response that enables the body to recognize and attack organisms that express the proteins the next time they are encountered. Under natural conditions, pathogens never evolve antigens that maximize the immune response because it is in their survival interest to minimize it. But Maxygen's goal was to use DNA shuffling to modify viral antigens for use in vaccines by increasing their immunogenicity and cross-protective range, or ability to protect against multiple strains of a given pathogen.[14] In laboratory assays, the resulting vaccine candidates exhibited both characteristics.[15] Despite these promising results, the efficacy of vaccines produced by DNA shuffling has yet to be demonstrated in clinical trials.

Utility of the Technology

Directed evolution—for which DNA shuffling is a major but not the only approach—is now the principal means of generating proteins with new or improved properties.[16] It differs sharply from the "rational-design" approach, which uses an in-depth understanding of a protein's three-dimensional structure to improve its functional characteristics. (See Chapter 9.) Unlike rational design, DNA shuffling typically yields functional improvements by multiple, unrelated mechanisms and often in unexpected ways. It is also capable of optimizing multiple aspects of a protein simultaneously, such as potency and level of expression.

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[14] Cohen, "'Breeding' Antigens for New Vaccines."

[15] Christopher P. Locher, Madan Paidhungat, Robert G. Whalen, et al., "DNA Shuffling and Screening Strategies for Improving Vaccine Efficacy," *DNA and Cell Biology*, vol. 24, no. 4 (2005), pp. 256-263.

[16] Ling Yuan, Itzhak Kurek, James English, and Robert Keenan, "Laboratory-Directed Protein Evolution," *Microbiology and Molecular Biology Reviews*, vol. 69 (September 2005), p. 374. In addition to directed evolution, the other strategy mentioned in this paper for developing new proteins is "rational design," or the design of new proteins based on an understanding the structural and functional consequences of changing an original protein's composition. According to the Yuan et al., however, "our present knowledge of structure-function relationships in proteins is still insufficient to make rational design a robust approach."

Most applications of DNA shuffling seek to develop better enzymes, antibodies, therapeutic proteins, and other products, such as improving the heat-stability of enzymes for use in laundry detergents. Essentially every protein biotechnology company uses this approach.[17] Another important application of DNA shuffling is the large-scale production of the amino acid phenylalanine, which led to the commercialization of the non-nutritive sweetener aspartame.[18] DNA shuffling is also widely used in academic research, agriculture, and other fields. Although much of the methodology of DNA shuffling is under patent protection—Maxygen holds close to 100 patents[19]—researchers not directly affiliated with the company have developed alternate molecular techniques for performing directed evolution, such as random mutagenesis.[20] Like DNA shuffling, these processes generate a library of diverse variants of an initial gene or genome, which are then subjected to screening or selection techniques to identify the organisms with desired properties. Many of these techniques are under patent protection, but some are not.

Potential for Misuse

In principle, DNA shuffling could be used to optimize traits that cause harm, whether by toxicity, pathogenesis, resistance to therapeutic or prophylactic countermeasures, environmental hardiness, or some other means. Several of the studies described above illustrate the ability of DNA shuffling to increase a microbe's antibiotic resistance as a proxy for optimizing some other parameter, such as enzymatic activity or protein production. Accordingly, someone with malicious intent might use this method to render a biological warfare agent resistant to medical countermeasures or to enhance the production of a protein toxin. Although it is possible to generate antibiotic-resistant

[17] Author's e-mail communication with Prof. Frances Arnold, January 30, 2010.
[18] Examples are from an interview with Roger Brent, former President of the Molecular Sciences Institute, August 21, 2009. They involved directed evolution but likely not DNA shuffling.
[19] Crispin Littlehales, "Profile: Willem "Pim" Stemmer," *Nature Biotechnology*, vol. 27 (March 2009), p. 220.
[20] One early such paper is Frances H. Arnold, "Protein engineering for unusual environments," *Current Opinion in Biotechnology*, vol. 4, no. 4 (August, 1993), pp. 450-455. This paper develops the technique of "random mutagensis by PCR," in which the reaction that duplicates DNA strands introduces strands with mutations among strands that faithfully copy the original. Subsequent rounds of DNA duplication within this mixture produce strands having different combinations of errors, creating a diverse set of genes or genomes.

strains with simple selection methods, DNA shuffling could potentially generate bacteria that are resistant to multiple antibiotics simultaneously, without compromising other militarily desirable attributes.

The potential misuse of DNA shuffling to make a biological agent more harmful is possible because the steps needed to create biological diversity and screen for desired traits are largely independent of the purpose for which the diversity is generated. For example, an important commercial application of DNA shuffling is the optimization of plant viral vectors that have been engineered to carry foreign genes that code for proteins. Upon the infection of an appropriate host plant, these viruses transfer their payload of genes into the plant cells and induce them to manufacture the protein of interest. In general, the incorporation of a foreign gene into the viral vector tends to make the virus less pathogenic, limiting its ability to infect the host plant and reducing the yield of protein. Maximizing the efficiency of protein production therefore requires increasing the virulence of the viral vector. DNA shuffling is well suited to perform this task, which has obvious dual-use implications.[21]

In other research, Maxygen's vaccine unit shuffled genes for the immune system protein interleukin-12 (IL-12) from seven mammalian species—human, rhesus monkey, cow, pig, goat, dog, and cat—to produce a form of the protein that was 128 times more potent at stimulating the human immune system than ordinary human IL-12.[22] Although this work was performed for the purpose of developing vaccines and other therapeutic applications, it could potentially be misused to impair the human immune system or turn it against the host. These malicious applications may have been foreshadowed by the identifier that the Maxygen investigators unwittingly chose for the shuffled ("evolved") form of interleukin-12: EvIL.

[21] Author's interview with Dr. Hal Padgett, Chief Scientist, Novici Biotech, a company that has patented an improved approach to DNA shuffling (also called GRAMMR) and is applying it to virus-based manufacturing systems for pharmaceutical production in plants, August 21, 2009.
[22] Steven R. Leong, Jean C. C. Chang, Randal Ong, Glenn Dawes, Willem P. C. Stemmer, and Juha Punnonen, "Optimized expression and specific activity of IL-12 by directed molecular evolution," *Proceedings of the National Academy of Sciences USA*, vol. 100, no. 3 (February 4, 2003), pp. 1163–1168.

Ease of Misuse (Explicit and Tacit Knowledge)

While some approaches to DNA shuffling are patented, others are not, and the necessary equipment and materials exist in many molecular biology laboratories. State-level biological warfare programs could easily master DNA shuffling, as could groups or individuals with sufficient expertise, resources, and commitment. Indeed, directed-evolution techniques are accessible to any laboratory or company that is reasonably proficient in modern molecular biology techniques—a level of capability possessed by more than 10,000 laboratories around the world.[23]

Even so, it would be difficult to train members of a terrorist group who lacked a background in molecular biology. Although procedures for DNA shuffling published in the academic and patent literature are sufficient for anyone with a basic set of laboratory skills to create libraries of shuffled genes,[24] tacit knowledge acquired through practical experience is essential with respect to the downstream procedures needed to express the genes that have been created and to identify and isolate the variants of interest.[25]

Two factors suggest that tacit knowledge is important for DNA shuffling. First, the technique is not available in the form of a commercially available "kit" containing all necessary reagents, laboratory vials, and detailed instructions. (One reason that kits do not exist is that many of the methods have been patented, and the patent owners prefer to market DNA-shuffling services.) Kits remove many sources of error, making it possible to perform procedures that would otherwise succeed far less often, even in the hands of skilled practitioners. In the absence of a kit, a researcher must know which reagents to use and what procedures to follow. Nevertheless, studies have shown that even kits do not necessarily remove the need for tacit knowledge when performing a specific

[23] Estimate by Roger Brent, former editor, *Current Protocols in Molecular Biology* and former president, Molecular Science Institute, email communication to author, August 27, 2009.
[24] For example, see Huimin Zhao and Frances H. Arnold, "Optimization of DNA shuffling for high fidelity recombination," *Nucleic Acids Research*, vol. 25 (1997), pp. 1307–1308. Zhao and Arnold's DNA shuffling approach minimizes the number of additional point mutations that are introduced. (Some DNA shuffling methods deliberately seek to introduce, rather than minimize, point mutations.)
[25] Observations in both sentences from Hal Padgett, email communication to author, August 29, 2009.

experiment in a particular laboratory context.[26] A second indicator of the importance of tacit knowledge for DNA shuffling is the fact that a set of procedures for the technique is not included in *Current Protocols in Molecular Biology*, a peer-reviewed publication that contains methods for a wide range of biotechnologies.[27]

Accessibility of the Technology

A major constraint on the application of DNA shuffling for biological warfare is the need to screen the variant strains to identify those that most strongly express the desired property. If the intent is to develop a pathogen that is more infectious, deadly, or contagious in humans, *in vitro* assays could not simulate the complicated processes involved in infecting the host, defeating the immune response, causing disease, and transmitting the disease to others. If, however, the developer of the weapon was a ruthless organization that had no qualms about killing test subjects, it might identify which of the various strains was most effective by infecting a small number of test subjects (prisoners or suicide volunteers) or animals if the extrapolation to humans was understood.[28]

Awareness of Dual-Use Potential

Pim Stemmer, the inventor of DNA shuffling, recognized its dual-use potential almost immediately. "Arguably, it's the most dangerous thing you can do in biology," he observed.[29] DARPA program managers who funded early research on DNA shuffling were aware of its dual-use implications but focused more on its potential to transform research on vaccines and other medical countermeasures.[30] The broader life-sciences community, however, did not recognize the dual-use potential of DNA shuffling at the

[26] Michael Lynch, "Protocols, practices, and the reproduction of technique in molecular biology," *British Journal of Sociology*, vol. 53, no. 2, pp. 203-220 (June 2002, published online December 15, 2003).
[27] Frederick M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith, Kevin Struhl, editorial board, *Current Protocols in Molecular Biology* (Wiley Interscience, 2009).
[28] Note that precursor attacks could not serve such a screening function unless the perpetrators had access to the victims after they died. Moreover, pathogenesis would depend not only on the characteristics of the pathogen but on factors such as the number of infecting organisms and the mode of entry into the body, introducing additional complexity to the experiments.
[29] Littlehales, "Profile: Willem 'Pim' Stemmer," p. 220.
[30] Author's interview with Roger Brent, August 21, 2009; e-mail communication to author from former DARPA program manager Stephen S. Morse, August 27, 2009.

time it was developed. Indeed, according to a National Research Council report, "Only a few in the scientific community had raised concerns about the potential contributions of life sciences research to biological weapons programs and bioterrorism before the anthrax attacks of 2001."[31]

In recent years, dual-use biotechnologies other than DNA shuffling have received far more attention from the policy community. Synthetic biology, for example, became prominent after Eckard Wimmer and his colleagues synthesized poliovirus in 2002.[32] Since then, dozens of surveys, studies, and analyses of synthetic biology have been published, to the point that one observer complained that "synthetic biology represents 5 percent of the risk but is getting 95 percent of the attention."[33] DNA shuffling belongs to the less-examined 95 percent, and few studies have examined its dual-use implications.

Characteristics of the Technology Relevant to Governance

Embodiment. DNA shuffling does not rely on unique or specialized equipment but consists of a set of procedures that make use of, and build upon, the standard methods and tools of molecular biology: the ability to cut, transfer, and duplicate DNA, to combine shorter pieces of DNA into longer ones, to sort pieces of DNA by size, to insert DNA into a microorganism's genome such that the functions or processes it encodes are carried out, and to screen large numbers of microorganisms rapidly to identify those with properties of interest.

Maturity. Directed-evolution techniques are widely used in research and by biotechnology firms involved in engineering new proteins. The technology is not available for sale but can be created by those seeking its benefits.

Convergence. DNA shuffling is not a convergent technology and lies fairly centrally within biotechnology. Some bioinformatics is needed to identify the appropriate

[31] National Research Council, *A Survey of Attitudes and Actions on Dual Use Research in the Life Sciences: A Collaborative Effort of the National Research Council and the American Association for the Advancement of Science* (Washington, D.C.: National Academies Press, 2008), p. 11

[32] Jeronimo Cello, Aniko V. Paul, and Eckard Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template," *Science*, vol. 297 (August 9, 2002), pp. 1016-1018.

[33] Roger Brent, personal communication to author, 2009.

genes with which to initiate shuffling, and the high-throughput screening of variant organisms may involve the robotic manipulation of large numbers of samples, but the beauty of the approach is that it is not necessary to comprehend the underlying biology or to conduct sophisticated information processing.

Rate of advance. It is hard to measure the rate of progress of DNA shuffling because the technique has not been defined with sufficient precision to permit indexing by quantitative parameters. A possible indicator of how the technique has developed, if data were available, would be the approximate number of distinct genetic sequences that can be created.[34] Still, this number is only a partial measure of the power of DNA shuffling because what matters is the *functional* diversity of the sequences, meaning the number of different ways in which the resulting organisms behave. Generating many different strains is not helpful if they are the same with respect to the property being sought. Moreover, as the number of genetic variants increases, it may become more difficult to screen for sequences that optimize the characteristic of interest. From a qualitative standpoint, DNA shuffling has progressed in terms of the types of DNA that can be recombined and the methods by which the recombination takes place. More significant than advances in the technique itself, however, is the development of new applications.

International diffusion. The United States, the European Union, and Japan are the most powerful players in the life sciences and will likely remain so for the next five to 10 years.[35] Nevertheless, biotechnology is globalizing rapidly because the necessary equipment, materials, and facilities are relatively inexpensive when compared with capital-intensive industries such as semiconductor manufacturing and aviation. Trained biologists and biotechnologists in developing countries earn salaries that are considerably lower than those in Western industrialized countries, international academic exchanges

[34] One early paper estimated that DNA shuffling techniques were capable of producing libraries of up to $10^{10\text{-}15}$ molecules. See Willem P. C. Stemmer, "Searching Sequence Space," *Nature Biotechnology*, vol. 13 (June 1995), pp. 549

[35] Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006), p. 79.

are expanding, and research and industrial facilities around the world draw on a supporting infrastructure of companies that supply reagents and other materials.[36] Because of these trends, biotechnology clusters—geographically proximate and interconnected companies, research institutions, service providers, suppliers, and trade associations—have emerged in Argentina, Brazil, China, Cuba, Hong Kong, India, Malaysia, Singapore, South Africa, and Taiwan.[37] As developing and rapidly industrializing countries grow more adept at using biotechnology, they will be better able to conduct DNA shuffling. Although Maxygen's patents may limit the spread of DNA shuffling among legitimate users, alternate approaches to directed evolution are expected to proliferate widely.

Susceptibility to Governance

The tools, processes, materials, and equipment underlying DNA shuffling are all generic to molecular biology, placing the technique within reach of thousands of reasonably equipped laboratories around the world—although a fair amount of skill and expertise is required to apply it successfully. Accordingly, there is no way to control DNA shuffling without constraining biotechnology as a whole. Any broad-based controls that restrict the spread and further development of the technique would not only be impractical but, given biotechnology's importance for legitimate purposes, counterproductive and arguably immoral. Even if mandatory regulations were imposed, the lack of distinctive equipment, materials, or procedures associated with DNA shuffling would impede the effectiveness of controls unless its use was self-reported.[38]

Devising specific governance measures for DNA shuffling is also complicated by the fact that legitimate applications may be difficult to distinguish from illicit ones,

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[36] Gerald L. Epstein, *Global Evolution of Dual-Use Biotechnology* (Washington, DC: CSIS Press, 2005), p. 9.

[37] "Select global biotechnology and bioscience clusters," http://mbbnet.umn.edu/scmap/biotechmap.html. The countries listed here are pursuing biotechnology but do not necessarily have capacity specifically in DNA shuffling or directed evolution.

[38] It might be possible after-the-fact to determine that DNA shuffling had been performed if one had access to the organisms that had been produced and could analyze their genomes to look for the distinctly chimeric nature of a shuffled genome.

raising the prospect of penalizing or discouraging legitimate scientific research without a corresponding security benefit. As with other dual-use biotechnologies, the risk of harm from DNA shuffling is not tied to the technology *per se* but rather to the purpose for which it is used. Given that even seemingly suspicious activities (such as developing a gene-therapy vector to evade the human immune system, or maximizing the biological activity of a toxin) may have a legitimate purpose, knowing how DNA shuffling is being used might not be sufficient to distinguish between legitimate and illicit activities. It is possible that scientists working in established laboratories could conduct DNA shuffling for malicious purposes without others in the facility having reason to question their activity. (Possible exceptions might include the use of unusual procedures to ensure biosafety or to screen for the harmful characteristics being sought.) These factors do not preclude governance measures, but because their value would be modest, the costs of implementation must not be too high in terms of direct cost and foregone opportunities. For these reasons, minimizing the risk of misuse of DNA shuffling is best addressed with measures that reduce the risk of misuse of biotechnology in general.

Past and Current Approaches to Governance

The dual-use risks of certain types of experiments are usually discussed in terms of their potential results and not the experimental method employed. For example, the U.S. National Science Advisory Board for Biosecurity (NSABB) has identified the deliberate alteration of a pathogen's host range as warranting scrutiny from a dual-use perspective. In so doing, however, the advisory board did not call attention to DNA shuffling, which has been used for that purpose. With the exception of synthetic genomics, where specific guidelines have been developed for commercial vendors of synthetic DNA, current approaches to the governance of dual-use biotechnologies are fairly generic. "Soft-law" and normative measures include the review of proposed experiments that raise dual-use concerns, guidance on communicating the results of such experiments, reinforcing norms against malicious use, and raising awareness of dual-use concerns among life scientists.

Options for Future Governance

Four possible governance options for DNA shuffling fall into the category of measures for which the potential benefits would outweigh the costs. First, one way to facilitate the difficult task of detecting illicit applications of DNA shuffling would be to require that certain types of legitimate activity be reported to an appropriate authority, including all research that could reasonably be expected to enhance a pathogen's virulence or ability to resist countermeasures or to increase the range of species or tissue types it can infect.[39] Such a reporting requirement could be a useful way to reinforce biosafety guidelines or requirements. In addition to DNA shuffling activities that are intended (or could reasonably be expected) to optimize plant, animal, or human pathogens, it would be desirable to cover benign microbes that might become pathogenic through the shuffling process. In that case, the variability introduced by DNA shuffling could yield new and dangerous properties, even if that was not the intended objective. Apart from security concerns, such experiments could entail significant biosafety risks.

The reports might not only include technical data about the procedures being used but also information about the investigator, possibly including some sort of registration requirement for the personnel involved. Should a reportable activity be discovered that was *not* reported, it would be viewed with considerable suspicion. A reporting scheme would also force malefactors to work secretly or create an elaborate cover story, exposing them to some risk of detection and exposure. Without a reporting requirement, illegitimate work could be performed openly with little risk of being identified as such.

The benefits of the reporting scheme would depend on the number of activities that require reports and whether the criteria are sufficiently clear and objective so that practitioners know when to report. Another critical factor would be the willingness of practitioners to make the necessary reports to the appropriate government entity. If the risk was high that sensitive or proprietary information would be compromised despite

[39] National Science Advisory Board for Biosecurity, *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information* (Bethesda, MD: National Institutes of Health, June 2007).

guarantees of confidentiality, then researchers or vendors would probably refuse to report relevant activities, and the scheme would fail. Finally, there must be some basis for differentiating legitimate from illicit work on the basis of the information provided. If the reporting criteria are ambiguous or subjective, a requirement to report all dual-use experiments would not guarantee that the work is legitimate.

Second, it would be useful to create a mechanism by which anyone suspecting that a coworker, supplier, customer, or professional colleague was pursuing illicit activities would be able to bring these concerns to the attention of an appropriate authority, which could then take action. The details of such a mechanism—who would collect the reports, what steps would be taken to resolve a concern, and how to preserve due process and the right of redress for those reported—would have to be worked out.

Third, discretion may be advisable when communicating sensitive research results. The genetic variability generated by DNA shuffling raises the possibility that microbes with properties of interest for hostile purposes, such as a new mechanism of pathogenesis, may emerge in the course of legitimate research. Any experiment *intended* to produce highly pathogenic organisms should receive close scrutiny before being undertaken or communicated because it would entail some risk of violating the Biological Weapons Convention's proscription against developing biological weapons. However, any experiment that *unintentionally* produces microorganisms with increased pathogenicity would arguably face the same criteria in terms of communicating the results, even if they were tangential or irrelevant to the desired objective. As a group of scientific editors and publishers acknowledged in 2003, "On occasion an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published."[40] Although it would be inappropriate in most cases for governmental authorities to assume

[40] Journal Editors and Authors Group, "Statement on Scientific Publication and Security," *Science*, vol. 299 (February 21, 2003), p. 1149. Potential restrictions on communicating dual-use research are elaborated further in "Points To Consider in Assessing the Risks and Benefits of Communicating Research Information With Dual Use Potential," included as Appendix 5, pp. 53-54, of National Science Advisory Board for Biosecurity (NSABB), *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*, June 2007.

a formal role in reviewing scientific publications, scientific authors—like editors and publishers—must consider the consequences of their actions. Exercising restraint with respect to the publication of dual-use information, although pejoratively labeled “self-censorship” by some, is more appropriately called “scientific responsibility.” Every day scientists face a choice of what lines of research to pursue, and considering the potential misuse of the results is as legitimate a factor as any.

Conclusions

DNA shuffling is a powerful approach for generating diverse biological characteristics even when the underlying biological processes are unknown or poorly understood. As long as a biological outcome can be defined and efficiently screened for, DNA shuffling can help to enhance it. The only limitations are that the desired property must be biologically possible—the limits of which may not be known—and that the few organisms possessing the desired property can be screened efficiently from the great majority that do not. Any technique this powerful has tremendous potential to advance human welfare, but it might also be misused to create novel pathogens or toxins that can cause harm in ways beyond what is now possible. Accordingly, scientists performing DNA shuffling experiments should be encouraged to consider the consequences of their actions and to refrain from pursuing or publishing unanticipated findings that are more likely to facilitate misuse and harm than to improve human welfare.

Chapter 14: Gene Therapy

Gail Javitt and Anya Prince

Gene therapy, also known as "gene transfer" or "genetic modification," is the process of inserting genetic material into a person's cells or tissues in order to alter gene function and potentially treat or cure hereditary diseases. Although gene therapy was heralded in 1990 as a ground-breaking technology that would radically change the medical community's ability to fight disease, the ensuing two decades of research have been fraught with setbacks and complications. Researchers have faced many technical barriers to inserting genes into an individual for therapeutic purposes, and scientists continue to encounter challenges during clinical trials of gene therapy.

Some analysts have speculated about the ability of terrorists and other malicious actors to use gene-therapy techniques to create enhanced biological weapons. At present this possibility is hypothetical, but future technological advances could make the potential misuse of gene therapy more of a concern. Because the nascent state of the technology makes it difficult to envision effective governance strategies, progress in gene therapy should be monitored closely so that the appropriate policies can be introduced as the technology matures.

Overview of the Technology

Gene therapy research combines recombinant DNA technology with virology and immunology to deliver a therapeutic gene into a target cell.[1] (Recombinant DNA technology, also known as genetic engineering, is the process of combining DNA from different species to create organisms with new traits or capabilities.) The three key elements of gene therapy are the accurate delivery of a therapeutic gene to the target cell, the successful expression of the gene, and the lack of adverse reactions.

[1] Richard A. Merrill and Gail H. Javitt, "Gene Therapy, Law and FDA Role In Regulation," in Thomas J. Murray and Maxwell J. Mehlman, eds., *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology* (John Wiley and Sons, Inc., 2000), p. 322.

Genome modification can take place either in somatic (non-reproductive) cells or in germ-line cells. Somatic-cell gene therapy has the potential to alter genetic function only in the individual whose genes have been altered and does not create changes that can be passed on to the next generation.[2] Germ-line genetic modification, in contrast, seeks to introduce new genetic material directly into eggs or sperm, into the precursor cells that give rise to eggs or sperm, or into early human embryos. As a result, germ-line modification has the potential to create permanent, heritable changes in the offspring and descendants of a treated individual.[3]

A key challenge for the success of gene therapy is integrating the new genetic material into the target cell, whether somatic or germ-line. Several methods have been developed for delivering genes: viral vectors, non-viral delivery systems such as cationic polymers or lipids,[4] and artificial chromosomes. A vector is a virus that has been modified to deliver a gene of interest to the target cell without itself causing harm to the recipient. Viruses are, by their nature, highly efficient at transferring genes into foreign organisms.[5] Three types of viral vectors have been used in human gene therapy research: retrovirus, adenovirus, and adeno-associated virus.[6] Despite advances in vector technology, scientists have found it difficult to deliver vectors into target cells in a way that is standardized or repeatable.[7] Viral vectors have also been associated with adverse reactions, including death, in research subjects.[8] Although non-viral delivery systems are safer, they are less efficient at transferring genes.[9] Accordingly, this case study focuses

[2] National Human Genome Research Institute, "Germline Gene Transfer," National Institutes of Health (2006), http://www.genome.gov/10004764.
[3] Susannah Baruch, Audrey Huang, Daryl Pritchard, Andrea Kalfoglou, Gail Javitt, Rick Borchelt, Joan Scott, and Kathy Hudson, "Human Germline Genetic Modification: Issues and Options for Policymakers," Genetics and Public Policy Center (2005) p. 13.
[4] T. Niidome and .I. Huang, "Gene Therapy Progress and Prospects: Nonviral Vectors," *Gene Therapy*, vol. 9 (2002), p. 1647.
[5] Ana P. Cotrim and Bruce J. Baum, "Gene Therapy: Some History, Applications, Problems, and Prospects," *Toxicologic Pathology*, vol. 36 (2008), p. 97.
[6] John Logan Black, "Genome Projects and Gene Therapy: Gateways to Next Generation Biological Weapons," *Military Medicine*, vol. 168, no. 11 (2003), p. 865.
[7] Anya Prince telephone interview with Dr. Leroy Walters, Joseph P. Kennedy Professor of Christian Ethics at Georgetown University, August 17, 2009.
[8] Cotrim and Baum, "Gene Therapy," p. 101.
[9] Ibid., p. 97.

on the use—and potential misuse—of viral vectors for the genetic modification of an organism.

History of the Technology

Although equivalent terms were used in academic discussions as early as 1960, the phrase "gene therapy" was coined in a published article in 1970.[10] Research on the genetic engineering of plants and animals began in the early 1970s and became a global, multibillion-dollar industry by the 1980s. In 1989, the first reported gene-therapy study in humans was performed on a child with an inherited metabolic disorder called severe adenosine deaminase deficiency.[11] This trial was considered a success because the genes were transferred safely to the child and her white blood cells began to produce the missing enzyme. But because the treated cells did not give rise to healthy new cells, as the researchers had hoped, the patient must continue to receive periodic gene therapy, supplemented with a medication that helps to maintain the level of the needed enzyme in her blood.[12]

Another common problem with gene therapy is that the recipient's immune system may detect the viral vector carrying the therapeutic gene and destroy it before it can reach the target cells. Researchers have also had difficulty developing gene therapies that can be used repeatedly in the same individual because the immune system attacks viral vectors it has seen before.[13] Because of these problems, the clinical benefit of gene therapy has not fulfilled its initial promise.[14] Although more than 900 clinical trials were conducted worldwide between 1989 and 2004,[15] the U.S. Food and Drug Administration (FDA) has yet to approve a gene therapy product for clinical use. The field also

[10] Leroy Walters, "Gene Therapy, Law, Recombinant DNA Advisory Committee (RAC)," in Thomas J. Murray and Maxwell J. Mehlman, eds., *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology* (John Wiley and Sons, Inc., 2000), p. 336.
[11] Cotrim and Baum, "Gene Therapy," p. 97.
[12] "Hope for Gene Therapy," Public Broadcasting Service, October 23, 2001, <http://www.pbs.org/saf/1202/features/genetherapy.htm>.
[13] Human Genome Program, "Gene Therapy," U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, June 11, 2009, <http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml>.
[14] Prince interview with Walters.
[15] Cotrim and Baum, "Gene Therapy," p. 97.

experienced a major setback in 1999 when a human subject, Jesse Gelsinger, died while participating in a clinical trial.[16] This event led to Congressional hearings, which called into question the adequacy of oversight of gene therapy research and led to the increased involvement of the FDA and the National Institutes of Health (NIH).

Although a few successful clinical trials of gene transfer have resulted in correct gene expression, many of the patients in these trials have experienced adverse reactions. In 2000, for example, scientists transferred curative genes to children with severe combined immunodeficiency disorder, using as a vector the Moloney murine leukemia virus. Although the gene transfer was successful, several of the treated children subsequently developed a rare form of leukemia because the viral vector activated another gene during its integration into the host DNA.[17]

Over the past two decades, gene therapy research has progressed from preclinical safety studies to clinical studies for more than 45 diseases.[18] As of June 2009, more than 960 human gene-transfer protocols were registered with the NIH.[19] Although scientists have not perfected the key parameters as quickly as was initially hoped, the field is advancing slowly. In 1990, gene-therapy advocates believed that new cures were right around the corner, but human genetic modification is still considered experimental in the United States.[20]

Utility of the Technology

As the term "therapy" implies, gene therapy is of significant research interest because it potentially could be used to cure, ameliorate, or prevent inherited diseases of

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[16] Ibid., p. 101.
[17] Ibid., p. 102.
[18] Eric Alton, Stefano Ferrari, and Uta Griesenbach, "Progress and Prospects: Gene Therapy Clinical Trials (Part 1)," *Gene Therapy*, vol. 14 (2007), p. 1439; Eric Alton, Stefano Ferrari, and Uta Griesenbach, "Progress and Prospects: Gene Therapy Clinical Trials (Part 2)," *Gene Therapy*, vol. 14 (2007), p. 1555; National Institutes of Health, "Human Gene Transfer Protocols," June 5, 2009, <http://oba.od.nih.gov/rdna/rdna_resources.html>.
[19] "Human Gene Transfer Protocols," National Institutes of Health, June 5, 2009, <http://oba.od.nih.gov/rdna/rdna_resources.html>.
[20] Human Genome Program, "Gene Therapy," U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, June 11, 2009, <http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml>.

metabolism or the immune system.[21] Germ-line genetic modification could allow the genetic change to be passed on to the patient's offspring, thereby eradicating an inherited disorder from future generations. While the primary focus of gene therapy research has been to alleviate disease,[22] some posit that in the future, gene therapy could be used to "enhance" human characteristics by conferring socially desirable traits such as height or intelligence, or to improve health by conferring resistance to infectious agents.[23] In some instances, it may be difficult to distinguish therapeutic applications from those undertaken for enhancement because they fall along a continuum.[24] Despite this somewhat blurry line, however, genetic enhancement raises more ethical and social concerns than does gene therapy.[25]

Potential for Misuse

To be effective, gene therapy will require additional technological advances, such as improved gene delivery and reliable gene expression in the targeted cells. Assuming that these advances materialize, the potential for misuse could arise either intentionally or inadvertently. A study in 1997 by the JASONs, a group of academic scientists who perform studies for the U.S. Department of Defense, reported six ways that genetic engineering could be used to create "enhanced" biological weapons, including the use of gene-therapy vectors.[26] One analyst has noted that if vector technology is perfected, viral vectors could be used to transmit harmful genes into a target population.[27] Alternatively, viral vectors might be turned into "stealth viruses" that could be introduced surreptitiously into the genetic material of the host, where they would remain dormant for

[21] Baruch et al., "Human Germline Genetic Modification," p. 13.
[22] M. Kiuru and R. G. Crystal, "Progress and Prospects: Gene Therapy for Performance and Appearance Enhancement," *Gene Therapy*, vol. 15 (2008), p. 329.
[23] Baruch et al., "Human Germline Genetic Modification," p. 13.
[24] Kiuru and Crystal, "Progress and Prospects," p. 330.
[25] Ibid.; Baruch et al., "Human Germline Genetic Modification," p. 14.
[26] Steven M. Block, "Living Nightmares: Biological Threats Enabled by Molecular Biology," in Abraham D. Sofaer, George D. Wilson, and Sidney D. Drell, eds., *The New Terror: Facing the Threat of Biological and Chemical Weapons* (Stanford, CA: Hoover Institution Press, 1999), p. 17.
[27] Col. Michael J. Ainscough, "Next Generation Bioweapons: The Technology of Genetic Engineering Applied to Biowarfare and Bioterrorism," *Counterproliferation Paper No. 14* (Maxwell Air Force Base, AL: U.S. Air Force Counterproliferation Center, April 2002), p. 21.

an extended period of time before causing disease. (A naturally-occurring example of a stealth virus is the herpes virus.) A malicious actor might even threaten to activate a stealth virus with an external signal if his demands were not met.[28] It is unclear, however, what the activating signal might be.[29]

It would also be technically difficult for a would-be bioterrorist to introduce a stealth virus surreptitiously into the target population without being detected and then activate the virus at a later time. Even if a "stealth" viral vector was employed, the fraction of the exposed population that suffers from impaired immune function might develop symptoms of the infection immediately.[30] It is also possible that some individuals might be exposed to the triggering agent naturally and would therefore begin to display symptoms before the malicious actor could activate the latent virus in the rest of the infected population.[31]

Ease of Misuse (Explicit and Tacit Knowledge)

In order to perform gene transfer, an individual must have a relatively sophisticated background in biomedical science. Dr. Leroy Walters, the Joseph P. Kennedy Professor of Christian Ethics at Georgetown University, believes that it is implausible that a malicious actor could perform gene transfer outside an established laboratory and without significant knowledge and training.[32] Biological warfare involving stealth viruses would also be highly complex because it would require exposing the targeted population twice (first to the virus and then to the activating signal), whereas standard biological warfare agents must infect the targeted population only once.[33] The development of a stealth viral weapon would require a multidisciplinary team, extensive

[28] James B. Petro, Theodore R. Plasse, and Jack A. McNulty, "Biotechnology: Impact on Biological Warfare and Biodefense," *Biosecurity and Bioterrorism*, vol. 1, no. 3 (2003), p. 164.
[29] Block, "Living Nightmares," p. 64.
[30] Black, "Genome Projects and Gene Therapy," p. 869.
[31] Ibid.
[32] Prince interview with Walters.
[33] Black, "Genome Projects and Gene Therapy," p. 868.

funding, and a good deal of tacit knowledge, making misuse by a state more likely than by a non-state actor.[34]

Accessibility of the Technology

The most difficult step in using gene therapy for biowarfare purposes would be to devise an effective means of delivering a harmful gene to the target population. In the future, viral vectors could potentially serve this function with "exquisite specificity."[35] With current technology, however, it would be very difficult for a terrorist or some other malicious actor to transfer genes surreptitiously. Today's researchers take blood from a subject, use a viral vector to transfer therapeutic genes into white blood cells, and then infuse the blood back into the patient.[36] If it were possible to deliver viral vectors in aerosol form, this capability would greatly increase the potential for misuse.[37] But although scientists have attempted to deliver adenoviruses into a patient's lungs by the aerosol route, this technique has not yet succeeded in clinical trials.[38]

Imminence and Magnitude of Risk

Although some scientists and policymakers have recognized the possibility that gene therapy could be misused for harmful purposes, they do not see it as an imminent risk. A common view is that natural pathogens are sufficiently deadly, making it unlikely that a terrorist group would undertake the complex process of engineering a viral vector as a weapon.[39] Colonel Michael Ainscough argues that while the risk of a terrorist attack involving gene transfer is low, the possibility should be taken seriously because the consequences could be severe.[40]

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[34] Anya Prince telephone interview with Dr. Gigi Kwik Gronvall, Senior Associate, Center for Biosecurity, University of Pittsburgh Medical Center, September 3, 2009.
[35] Petro, "Biotechnology," p. 164.
[36] Prince interview with Gronvall.
[37] Block, "Living Nightmares," p. 62.
[38] Prince interview with Walters.
[39] Petro et al., "Biotechnology," p. 162.
[40] Ainscough, "Next Generation Bioweapons," p. 28.

Awareness of Dual-Use Potential

A few scientists have pointed to the potential misuse of "stealth" viral vectors, but this topic has not been widely discussed in the academic literature.

Characteristics of the Technology Relevant to Governance

Embodiment. Gene therapy relies primarily on intangible information and know-how.

Maturity. Despite large increases in the level of research and investment in gene therapy, the field has not progressed beyond the clinical testing stage.[41] In addition, serious adverse events, such as Gelsinger's death in 1999, have raised persistent safety concerns.[42]

Convergence. Gene therapy research draws on three different disciplines: recombinant DNA technology, virology, and immunology.

Rate of advance. Researchers have made significant advances in understanding the strengths and weaknesses of particular gene-transfer vectors and which ones are appropriate for treating specific diseases.[43] Despite this progress, however, human gene therapy is still considered experimental.[44] More study is needed of the immune responses to vectors and transferred genes before such techniques can be employed clinically.[45]

International diffusion. As of 2007, 28 countries had conducted clinical trials of gene transfer.[46] Approximately 63 percent of all gene therapy trials have been performed in the United States and 94 percent in North America and Europe. The few developing

[41] Cotrim and Baum, "Gene Therapy," p. 101.
[42] Human Genome Program, "Gene Therapy," U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, June 11, 2009, <http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml>.
[43] Alton, Ferrari, and Griesenbach, "Progress and Prospects (Part 1)," p. 1439.
[44] Human Genome Program, "Gene Therapy," U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research, June 11, 2009, <http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml>.
[45] Ibid.
[46] The countries in question are: Australia, Austria, Belgium, Canada, China, Czech Republic, Denmark, Egypt, Finland, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Norway, Poland, Russia, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, the United Kingdom, and the United States. See Michael L. Edelstein, "Gene Therapy Clinical Trials Worldwide," *Journal of Gene Medicine* (March 2009), <http://www.wiley.co.uk/genmed/clinical/>.

countries that have conducted clinical trials have performed only one or two to date.[47] About 65 percent of the gene-therapy trials have targeted cancers.[48] Dr. Walters believes that because cancer affects a small minority of the population, only advanced industrialized countries have the luxury to research a technology that could benefit such a limited number of people.[49] But Dr. Gigi Kwik Gronvall, a senior associate with the Center for Biosecurity at the University of Pittsburgh Medical Center, contends that the two main factors affecting the rate of diffusion of gene therapy are its high cost and the nascent status of the technology.[50] As gene-therapy research advances, she argues, the cost will decline and a greater number of countries and actors will gain access to it.

Susceptibility to Governance

As a technology that is already heavily regulated on health and safety grounds, gene therapy has shown itself to be susceptible to governance. In principle, it would be fairly easy and low-cost to modify the existing regulatory framework by adding rules to prevent the deliberate misuse of gene transfer. Dr. Gronvall notes, however, that it is difficult to create regulations when one does not know the identity of the actors of concern and what types of harmful applications they might pursue.[51] At present, the technological hurdles involved make deliberate misuse by state or non-state actors unlikely. Although technical breakthroughs may occur in the future, regulators cannot predict what they might be. Given these unknowns, increased regulation would tend to hamper legitimate research while doing little to reduce the risk of misuse.[52]

Past and Current Approaches to Governance

To date, U.S. government regulation and oversight of gene therapy have focused almost exclusively on biosafety issues. Gene therapy was overseen initially by the

[47] Ibid.
[48] Ibid.
[49] Prince interview with Walters.
[50] Prince interview with Gronvall.
[51] Ibid.
[52] Ibid.

Recombinant DNA Advisory Committee (RAC), which the NIH established in 1974 to ensure the safety of genetic-engineering technology.[53] During the 1980s, the RAC created a Human Gene Therapy Subcommittee (HGTS), but when gene therapy began to involve human clinical trials, the FDA asserted regulatory authority.[54] During this period, the relationship between the RAC and the FDA grew strained as both bodies claimed jurisdiction over gene therapy but took different approaches to regulation.[55] A major point of contention was the RAC's emphasis on public review, which conflicted with the FDA's preference for confidentiality.[56] In the mid-1980s, the FDA was assigned the lead role for reviewing clinical gene-therapy studies, but tensions with the RAC persisted.[57]

Following the death of Jesse Gelsinger in 1999, the NIH and the FDA intensified their oversight of gene therapy. Investigations by both agencies determined that clinical trials of gene therapy throughout the country had not been in compliance with federal regulations governing research on human subjects, and that adverse reactions had not been properly reported to federal authorities.[58] As a result of these revelations, the NIH and the FDA launched a new program called the Gene Therapy Clinical Trial Monitoring Plan, which sought to ensure that adverse reactions during clinical trials would be reported.[59] In addition, the FDA instituted random inspections of ongoing clinical trials[60] and modified the informed-consent documents to give research subjects a better understanding of the risks of participation.[61] Since 2000, federal regulations have required that before an Institutional Biosafety Committee can grant final approval for a

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[53] Theodore Friedmann, Philip Noguchi, and Claudia Mickelson, "The Evolution of Public Review and Oversight Mechanisms in Human Gene Transfer Research: Joint Roles of the FDA and NIH," *Current Opinion in Biotechnology*, vol. 12, no. 3 (June 2001), p. 304.
[54] Merrill and Javitt, "Gene Therapy, Law and FDA Role in Regulation," p. 322.
[55] Evan Diamond, "Reverse-FOIA Limitations on Agency Actions to Disclose Human Gene Therapy Clinical Trial Data," *Food and Drug Law Journal*, vol. 63 (2008), p. 330; Merrill and Javitt, "Gene Therapy, Law and FDA Role in Regulation," p. 322.
[56] Diamond, "Reverse-FOIA Limitations," p. 330; Prince interview with Walters.
[57] Friedmann et al., "The Evolution of Public Review," p. 304.
[58] Ibid., p. 305.
[59] Larry Thompson, "Human Gene Therapy: Harsh Lessons, High Hopes," *FDA Consumer* (September 2000), p. 2.
[60] Ibid.
[61] NIH Report, "Assessment of Adenoviral Vector Safety and Toxicity: Report of the National Institutes of Health Recombinant DNA Advisory Committee," *Human Gene Therapy*, vol. 13 (January 1, 2002), p. 8.

new gene-therapy protocol, the RAC must either agree to review the protocol or determine that a review is unnecessary.[62] The RAC also provides a forum for public discussion of ethical and safety issues arising from novel gene-therapy protocols.[63]

Today, the FDA regulates all gene-therapy clinical trials performed in the United States, as well as those conducted abroad if the resulting data will be included in a licensing application to the agency. Sponsors seeking to conduct a clinical trial must submit an Investigational New Drug (IND) application.[64] The FDA can reject the application if it determines that the potential risks outweigh the potential benefits, or for other reasons. As a condition of obtaining an IND, the sponsors must submit the research protocol to an Institutional Review Board (IRB) that reviews experiments involving human subjects and comply with all FDA regulations governing such research.[65]

Although the NIH does not have direct regulatory authority over gene therapy protocols, the RAC still provides some oversight of federally funded research.[66] In addition to a general RAC review, federally-funded gene therapy research protocols must be registered with the NIH, which maintains a publicly accessible database of information about clinical trials and adverse reactions.[67] Privately-funded researchers can submit their protocols to the NIH and the RAC on a voluntary basis. Also, under the NIH guidelines, an Institutional Biosafety Committee (IBC) must approve federally funded clinical trials of gene therapy.[68]

Options for Future Governance

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[62] Kenneth Cornetta and Franklin O. Smith, "Regulatory Issues for Clinical Gene Therapy Trials," *Human Gene Therapy*, vol. 13 (July 1, 2002), p. 1145.
[63] Office of Biotechnology Activities, National Institutes of Health, "About Recombinant DNA Advisory Committee (RAC)," <http://oba.od.nih.gov/rdna_rac/rac_about.html>.
[64] Leroy Walters, "The Oversight of Human Gene Transfer Research," *Kennedy Institute of Ethics Journal*, vol. 10, no. 2 (2000), p. 171; Cotrim and Baum, "Gene Therapy," p. 101.
[65] 21 C.F.R. Part 50.
[66] Diamond, "Reverse-FOIA Limitations," p. 332.
[67] Office of Biotechnology Activities, National Institutes of Health, "About Recombinant DNA Advisory Committee (RAC)."
[68] Stacy M. Okutani, "Federal Regulation of Scientific Research," Center for International and Security Studies at Maryland, University of Maryland (August 2001), p. 8 <www.cissm.umd.edu/papers/display.php?id=361>.

Because gene therapy is already highly regulated, one way to prevent misuse for hostile purposes would be to rely on the existing regulatory framework, including FDA oversight of clinical trials and additional NIH oversight of federally funded research. Nevertheless, this approach has two drawbacks. First, it is unlikely that malicious actors would submit their research for review, enabling them to evade government oversight. Second, the NIH Guidelines for recombinant DNA research focus on minimizing the biosafety risks associated with the *unintended* creation of harmful recombinant organisms, so additional governance measures would be needed to prevent the *deliberate* use of gene transfers for malign purposes.[69]

Education and training. Most life scientists have had little direct exposure to the issues of biological weapons and bioterrorism and tend not to consider the misuse potential of their own research.[70] British biosecurity expert Brian Rappert has called for greater awareness of dual-use issues on the part of scientists, while noting the difficulty of achieving it.[71] Dr. Walters believes that educating researchers about dual-use issues can play a useful role in preventing the misuse of gene-transfer technology.[72] He suggests that educators stress the moral obligation of whistleblowing if a scientist learns or suspects that a fellow researcher is engaging in foul play. This type of self-regulation could potentially be more effective than stronger FDA oversight.[73] Dr. Gronvall worries, however, that focusing prematurely on the dual-use potential of gene therapy will cause the public to perceive it as sinister, hampering beneficial research in this field.[74]

Apply review procedures to private industry. A 2003 report by the National Research Council (NRC) suggested that the RAC review process be expanded to cover all relevant research institutions, not simply those under the direct purview of the NIH.[75]

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[69] National Research Council of the National Academies, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, *Biotechnology Research in an Age of Terrorism: Confronting the Dual Use Dilemma* (Washington, DC: National Academies Press, 2003), p. vii.
[70] Ibid., p. 4.
[71] Brian Rappert, "Biological Weapons, Genetics, and Social Analysis: Emerging Responses, Emerging Issues – Part II," *New Genetics and Society*, vol. 22, no. 3 (December 2003), p. 304.
[72] Prince interview with Walters.
[73] Ibid.
[74] Prince interview with Gronvall.
[75] National Research Council, *Biotechnology Research in an Age of Terrorism*, p. 6.

At present, scientists whose work is supported entirely by private funds do not have to submit their research protocols to the RAC, although they are encouraged to do so voluntarily.[76] Nevertheless, scientists funded by private sources must undergo RAC review if the research sponsor, or the institution where the research takes place, receives any NIH money.[77] In addition, if the research utilizes recombinant DNA techniques that were developed with NIH funds, and the institution that developed those techniques is a participant in the project, the research protocol must be submitted to the RAC even if it is privately funded.[78] Thus, given the broad coverage that already exists under current oversight mechanisms, requiring all privately funded researchers to submit gene-transfer protocols for RAC approval might not significantly increase the number of experiments under review. This approach would also fail to address the concern that actors with malicious intent could simply ignore the requirement to report their research to the FDA or the NIH.[79]

Increased communication. The Third Cabo Gene Therapy Focus Panel, which discussed the contributions to biodefense of gene therapy and viral vectors, noted the importance of communication among academic researchers, the intelligence community, and the military.[80] To strengthen these communication channels, Col. John Logan Black has proposed the development of a comprehensive, continuously updated database containing the history, genetic sequence, and physical characteristics of all viral vectors used in gene therapy. Black has also called for accelerated research on detection systems for viral vectors.[81]

Limits on scientific publication. The U.S. National Academies report *Biotechnology Research in an Age of Terrorism* concluded that pre-publication review is an essential element of protection against the misuse of dual-use research in the life

[76] "Frequently Asked Questions (FAQs) about the NIH Review Process for Human Gene Transfer Trials," Office of Biotechnology Activities, NIH.
[77] Ibid.
[78] Ibid.
[79] Prince interview with Walters.
[80] Robert M. Frederickson, "The Third Cabo Gene Therapy Focus Panel: On the Offensive for Biodefense," *Molecular Therapy*, vol. 8, no. 2 (August 2003), p. 178.
[81] Black, "Genome Projects and Gene Therapy," p. 869.

sciences, although it recommended that such reviews be based on voluntary self-governance by scientific journals rather than on formal government regulation.[82] Given the current low risk that gene therapy could be misused, however, limiting the publication of beneficial results would hamper scientific progress more than it would prevent terrorists from learning how to exploit the technology for harmful purposes.[83]

Conclusions

To date, efforts to regulate gene therapy have focused on concerns about patient safety rather than dual-use, and the focus of governance measures has been almost entirely domestic rather than international. Although the deliberate misuse of gene therapy for harmful purposes is theoretically possible, it remains unlikely because of major technical hurdles, which would require a high level of scientific expertise to overcome. Until more is understood about gene therapy's potential for misuse, increased regulation is not recommended because it would tend to hinder beneficial research without effectively blocking malicious applications. Priority should therefore be given to the governance of dual-use biotechnologies that pose a more imminent threat. Nevertheless, policymakers should monitor the field of gene therapy and be prepared to intervene should the risk of deliberate misuse become more likely.

[82] National Research Council, *Biotechnology Research in an Age of Terrorism*, p. 6.
[83] Prince interview with Walters.

Chapter 15: Personal Genomics

Nishal Mohan

Thanks to advances in DNA sequencing technology and the discovery of genes associated with common diseases, the era of personalized medicine has arrived. Genetic information can be used for disease prevention, early detection, and targeted treatment that tailors drug regimens to a patient's genetic makeup. Given these potential benefits, the number of companies providing direct-to-consumer (DTC) genetic testing services is expanding rapidly. At present, the small pool of credible data on human genome epidemiology limits the usefulness of personal genomics for diagnosing and preventing diseases, but as the price of the service decreases, the amount of human genetic data will grow exponentially. When high-throughput DNA sequencing reaches a level of cost and accuracy at which the routine sequencing of entire human genomes becomes feasible, it may have a revolutionary impact on clinical medicine.

Personal genomics also has potential dual-use implications. If human genetic information is made publicly available, systematic "data-mining" could lead to the identification of genetic similarities and differences among ethnic groups. Conceivably, this information might be exploited to develop biological or chemical agents that can harm specific populations in a selective manner. Because the overall data set is still small, however, scientists have not yet identified genetic traits that could be used for discrimination and targeting purposes. Accordingly, the dual-use implications of personal genomics do not yet warrant the development of specific governance measures.

Overview of the Technology

The major technological advances driving the field of personalized medicine are in the area of genotyping, or determining specific genetic differences among individuals. One approach to personal genotyping involves the identification of single-nucleotide polymorphisms (SNPs, pronounced "snips"), which are single substitutions, deletions, or insertions in the sequence of DNA nucleotide "letters" that make up the human genome. These subtle changes distinguish one individual from other members of the species and may affect the body's susceptibility to disease

or its response to infections and drugs.[1] To identify SNPs, a sample of DNA from an individual's cells is extracted, purified, and exposed to a "DNA chip," a silicon microarray to which hundreds of thousands of single-stranded DNA fragments carrying known SNPs have been attached. Through a process called hybridization, fragments of the individual's DNA bind to complementary DNA sequences bound to the chip, making it possible to determine which SNPs are present.[2] [3] [4] As research identifies additional SNPs, more complex DNA chips will become available for purchase. The second approach to personal genotyping involves determining the whole or partial sequence of an individual's genome with an automated DNA sequencer. Although this technique is more time-consuming and costly, it offers the advantage that it can identify multiple, sequential, or rare SNPs associated with disease risk.

Both approaches to personal genotyping have certain limitations. SNP chips are still expensive and not easily reusable, and the sequencing and annotation of an entire human genome currently costs approximately $250,000. Because of rapid technological improvements, however, the cost of whole-genome sequencing is declining rapidly. According to one estimate, the cost in 2011 is expected to drop to between $5,000 and $10,000.[5]

Regardless of the state of DNA sequencing technology, personal genotypes are only as useful as the available scientific data supporting a link between SNPs and specific diseases or drug reactions. Drawing on published scientific research, public and private databases are now available that make such linkages.[6] [7] [8] [9] In addition, using an individual's full or partial genomic

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[1] J.Y. Hehir-Kwa, M. Egmont-Petersen, I.M. Janssen, et al., "Genome-wide copy number profiling on high-density bacterial artificial chromosomes, single-nucleotide polymorphisms, and oligonucleotide microarrays: a platform comparison based on statistical power analysis," *DNA Research*, vol. 14, no. 1 (February 28, 2007), pp. 1-11.
[2] P. Yue, J. Moult, "Identification and analysis of deleterious human SNPs," *Journal of Molecular Biology*, vol. 356, no. 5 (March 2006), pp. 1263–74.
[3] U. Väli, M. Brandstrom, M. Johansson, et al., "Insertion-deletion polymorphisms as genetic markers in natural populations," *BMC Genetics*, vol. 9 (January 22, 2008), p. 8.
[4] A. Vignal, D. Milan, M. SanCristobal, et al., "A review on SNP and other types of molecular markers and their use in animal genetics," *Genetics, Selection, Evolution*, vol. 34, no. 3 (May-June 2002), pp. 275-305.
[5] Nicholas Wade, "A Decade Later, Genetic Map Yields Few New Cures," *New York Times*, June 12, 2010, p. A1.
[6] D. L. Wheeler, T. Barrett, D. A. Benson, et al., "Database resources of the National Center for Biotechnology Information," *Nucleic Acids Research*, vol. 35 (January 2007), pp. D5–12.
[7] Michael Cariaso, "SNPedia: A Wiki for Personal Genomics," *Bio-IT World* (December-January 2007), pp. 12-17.
[8] G. A. Thorisson, O. Lancaster, R. C. Free, R. K. Hastings, P. Sarmath, D. Dash, S. K. Brahmachari, A. J. Brookes, "HGVbaseG2P: A central genetic association database," *Nucleic Acids Research*, vol. 37 (January 2009), pp. D797-802.
[9] A. Hamosh, A.F. Scott, J.S. Amberger, et al., "Online Mendelian inheritance in man (OMIM), a knowledge base of human genes and genetic disorders," *Nucleic Acids Research*, vol. 33 (2005), p. D514-D517.

sequence, bioinformatics software tools are commercially available that can identify known SNPs and the associated disease risks.

History of the Technology

In 2003, after 13 years of effort by scientists worldwide, the Human Genome Project completed the sequence of the 3 billion chemical base pairs that make up the human genome. That sequence has since been used to advance medicine, human biology, and the knowledge of human origins. Although decoding the human genome cost an estimated $2.7 billion, rapid advances in high-throughput DNA sequencing have reduced the cost of full-genome sequencing by several orders of magnitude.

In 2006, Harvard Medical School geneticist George Church founded the Personal Genomics Project, which is developing "a broad vision for how personal genomes may be used to improve the understanding and management of human health and disease."[10] The project has the long-term goal of sequencing the genomes of some 100,000 persons. In 2007, taking advantage of improved DNA sequencing technology, start-up companies began offering direct-to-customer (DTC) personal genomics services. Commercial personal genomics firms such as 23andMe (Mountain View, CA) and Navigenics (Redwood Shores, CA) genotype the SNPs in an individual's genome with known links to disease and sell this information to the customer.[11] An Iceland-based personal genomics company, DeCode Genetics, filed for bankruptcy protection in 2009.

Utility of the Technology

One of the major benefits of personal genomics is its use in preventative medicine to assess an individual's risk of developing certain diseases and for early detection and intervention.[12] At present, family history is widely used in disease diagnosis, but combining it with personal genomics provides a more accurate and complete means of predicting disease risk. Determining an individual's predisposition to a particular disease can suggest lifestyle changes

[10] Personal Genome Project, <http://www.personalgenomes.org/>.
[11] Erick Check Hayden, "Personal genomes go mainstream," *Nature*, vol. 450 (October 30, 2007), p. 11.
[12] M. J. Khoury, C. McBride, S. D. Schully, et al, "The Scientific foundation for personal genomics: recommendations from a National Institutes of Health-Centers for Disease Control and Prevention multidisciplinary workshop," *Genetic Medicine*, vol. 8 (August 11, 2009), pp. 559-567.

that reduce the odds that it will develop. Personal genetic information can also help physicians select the best drugs to treat their patients for maximum effectiveness, while minimizing the risk of harmful side effects. This application of personal genomics is particularly powerful because adverse drug reactions cause approximately 100,000 deaths each year in the United States alone.[13]

Because the human genomics data-set is currently limited, much more information is needed on the relationships between specific genes and disease. An international research consortium called The 1000 Genomes Project plans to sequence the genomes of over a thousand people around the world in order to create a detailed, publically available map of human genetic variation and its relevance to health and disease.[14] Another resource is SNPedia, an open-source database that maps the effects of genetic variation, drawing on information from peer-reviewed scientific publications. [15] The SNPedia database can be accessed with Promethease, a free informatics tool that compares and analyzes personal genomic sequences.[16] As more SNPs are identified, it will become increasingly possible to determine an individual's predisposition to certain diseases and drug-response patterns.

The National Human Genome Research Institute of the U.S. National Institutes of Health has projected that by 2014, it will be possible to sequence an entire human genome for only about $1,000—the cost threshold at which genome sequencing could start to become a routine part of medical practice.[17] Several next-generation DNA sequencing machines are currently under development. The IBM Corporation, for example, recently joined the race with a new technology that it expects will eventually permit the sequencing of an entire human genome in a matter of hours.[18] Another important factor is accuracy. For clinical genetics applications, DNA sequences need to be decoded with an accuracy of only one error per every 10,000 to 100,000 DNA units.[19] By the end of 2009, only seven human genomes had been sequenced in their

[13] J. Lazarou, B. H. Pomeranz, and P. N. Corey, "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies," *Journal of the American Medical Association*, vol. 279 (1998), pp.1200-1205.
[14] 1000 Genomes, <http://www.1000genomes.org/page.php>.
[15] SNPedia, <http://www.snpedia.com/index.php/SNPedia>.
[16] Promethease, <http://www.snpedia.com/index.php/Promethease>.
[17] "NIH promises funds for cheaper DNA sequencing," *Nature*, vol. 454, (2008), p1041.
[18] "I.B.M. Joins Pursuit of $1,000 Personal Genome," *New York Times*, October 6, 2009, p. D2.
[19] Nicholas Wade, "Cost of Decoding a Genome is Lowered," *New York Times*, August 11, 2009, http://www.nytimes.com/2009/08/11/science/11gene.html

entirety, but improved technology and declining costs have created the conditions for this number to increase dramatically in the near future.[20]

Potential for Misuse

Information generated by personal genomics techniques can be a powerful tool for predicting adverse drug responses in individuals, leading to changes in pharmacotherapy that have saved lives. [21] [22] [23] In principle, however, it may be possible to exploit pharmacogenomics to identify and develop drugs that cause significant harm to a subset of the population because of its genetic vulnerabilities. Although no one has yet tried to exploit personal genomics for hostile purposes, the theoretical possibility exists. For example, in February 2010 an international team announced that it had sequenced the genomes of South African Archbishop Desmond Tutu and an indigenous bushman from Namibia as part of a program designed to enable researchers and drug companies to bring the benefits of personalized medicine to people in developing countries. This analysis identified 1.3 million genetic variations that had not previously been identified, potentially making it possible to tailor drug therapies for people living in southern Africa. Certain drugs for treating AIDS, for example, are less effective in Africans than in Europeans. Yet critics of the research, such as the ETC Group in Canada, suggested that the information might be used to create drugs for profit or even to design biological weapons capable of targeting specific ethnic groups.[24]

Ease of Misuse (Explicit and Tacit Knowledge)

At present, identifying the pharmacogenetic vulnerabilities of a particular population would be difficult and prohibitively expensive, for a number of reasons. First, DNA samples would have to be collected from the selected population, and a great deal of time and effort would be required to generate personal genomics data using DNA sequencing technologies.

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[20] Ibid.
[21] P. C. Ng, Q. Zhao, S. Levy, et al, "Individual genomes instead of race for personalized medicine," *Clinical Pharmacology Theory*, vol. 85, no. 2 (February 2009), pp. 306-309.
[22] D. Ge, J. Fellay, A. J. Thompson, et al, "Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance," *Nature*, vol. 461, (2009), p. 399-401.
[23] S. J. Gardiner and E. J. Begg, "Pharmacogenetics, drug-metabolizing enzymes, and clinical practice," *Pharmacology Review*, vol. 58 (2006), pp. 521-590.
[24] Rob Stein, "Genomes of Archbishop Tutu, Bushman decoded in developing-world health push," *Washington Post*, February 18, 2010.

Second, few verified correlations exist between genetics and adverse drug effects, and none of them could easily be exploited to cause large-scale harm. Even when such correlations have been identified, the expertise needed to translate genetic data into harmful drugs would require the skills and tacit knowledge of a multidisciplinary team of experts. Although such an undertaking might be accomplished by countries with a reasonably sophisticated biotechnology industry, it is clearly beyond the capacity of terrorist organizations. Moreover, even in the unlikely event that such a technology could be developed, producing and delivering a genetically targetable biochemical weapon would probably depend on several other technologies, such as nanotechnology, that are themselves at an early stage of development.

Accessibility of the Technology

DNA sequencing technology for the identification of SNPs is available to most biological research laboratories, either from in-house facilities or commercial suppliers. DNA sequencing machines have been developed and marketed by large biotechnology companies in Europe and North America, such as Roche, Illumina, and Applied Biosystems, Inc. The use of these machines relies on standardized protocols that can be performed by trained technicians who lack an advanced degree in molecular biology. To date, the major factor limiting the spread of the DNA sequencing technology has been the expense of the machines. With the aggressive push in recent years to reduce costs, however, it is only a matter of time before DNA sequencers become more affordable and thus more available to people who want them. Private firms in various parts of the world also provide commercial sequencing and genotyping services for individual customers or institutions that lack their own hardware.

Although some genomic databases are currently available free of charge while others are controlled by private companies, few if any governmental regulations address the privacy and availability of genetic data. In principle, databases from direct-to-consumer (DTC) companies could be sold to the highest bidder. As concerns grow about the sensitivity of personal genetic data, however, public databases may cease to be updated and may even disappear. Recent U.S. and European legislation limiting the use and availability of personal genomic data will probably have a similar effect on the availability of SNP databases.

Imminence and Magnitude of Risk

Given the current high cost of personal genomic technologies and the limited number of correlations between genetic variations and disease, personal genomics technology does not pose an imminent threat of misuse. Even if terrorists or criminals were to gain access to a large database of human genetic data and identified a drug likely to cause harm in a subset of the population, they would have to overcome the major technical obstacles involved in creating genetically targetable weapon, which would need to be mass-produced and mated with a delivery system for effective dissemination. Moreover, in the unlikely event that these technical hurdles could be overcome, the genetically vulnerable population would not necessarily be concentrated in a single geographic area, making it difficult to harm a large number of people in a selective manner.[25]

Awareness of Dual-Use Potential

To date, little attention has been given to the possibility that personalized medicine could be misused to cause physical harm, and certainly not in the form of targeted biochemical weapons. Instead, government policymakers and outside researchers have been concerned primarily with the protection of privacy rights, the risk that individuals could interpret genetic information incorrectly, and the potential misuse of personal genomic information for discrimination by employers and service providers. More recently, the scientific community has noted the potential harm to customers of DTC companies that could result from inaccuracies and false-positives in genetic risk predictions.[26] [27]

Characteristics of the Technology Relevant to Governance

Embodiment. Personal genomics is primarily an intangible technology based on stored genomic sequences stored in large databases. Of course, DNA sequencing hardware is an enabling technology, but it is advancing independent of the field of personal genomics.

Maturity. The technology is available from commercial, direct-to-customer suppliers. Today the chief limitation on the usefulness of personal genomics is the lack of accurate

[25] Ng et al., "Individual genomes instead of race for personalized medicine," pp. 306-309.
[26] NIH Background Fact Sheet on GWAS Policy Update, http://grants.nih.gov/grants/gwas/background_fact_sheet_20080828.pdf.
[27] P. C. Ng, S. S. Murray, S. Levy, "An agenda for personalized medicine," *Nature*, vol. 461 (2009), p724-726

databases of known SNPs and their association with disease risk. Because only a few such databases are publically available, the technology is still evolving and remains somewhat unpredictable.

Convergence. To achieve its potential to enhance human health, personal genomics requires the systematic integration of DNA sequencing technology, epidemiology, systems biology, bioinformatics, and clinical biology.

Rate of advance. Since 2007, the speed, accuracy, and cost parameters of DNA sequencing have all improved exponentially, helping to drive the emergence of personal genomics.

International diffusion. Most DTC personal-genomics companies are based in North America and Europe but extend their services to other regions of the world.

Susceptibility to Governance

Governance of personal genomics is difficult because DNA sequencing technology is widely available commercially and plays a vital role in biomedical research in both academia and industry worldwide. It is too late to regulate the sale of DNA sequencers, which are widely available from commercial sources. Many for-profit personal genomics companies offer genetic data to anyone who can afford their services. Imposing strict controls on the use of data generated from personal genomics tests might impede efforts to identify correlations between genetic changes in a population and various diseases, thereby limiting the potential for misuse of this information. But stringent regulation would also hamper the potential benefits of using genomic data for the assessment of disease risk and personalized therapy.

Past and Present Approaches to Governance

In the mid-1990s, Congress recognized that advances in DNA sequencing technology would lead inevitably to the ability to sequence whole human genomes quickly and cheaply, and began to develop legislation to protect Americans against genetically based discrimination from employers and health insurance companies. The Genetics Information Nondiscrimination Act (GINA) was debate for 13 years before finally passing in 2008.[28] GINA prohibits insurance

[28] Genetic Information Nondiscrimination Act of 2008, Pub. L. no. 110-343 (October 3, 2008).

companies or other service providers from using genetic information to deny coverage or determine payment rates, and also makes it illegal for employers to purchase genetic information from third parties about current or prospective employees. Thanks to these protections, GINA will help the public to embrace personalized medicine without fear of discrimination. In 2008, for example, the U.S. National Institutes of Health removed its genomic data from the public domain for privacy reasons after it was shown that an individual could be identified from this seemingly anonymous pool.[29]

In the United Kingdom, the House of Lords Report on Genomic Medicine did not recommend legislation against genetic discrimination but advised that DTC genetic-testing companies adopt a unified code of conduct for assessing the medical utility of such services and the need for genetic counseling of customers.[30] Both the United States and the United Kingdom believe that personal genomics is evolving so rapidly and unpredictably that it would be premature to adopt specific regulations. Germany, in contrast, has taken a more restrictive approach to genetic testing and data in an effort to prevent misuse.[31] The Human Genetic Examination Act, which went into effect on February 1, 2010, permits genetic testing only when performed by a doctor with adequate informed consent of the patient, and imposes specific penalties for violations. The German legislation also limits genetic testing on fetuses for medical reasons, prohibits genetic testing on individuals for diseases that appear later in life, and prevents insurance companies and employers from demanding or using existing genetic information. As a result, the Human Genetic Examination Act has indirectly made the services of DTC personal-genomics companies illegal in Germany. The German case is anomalous, however.

Options for Future Governance

With the rapid production of genomic data, the increasing availability of DTC genomic services, and the continuing decline in sequencing costs, now is the time to start thinking about oversight mechanisms and regulations to prevent the deliberate misuse of personal genomics. It is clearly too late to regulate DNA sequencing technology, which has become pervasive. One strategy for governance would be to add regulatory groups for personal genomics to existing

[29] E. A. Zerhouni and E. G. Nabel, "Protecting Aggregate Genomic Data," *Science*, vol. 322, no. 5898 (October 3, 2008), p. 44.
[30] House of Lords, HL Paper 107-I, July 7, 2009.
[31] German Federal Parliament (Bundestag), "Human Genetic Examination Act," April 24, 2009.

oversight committees such as the Advisory Committee on Genetics in the United States. A more direct approach would be for Congress to pass legislation regulating personal genomics testing and data. Such legislation would be similar to the regulations governing the privacy of medical records: it would clearly define the ownership of genetic data and its acceptable uses, protect the privacy of an individual's genetic data, and require stricter security and screening procedures for submitting samples to DTC companies and similar institutions. Any such legislation should also address privacy issues related to the DNA sequencing of material obtained without the permission of the owner.

Conclusions

The age of personal genomics has arrived, and personalized drug therapy is poised to be the next step in the evolution of medicine. Although the potential benefits of personal genomics are clear, the main downside risk at present is that personal genetic data could be used for genetic discrimination. Both the United States and Germany have passed legislation to address this concern. Far more speculative is the possibility of using pharmacogenetic data to create "ethnic weapons," such as biochemical agents that would selectively cause physical harm to a genetic subgroup of the population. Because such a scenario is extremely unlikely, however, the costs of preventive measures would outweigh the benefits.

Chapter 16: Rational Vaccine Design

Nancy Connell

The introduction of antimicrobial drugs initially produced dramatic victories against infectious diseases, but most bacteria and many viruses and parasites can develop resistance mechanisms that render these drugs ineffective. As a result, vaccination remains an efficient and cost-effective approach for preventing infectious diseases and controlling their spread. Although early vaccines were developed largely by trial and error, today the field of vaccinology seeks to harness insights into the operation of the human immune system to design vaccines that induce optimal immune responses. There is also a new emphasis on developing vaccines for the treatment of non-infectious diseases, such as autoimmune and neurological disorders, cancer, heart disease, allergies, and Alzheimer's disease.[1]

Rational vaccine design has a potential for misuse because discoveries in vaccine immunology might be combined with new delivery methods to yield lethal biological warfare agents. Although delivery technologies provide fertile ground for dual-use analysis, this case study focuses on the manipulation of the immune response. Because the potential for misuse of rational vaccine design is inseparable from its benefits, restricting this technology is not a practical option. Nevertheless, existing oversight mechanisms and "soft-law" governance measures could be adapted to mitigate the dual-use risks of new vaccine technologies.

Overview of the Technology

Vaccines have served for over two centuries to protect against infectious disease. A vaccine works by directing the immune system to recognize specific molecules called antigens (made up of proteins, lipids, and/or carbohydrates) on the surface of an infectious agent, such as a bacterium or a virus. Based on the characteristics of the antigen molecules, the vaccine induces the host's immune system to mount an "adaptive"

[1] M.R. Dyer, W.A. Renner, and M.F. Bachmann, "A second vaccine revolution for the new epidemics of the 21st century," *Drug Discovery Today*, vol. 11 (2006), pp. 1028-1033.

immune response involving the activation of white blood cells and the production of antibodies to protect against subsequent infection by the same agent. Even before an antigen triggers the adaptive immune response, a parallel system called the "innate" immune response is activated within minutes of an invasion by a foreign pathogen. In this case, a different set of white blood cells (macrophages, natural-killer cells, etc.) and other mechanisms provide immediate but non-specific defenses. The innate immune response also influences the subsequent development of the adaptive response by triggering cellular signaling pathways. The field of systems biology has sought to map the immense complexity of these interactions. One analysis estimated that the simulation of a single receptor called TLR4 in the innate immune system leads to 2,531 interactions involving 1,346 different genes or proteins.[2]

The adaptive immune response, which follows from and is influenced by the innate immune response, can persist for decades through the creation of "memory immunity" and provides a strong, rapid, and highly specific defense against a subsequent infection by the same organism. The two arms of adaptive immunity in mammals are the *humoral* response, characterized by antibody-producing B cells; and the *cell-mediated* response, directed primarily by T cells. There are, in turn, two broad types of T cells: helper T cells, which produce signaling molecules called cytokines, and cytotoxic T cells, which kill infected cells directly. Scientists have learned what subtypes of T cells are required to combat different kinds of infections and how cytokines organize, increase, or decrease their activities.

T cells have two types of responses, called Th1 (the inflammatory arm) and Th2 (the anti-inflammatory arm). Th1 is largely characterized by the production of cytotoxic T cells and cytokines that induce inflammation, while Th2 signals B cells to produce antibodies. The Th1 response is largely responsible for protection against viral or intracellular bacterial infections, while the Th2 response plays a greater role in extracellular bacterial and parasitic diseases. In addition, many of the cytokines expressed

[2] J.L. Gardy, D. J. Lynn, F.S. Brinkman, and R.E. Hancock, "Enabling a systems biology approach to immunology: Focus on innate immunity," *Trends in Immunology*, vol. 30 (2009), 249-62.

during the Th1 response suppress the Th2 response, and vice versa. On the one hand, the reciprocal relationship between the two types of T cell responses prevents the immune system from overreacting to infection in a harmful manner. On the other hand, the slightest imbalance between the two types of T cell responses can lead to a potentially disastrous outcome. In addition to the reciprocal Th1/Th2 relationship, other complex interactions exist between T and B cells and between the immune, nervous, and endocrine systems.[3]

The earliest vaccines for smallpox, rabies, cholera, and other infectious diseases consisted of avirulent (non-disease-causing) forms of the infectious agent and were developed by trial and error. As the operations of the immune system have been gradually elucidated, however, it has become possible to design vaccines that manipulate specific elements of the immune response for effective protection. For example, viral vectors developed by gene-therapy researchers to deliver genetic material into cells (adenovirus, vaccinia virus, and lentivirus) can also serve as vehicles for delivering antigens to immune cells. Viral vectors can also be engineered to carry genes encoding proteins called immunomodulators, which influence the immune response.

History of the Technology

The first documented vaccine was developed in 1796 by the English country doctor Edward Jenner, who inoculated a 13-year-old boy with cowpox virus obtained from a milkmaid and observed that the boy was protected from infection when subsequently challenged with the variola (smallpox) virus. Today, dozens of infectious diseases are preventable by vaccination.[4] The timeline of major discoveries since Jenner suggests that advances in the understanding of immune mechanisms have driven progress in vaccine design. During the nineteenth century, Louis Pasteur confirmed that the host is capable of an effective defense against infectious agents. He coined the term “vaccine” (derived from the Latin word for cow) as a tribute to Jenner’s use of cowpox virus to

[3] S. Bambini and R. Rappuoli, “The use of genomics in microbial vaccine development,” *Drug Discovery Today*, vol. 14 (2009), 252-60.
[4] F.E. Andre, “Vaccinology: past achievements, present roadblocks and future promises,” *Vaccine*, vol. 21 (2003), pp. 593-5.

protect against smallpox. By the early twentieth century, several mechanisms and cell types involved in innate immunity had been identified, and the 1940s witnessed a number of breakthroughs in the study of cellular (T cell) immunity. Over the next few decades, the cooperative interactions between T and B cells came into focus.

During the 1980s, the discovery of two key signaling molecules, interleukins 1 and 2, led to an explosion of research into the field of immune signaling. The Th1/Th2 paradigm of the T cell response was delineated in 1986. Charles A. Janeway, Jr. at Yale Medical School predicted in 1989 that pattern-recognition receptors mediate the body's ability to recognize invasion by microorganisms. Although Janeway made this striking prediction on theoretical grounds, subsequent experimental work in his laboratory demonstrated the existence of two key sets of molecules in the innate immune system: pathogen-associated molecular patterns (PAMPs) and Toll-like receptors (TLRs). In 2001, Ralph M. Steinman and his coworkers at the Rockefeller University in New York showed that dendritic cells—the first cells of the innate immune system to interact with an invading pathogen—play a key role in the collection, processing, and presentation of antigenic material to T cells.[5] Steinman's work led to the revolutionary notion that receptor signaling in the innate immune system serves as the trigger for the adaptive immune response.

Utility of the Technology

Insights into the innate and adaptive immune responses have opened up new avenues for manipulating the immune system to prevent and treat disease. New vaccines designed to modify the immune response are under development in a wide variety of institutional environments, including academic, pharmaceutical, and military research organizations. Vaccine vectors have been created that carry genes encoding specific cytokines, which direct the immune system to respond in a desired manner. In addition,

[5] D. Hawiger, K. Inaba, Y. Dorsett, M. Guo, K. Mahnke, M. Rivera, J.V. Ravetch, R.M. Steinman, and M.C. Nussenzweig, "Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo," *Journal of Experimental Medicine*, vol. 194 (2001), pp. 769-779.

signaling molecules in the innate immune system called "Toll-like receptors" (TLRs) have been used to modulate and direct subsequent immune responses.

Several laboratories have developed experimental viral vaccines that home in on and deliver antigen genes to dendritic cells to increase the efficacy of the immune response in cancer immunotherapy.[6] For example, dendritic cells obtained from patients have been genetically engineered to express specific antigens associated with brain tumors called glioblastomas and then reintroduced into the patients to combat the disease.[7] (Unfortunately, preliminary clinical trials of dendritic-cell immunotherapy have encountered a number of setbacks, including the deletion of key effector cells and the development of autoimmunity.[8])

The field of vaccinology has also moved beyond infectious disease into several other areas of medical therapeutics. So-called "lifestyle" vaccines are being developed to treat weight gain, addiction to nicotine and other drugs, and dental caries in otherwise healthy individuals, as well as for contraception.[9] One lifestyle vaccine targets ghrelin, a weight-gain-signaling protein that was first identified in 1999.[10] An anti-ghrelin vaccine has been tested in rats, with the goal of inducing antibodies against the protein and blocking its access to the brain, where it stimulates appetite.[11] A recent review paper described the promise of anti-ghrelin vaccines to combat the epidemic of obesity.[12]

On a more speculative note, genetic analyses have uncovered specific genes that appear to be associated with criminal behavior, raising the possibility of manipulating

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[6] P.J. Tacken, I.J. de Vries, R. Torensma, and C.G. Figdor, "Dendritic-cell immunotherapy: from ex vivo loading to in vivo targeting," *Nature Reviews Immunology*, vol. 7 (2007), pp. 790-802.
[7] E.L. Smits, S. Anguille, N. Cools, Z. N. Berneman, and V. F. Van Tendeloo, "Dendritic cell-based cancer gene therapy," *Human Gene Therapy*, vol. 10 (2009), pp. 1141-1146.
[8] K. Shortman, M.H. Lahoud, and I. Caminschi, "Improving vaccines by targeting antigens to dendritic cells," *Experimental Molecular Medicine*, vol. 41 (2009), pp. 61-66.
[9] P. Mettens and P. Monteyne, "Life-style vaccines," *British Medical Bulletin*, vol. 62 (2002), pp. 175-186.
[10] M. Kojima, H. Hosoda, Y. Date, M. Nakazato, H. Matsuo, and K. Kangawa, "Ghrelin is a growth-hormone-releasing acylated peptide from stomach," *Nature*, vol. 402 (1999), pp. 656-660.
[11] E.P. Zorrilla, S. Iwasaki, J. A. Moss, J. Chang, J. Otsuji, K. Inoue, M. M. Meijler, and K. D. Janda, "Vaccination against weight gain," *Proceedings of the National Academy of Sciences USA*, vol. 103 (2006), pp. 13226-13231.
[12] H. Schellekens, T. G. Dinan, and J. F. Cryan, "Lean mean fat reducing 'ghrelin' machine: Hypothalamic ghrelin and ghrelin receptors as therapeutic targets in obesity," *Neuropharmacology*, vol. 58, no. 1 (January 2010), pp. 2-16.

them by immunological means. An editorial in the journal *Vaccine* discussed the prospect of vaccines that could down-regulate specific neurotransmitter systems in the brain to "achieve the regulation of the emotionality of humans who are physically incapable of controlling their emotions. Such individuals, when abused in childhood, make up a significant proportion of the criminally inclined. It may therefore be possible to make an anti-criminal vaccine to protect society against those whose natural monoamine oxidase [an enzyme in the brain] is not capable of sufficiently deactivating the neurotransmitters dopamine, norepinephrine, and epinephrine."[13]

Potential for Misuse

The dual-use potential of rational vaccine design is exemplified by two experiments that produced unexpectedly adverse results. In 2000, a team of Australian researchers sought to develop a contraceptive vaccine for the control of wild mouse populations. The plan was to induce female mice to produce antibodies against surface proteins present on their own eggs, rendering them infertile, by inserting genes coding for the egg antigens into ectromelia (mousepox) virus and then infecting mice with the recombinant virus. In order to enhance antibody production against the egg antigens, the researchers also inserted into the engineered mousepox virus a mouse gene coding for interleukin-4 (IL-4), an immune regulatory protein. Before performing this experiment, the scientists sought approval from their local Institutional Biosafety Committee (IBC) and the Australian government's Genetic Manipulation Advisory Committee.[14] Although the researchers considered the possibility that the inserted gene might increase the virulence of the mousepox virus, this outcome was judged unlikely because the strain of mouse used in the experiment was genetically resistant to mousepox infection.

As it turned out, the IL-4 gene did indeed stimulate antibody production in the experimental animals, but it also had the unintended effect of shutting down the cellular arm of the immune response, which plays a key role in defending against viral infection.

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[13] R. Spier, "'Vaccine': 25 years on," *Vaccine,* vol. 26 (2008)**,** pp. 6173-6176.
[14] Federation of American Scientists, "Mousepox Case Study," *Case Studies in Dual Use,* < http://www.fas.org/biosecurity/education/dualuse/index.html>

As a result, the inserted gene rendered the mousepox virus highly lethal in mice, even in those animals that were genetically resistant to the virus or had been vaccinated against it. In retrospect, it was clear what had happened: the inserted IL-4 gene simulated the Th2 (antibody) response and consequently suppressed the Th1 (cellular immune) response, which in this case was essential to protect the host. Sufficient preliminary data existed at the time about the ability of IL-4 to down-regulate the cellular immune system that the investigators should have predicted the "surprising" result of the mousepox experiment, but apparently they did not.[15]

Once the troubling findings of the IL-4/mousepox experiment had been confirmed, the Australian authors debated about whether or not to publish the results. The obvious concern was that actors with nefarious intent might seek to repeat the experiment with a poxvirus that infects humans, such as variola virus or monkeypox virus, potentially creating a highly lethal strain that could defeat the standard protective vaccine. If such an agent could be produced, it would pose an increased threat of biological warfare or terrorism. In September 2000, U.S. poxvirologists Peter Jahrling and Richard Moyer learned of the IL-4/mousepox experiment and warned that its publication would provide "a blueprint for the biological equivalent of a nuclear bomb."[16] Yet when the Australian authors consulted other leading experts on smallpox (such as D.A. Henderson and Frank Fenner) about the security implications of their work, all of them concluded that publication was warranted in view of previously published papers that described similar results.[17] The Australian government agreed, and in February 2001, the IL-4/mousepox paper was published in the *Journal of Virology*.[18]

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[15] D.P. Sharma, A.J. Ramsay, D.J. Maguire, M.S. Rolph, and I.A. Ramshaw, "Interleukin-4 mediates down regulation of antiviral cytokine expression and cytotoxic T-lymphocyte responses and exacerbates vaccinia virus infection in vivo," *Journal of Virology*, vol. 70 (1996), pp. 7103-7107.

[16] Richard Preston, *The Demon in the Freezer* (New York: Random House, 2002), p. 158.

[17] R.J. Jackson, D.J. Maguire, L.A. Hinds, and I.A. Ramshaw, "Infertility in mice induced by a recombinant ectromelia virus expressing mouse zona pellucida glycoprotein 3," *Biology of Reproduction*, vol. 58 (1998), pp. 152-159.

[18] R.J. Jackson, A.J. Ramsay, C.D. Christensen, S. Beaton, D.F. Hall, and I.A. Ramshaw, "Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox." *Journal of Virology*, vol. 75 (2001), pp. 1205-1210.

On January 10, however, one month before the scientific paper appeared and with the involvement of the authors, the British popular science magazine *New Scientist* published an article describing the research, titled "Killer Virus: An Engineered Mouse Virus Leaves Us One Step Away From the Ultimate Bioweapon."[19] Peppered with quotes from experts on biological weapons and smallpox, the article triggered an explosion of concern in the scientific and lay press. At the same time, experimentation with IL-4 recombinant poxviruses continued. In October 2003, *New Scientist* published a second article titled "US Develops Lethal New Viruses," describing the work of virologist Mark Buller, then at University of St. Louis.[20] This article quoted Buller as saying that the construction of an "optimized" IL-4/mousepox virus was necessary to test antiviral drugs as potential defenses against bioterrorist weapons based on recombinant poxviruses. In addition, Buller reportedly stated that a similar construct, created by inserting the mouse IL-4 gene into cowpox virus (which, unlike mousepox virus, can infect humans), would be tested at the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, Maryland. In 2004, Buller published an article in the journal *Virology* focusing on new antiviral drug treatments for mousepox infection.[21] But no paper on the IL-4/cowpox experiment ever appeared, suggesting that Buller may have decided that his findings were too sensitive to publish.

To date, the IL-4/mousepox experiment remains the most widely cited example of the "dual-use dilemma" in biomedical research. It is also a classic example of modifying a virus-based vaccine with the aim of directly modifying the immune response elicited by the vaccine. Although IL-4 is only one of hundreds of cytokines and other immune-regulatory molecules whose function could contribute to the effectiveness of vaccines, there was—and still is—no formal process to evaluate such potentially risky experiments.

A second troubling experiment also demonstrated the dual-use potential of rational vaccine design. In March 2006, a research group in Britain began a clinical trial

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[19] Rachel Nowak, "Killer virus: An engineered mouse virus leaves us one step away from the ultimate bioweapon," *New Scientist*, January 13, 2001, pp. 4-5.
[20] Debora MacKenzie, "US develops lethal new viruses," *New Scientist*, October 29, 2003, p.6.
[21] R.M. Buller, G. Owens, J. Schriewer, L. Melman, J.R. Beadle, and K.Y. Hostetler, "Efficacy of oral active ether lipid analogs of cidofovir in a lethal mousepox model," *Virology*, vol. 318 (2004), pp. 474-481.

of TGN1412, a monoclonal antibody directed against a cell-surface marker on T cells known as CD28.[22] Studies in animals, including primates, had shown that the binding of antibodies to CD28 results in a modest level of cytokine production followed by a reversible increase in the number of T cells. Accordingly, the monoclonal-antibody treatment was designed for a specific type of leukemia that is accompanied by a severe T cell deficiency.

During the clinical trial, however, the experimental treatment had unexpectedly adverse effects. Within 90 minutes after the intravenous infusion of TGN1412 antibodies into six healthy young volunteers, all of them developed a systemic inflammatory response with high levels of circulating cytokines. Over the next 12 hours, the six subjects became critically ill and eventually suffered multiple organ failure. Although all six survived, they appear to have suffered permanent damage to the immune system that could render them vulnerable to cancer and other diseases. Many questions remain about the study design, the investigator qualifications, and the immune mechanisms that led to this unfortunate result.[23]

The IL-4/mousepox experiment and the clinical trial of TGN1412 both suggest that rational vaccine design has a potential for deliberate misuse. There are several areas of possible concern. First, *vaccines that affect cytokine levels can have serious harmful effects*. IL-4 is just one of many cytokines that regulate the innate immune response. Whenever the Th1-based, cell-mediated response is required for protection against certain pathogens, the increased expression of IL-4 can dramatically increase the host's susceptibility to infection. This finding was suggested both by the IL-4/mousepox study and by related experiments that examined the molecular and genetic basis of susceptibility to mousepox infection in different mouse strains. In particular, pure-bred mice with high levels of Th2 cytokines (such as IL-4) and/or low levels of Th1 cytokines

[22] G. Woerly, N. Roger, S. Loiseau, D. Dombrowicz, A. Capron, and M. Capron, "Expression of CD28 and CD86 by human eosinophils and role in the secretion of type 1 cytokines (interleukin 2 and interferon gamma): inhibition by immunoglobulin a complexes," *Journal of Experimental Medicine,* vol. 190 (1999), pp. 487-495.
[23] E. William St. Clair, "The calm after the cytokine storm: Lessons from the TGN1412 trial," *Journal of Clinical Investigation,* vol. 118, no. 4 (April 2008)**,** pp. 1344-1347.

are exquisitely sensitive to poxvirus infection.[24] Another example of a dangerous immunological manipulation is the inappropriate stimulation of Toll-like receptors with pathogen-associated molecular patterns (PAMPs), leading to an extreme overexpression of inflammatory cytokines—a "cytokine storm"—that results in autoimmunity, shock, multiple organ failure, and death.

Second, *vaccines can be used to modify neural circuitry*. Developing a vaccine for the treatment or prevention of Alzheimer's disease is an active and promising area of neuroscience research.[25] The primary target of vaccine therapy is the protein amyloid beta, the major constituent of the brain plaques associated with this type of dementia. As the molecular mechanism of plaque formation is better understood, it may be possible to develop "neurotropic" vaccines that inhibit plaque formation. Nevertheless, the knowledge and approaches developed to vaccinate against Alzheimer's disease might be misused for harmful purposes by attacking certain key neural circuits in the brain.

Third, *vaccines could be modified to interfere with the interactions of the nervous, immune, and endocrine systems*. Extensive study of the neuro-endocrine-immune axis has led to increased understanding of how the human body maintains homeostasis in the face of external and internal stresses. This understanding could potentially be misused to create vaccines that interfere with vital regulatory systems.

Ease of Misuse (Explicit and Tacit Knowledge)

Although basic information about vaccines with harmful effects is freely accessible, actually designing novel vaccines for hostile purposes would require a high level of expertise and tacit knowledge, as well as the equipment and resources of an academic or government vaccine research laboratory.

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[24] G. Chaudhri, V. Panchanathan, R.M. Buller, A. J. van den Eertwegh, E. Claassen, J. Zhou, R. de Chazal, J.D. Laman, and G. Karupiah, "Polarized type 1 cytokine response and cell-mediated immunity determine genetic resistance to mousepox," *Proceedings of the National Academy of Sciences USA*, vol. 101 (2004), pp. 9057-9062.

[25] C.A. Lemere, "Developing novel immunogens for a safe and effective Alzheimer's disease vaccine," *Progress in Brain Research*, vol. 175 (2009), pp. 83-93.

Accessibility of the Technology

Designer vaccines that have demonstrated unexpected harmful effects during testing in animal models (mousepox/IL4) or in humans (the TNG1412 clinical trial) suggest that similar vaccines might be developed for harmful purposes. These two examples also illustrate that the line between beneficial and harmful research is defined largely by intent. Once dual-use knowledge has been created, it has a potential for misuse regardless of the original motivation of those who produced it.

Imminence and Magnitude of the Risk of Misuse

Although a state biological warfare program might have the resources and expertise to exploit rational vaccine design for weapons purposes, it is highly unlikely that a terrorist organization would have the resources do so. Taking these factors into account, the imminence and magnitude of dual-use risk associated with this technology appear to be moderate.

Awareness of Dual-Use Potential

Beyond the IL-4/mousepox experiment, which received a great deal of publicity, most immunologists appear to have little awareness of the dual-use risks associated with new vaccine technologies. Indeed, surveys have shown that most practicing life scientists have little or no awareness of the potential harmful applications of their research.[26]

Characteristics of the Technology Relevant to Governance

Embodiment. Rational vaccine design is based almost entirely on intangible information and is not associated with specific hardware.

Maturity. The field of rational vaccine design is in the stage of advanced research and development, with limited commercial availability.

Convergence. Rational vaccine design draws on several areas of science and technology, including bioinformatics, systems biology, and cellular immunology.

[26] Malcolm Dando and Brian Rappert, "Codes of Conduct for the Life Sciences: Some Insights from UK Academia," *Briefing Paper No. 16* (Bradford, UK: University of Bradford, May 2005).

Another key aspect of vaccine technology is the development of delivery systems, which draws on fields such as nanotechnology[27], microencapsulation[28], DNA shuffling[29], aerosolization and stabilization[30], and microbiology (e.g., the incorporation of vaccines into microbial spores).[31]

Rate of advance. In several cases, the discovery of a specific immunological mechanism, such as dendritic cell targeting or the role of ghrelin in weight gain, has led to the development of clinical applications within four to six years. Serious complications have often resulted, however, suggesting the need for a more nuanced assessment of progress.

International diffusion. Although most advances in vaccinology are published in the open scientific literature, the future of rational vaccine design will be dictated primarily by local needs. Whereas developing countries are concerned with infectious diseases, developed countries have recently shifted the focus of vaccine development toward chronic diseases and "lifestyle" problems, such as addiction and obesity.

Susceptibility to Governance

The rapid evolution and diffusion of new vaccine technologies, coupled with the intensity of commercial competition, make it nearly impossible to provide governance by restricting activity. Such restrictions might also impede crucial advances in immunology research and the development of new life-saving vaccines. Nevertheless, a number of soft-law and normative governance measures might be adapted to this technology.

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[27] M. Foldvari and M. Bagonluri, "Carbon nanotubes as functional excipients for nanomedicines: II. Drug delivery and biocompatibility issues," *Nanomedicine*, vol. 4 (2008), pp. 183-200.

[28] K.D. Wilson, S. D. de Jong, and Y.K. Tam, "Lipid-based delivery of CpG oligonucleotides enhances immunotherapeutic efficacy," *Advances in Drug Delivery Reviews*, vol. 61 (2009), pp. 233-42.

[29] C.P. Locher, V. Heinrichs, D. Apt, and R.G. Whalen, "Overcoming antigenic diversity and improving vaccines using DNA shuffling and screening technologies," *Expert Opinion in Biological Therapeutics*, vol. 4 (2004), pp. 589-97.

[30] J.L. Burger, S.P. Cape, C.S. Braun, D.H. McAdams, J.A. Best, P. Bhagwat, P. Pathak, L.G. Rebits, and R.E. Sievers, "Stabilizing formulations for inhalable powders of live-attenuated measles virus vaccine," *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, vol. 21 (2008), pp. 25-34.

[31] N.Q. Uyen, H.A. Hong, and S.M. Cutting, "Enhanced immunisation and expression strategies using bacterial spores as heat-stable vaccine delivery vehicles," *Vaccine*, vol. 25 (2007), pp. 356-65.

Past and Current Approaches to Governance

To date, there has been no attempt to regulate rational vaccine design beyond the stringent U.S. Food and Drug Administration (FDA) regulations that already apply to the field of vaccine development and production.

Options for Future Governance

At the local level, Institutional Biosafety Committees (IBCs) should be assigned responsibility for raising awareness about the dual-use risks of rational vaccine design and for reviewing proposed experiments in order to prevent adverse outcomes. In the case of unexpected findings with dual-use implications, as occurred in the mousepox/IL-4 and TGN1412 experiments, an ongoing review process is needed.

At the national level, federal and private funding agencies and professional societies are exploring awareness training as a means of alerting bench scientists and graduate students to the dual-use potential of immunological research. The U.S. National Science Advisory Board for Biosecurity (NSABB), a federal advisory body established in the wake of the 2001 anthrax letter attacks, provides a framework for discussion of dual-use research of concern.[32] In addition, a variety of professional scientific organizations have begun to educate life scientists about these issues, including the Federation of American Scientists, the American Society for Microbiology, and the American Association for the Advancement of Science.

At the international level, the potential misuse of vaccine technology for hostile purposes falls outside the scope of both the 1972 Biological Weapons Convention (BWC) and the 1993 Chemical Weapons Convention (CWC). To tackle the monitoring of dual-use research in this gray area, Alexander Kelle and his colleagues have proposed the negotiation of a framework convention.[33] A second international policy option would be to establish a "global issues network" focusing on the dual-use problem, as was proposed by the U.S. National Research Council report *Globalization, Biosecurity and the Future*

[32] National Research Council, *Biotechnology Research in an Age of Bioterrorism: Confronting the Dual-use Dilemma* (Washington, DC: National Academies Press 2004).
[33]Alexander Kelle, Kathryn Nixdorff, and Malcolm Dando, *Controlling Biochemical Weapons: Adapting Multilateral Arms Control for the 21st Century* (Basingstoke, UK: Palgrave Macmillan, 2006).

of the Life Sciences.[34] Such a network would serve as a watchdog by monitoring new developments in the field of immunology, including rational vaccine design, and increasing awareness of their dual-use potential.

Conclusions

Current research efforts are elucidating the profound complexity of the immune system, the delicate balance of its regulation, and its close integration with the nervous and endocrine systems. The time interval between the discovery of a new immune regulatory mechanism and the clinical trial of a related therapeutic drug has shrunk to as little as five years. Mouse and human trials of new vaccine candidates have already yielded unanticipated results, some with catastrophic effects on host survival. These developments, linked to the development of increasingly effective delivery systems, have increased the risk of misuse of rational vaccine design for harmful purposes. Because vaccine development is beyond the direct control of governments and existing international treaties, this field should be subjected to a web of oversight mechanisms at the local, national, and international levels.[35]

[34] National Research Council, *Globalization, Biosecurity, and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006), pp. 251-256.
[35] Graham S. Pearson, "Prospects for chemical and biological arms control: The web of deterrence," *Washington Quarterly*, vol. 16 (1993), pp. 145-162.

Chapter 17: Aerosol Vaccines

Raymond A. Zilinskas and Hussein Alramini[1]

Studies in animals and humans have shown that delivering a vaccine in the form of an aerosol—an airborne suspension of fine particles—can be more effective than administering it orally or by injection. Over the past decade, one human aerosol vaccine for intranasal delivery has been developed to the marketing stage and a few others are in advanced clinical trials. Aerosol vaccines for deep-lung delivery have also been developed and shown to provide effective protection against various infectious diseases, but they have not yet been approved and marketed for human use.

The delivery of an aerosol vaccine requires an aerosol generator, which employs pressurized air or gas to break up the preparation into a suspension of airborne particles small enough to enter the respiratory tract. Although aerosol generators are known to be suitable for the delivery of biological warfare agents, this chapter addresses the broader topic of aerosol vaccine technology, including the development of a vaccine formulation that is medically efficacious when administered in aerosol form. The chapter assesses the potential for misuse of this technology and concludes with some options for governance.

Overview of the Technology

An aerosol vaccine consists of a preparation of living but attenuated (non-virulent) bacteria or viruses, which are delivered in the form of an airborne suspension of microscopic particles or droplets. The challenge facing developers is to introduce living microbes into the recipient's tissues in a manner that stimulates immunity against the target pathogen without causing harm to the host.

The preparation of an aerosol vaccine involves several steps. After an attenuated bacterium or virus has been cultivated in a fermenter, bioreactor, or cell culture, it is separated from the growth medium and resuspended in a special solution containing chemical preservatives and nutrients, which stabilize the microbes during storage and protect them from environmental stresses after release into the open air. This mixture of microorganisms and chemical additives is called a "formulation." Each bacterial or viral

[1] The authors are grateful to Dawn Verdugo for her comments on drafts of this chapter.

species used as a vaccine requires a tailored formulation to ensure that the microbes will survive the stresses of aerosol delivery. Aerosol vaccines can be prepared as a "wet" or "dry" formulation. Some microbes function best as part of a liquid, while others are more effective when dispersed as a dry powder. In general, a dry formulation is more difficult to produce. The biomass must be dried in a special piece of equipment, such as a spray-dryer, and milled into a fine powder. Chemicals may then be added to prevent the dry aerosol particles from clumping due to static electricity.

Developing aerosol vaccine formulations is more of an art than a science. No accepted scientific method can predict which combination of chemicals will interact with a pathogen to stabilize and protect it. Instead, developers must work by trial and error, testing various combinations of chemicals in the laboratory and then in clinical or field trials. At one time a technique called microencapsulation, which involves coating particles or droplets with an inert polymer, was believed to protect microbes that were too fragile for aerosol delivery. In fact, microencapsulation has not been shown to enhance microbial survival or persistence, although in some cases it can protect against the harmful effects of ultraviolet radiation.[2]

There are two categories of aerosol vaccines, the first for delivery into the oral-nasal cavity and the second for delivery into the deep regions of the lungs. In the former case, the aerosol particles are designed to remain in the nasopharynx until they are absorbed through the nasal mucosa. This feature implies two requirements that vaccine developers must meet: the aerosol particles must be relatively large—between 20 and 50 microns in diameter—to prevent them from being carried into the lungs. (One micron is equal to one-billionth of a meter.[3]) The particles must also be properly formulated with muco-adhesive chemicals to enhance their residence time on the nasal mucosa.

Nebulizers and inhalers designed for nasopharyngeal delivery are portable devices that deliver a large-particle aerosol containing a measured dose of a drug or vaccine to an individual recipient. The aerosol can be generated in various ways, including pump action supplied by muscle power, compressed gas stored within the device, or gas supplied by

[2] V.K Rastogi and K.P. O'Connel, *Studies on the Microencapsulation of Bacteria with Polymer, DL-lactide co-glycolide (PLGA) and Starch/gelatin* (Edgewood Chemical and Biological Center, Research and Technology Directorate, ECBC-TR-550, 2007).
[3] For comparison, the diameter of an average human hair is approximately 100 microns.

an outside source. Some modern inhalers sense when the user is inhaling and automatically deliver the drug into the nasopharynx.

The second type of aerosol vaccine is designed for delivery to the deep regions of the lungs, where maximum absorption occurs in the tiny air sacs called alveoli. To achieve deep lung penetration, the vaccine particles must be less than 10 microns in diameter. An aerosol vaccine designed for deep-lung delivery must also overcome the physiological and immunological defense systems of the host, which normally prevent foreign microbes from reaching the alveoli.[4] Epithelial cells that line the respiratory tract secrete mucus to entrap particles and are equipped with cilia that propel the trapped particles into the esophagus and from there to the stomach, where the acid environment destroys them. Particles that evade the defenses in the airways of the head travel through the nasal valve and into the pharynx, larynx, trachea, and bronchi before reaching the deep regions of the lungs. Along the way, the inhaled microbes are subject to "mucosal immunity," meaning entrapment and destruction by secretions containing antimicrobial chemicals and by immune-system cells (pulmonary macrophages, dendritic cells, and antibody-secreting B cells), which populate the lining of the respiratory tract.

History of the Technology

The first published account of an aerosol vaccine designed for deep-lung delivery appeared in 1910, but intensive research did not begin until after World War II, primarily by Soviet military scientists.[5] Because the most effective method for delivering biological warfare (BW) agents was in the form of an aerosol cloud, it made sense to consider administering biodefense vaccines by the same route. The earliest mention of such work in the Soviet literature dates from the mid-1950s. An article in a Soviet military medical journal describes how a research team led by K. I. Aleksandrov at the Kirov Military Medical Academy in Leningrad began to develop and test "aerogenic" vaccines to protect against diseases of BW concern, including brucellosis, plague, and tularemia. The aerosol

[4] Bruce Lighthart and Alan J. Mohr, *Atmospheric Microbial Aerosols: Theory and Applications* (New York: Chapman & Hall, 1994). See also, Robert F. Phalen, *Inhalation Studies: Foundations and Techniques*, 2nd ed. (New York: Informa Healthcare USA, 2009).

[5] K. Petzoldt, C. von Benton, and W. Floer, *Study, Based on Published Sources, of the Applications and Limitations of Mass Aerogenous Immunization Against Bacterial Infections Under Field Conditions* [in German] (Bonn: Forschungsbericht aus der Wehrmedizin, Bundesministerium der Verteidigung, 1976).

vaccines consisted of live attenuated bacteria in dry formulations. Initial testing in animal models (guinea pigs, rabbits, and sheep) suggested that the vaccines were safe and efficacious. In 1957-58, Soviet military scientists exposed 487 human subjects to the aerosol vaccines in sealed test chambers. The recipients experienced minimal side-effects, and clinical and serological tests indicated that they had acquired protective immunity against plague, tularemia, and brucellosis.[6]

Aleksandrov and his colleagues subsequently developed a dry aerosol vaccine against anthrax, consisting of a non-pathogenic strain of live *Bacillus anthracis* spores.[7] Clinical trials demonstrated that aerosol vaccination could immunize a large number of people simultaneously. In a 40 cubic meter room, up to 300 persons were subjected to five-minute exposures over the course of an hour. Using three small rooms or tents, each with a volume of 40 to 50 cubic meters, five or six men could vaccinate more than 1,000 persons per hour.[8]

U.S. military scientists working in the pre-1969 offensive BW program read the Soviet publications on aerosol vaccination and tried to emulate them.[9] In 1962, a team from the U.S. Army Biological Laboratories at Fort Detrick, Maryland, reported on efforts to develop an aerosol vaccine against the bacterium that causes tularemia, a putative BW agent. Unlike their Soviet counterparts, the U.S. Army scientists received permission from higher authorities to conduct human trials with live pathogens. During Operation Whitecoat (1954-1973), several thousand volunteers were exposed to the bacteria that cause Q fever and tularemia in closed chambers and open-air tests.[10] The U.S. scientists also used prison inmates as volunteer subjects. In one experiment, aerosolized tularemia vaccine was delivered through breathing masks to 253 prisoners divided into five groups, each of which received concentrations of live vaccine ranging

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[6] N.I. Aleksandrov, N.Y. Gefen, N.S. Garin, et al., "Reactogenicity and effectiveness of aerogenic vaccination against certain zoonoses" [in Russian], *Voyenno-Meditsinskiy Zhurnal*, no. 12 (1958), pp. 51-59.
[7] N.I. Aleksandrov, N.Y. Gefen, N.S. Garin, et al., "Experiment of mass aerogenic vaccination of humans against anthrax" [in Russian], *Voyenno-Meditsinskiy Zhurnal*, no. 8 (1959), pp. 27-32.
[8] Ibid., p. 32.
[9] M Division, *Theories Pertaining to the Action of the Rotary-Air Grinder; Some Guiding Principles for the Generation of Aerosols and a Proposed Laminar Flow Nozzle*, Special Report No. 107 (Camp Detrick, Maryland: Biological Department, Chemical Corps, May 25, 1949).
[10] U.S. Senate, *Is Military Research Hazardous to Veterans' Health? Lessons Spanning Half a Century*, Staff Report Prepared for the Committee on Veterans' Affairs, 103rd Congress, 2nd sess., S. Prt. 103-97, Chapter C, December 8, 1994.

from 10^4 to 10^8 bacteria. The five groups, plus a control group, were then challenged with an aerosol of a virulent strain of *Franciscella tularensis*, the tularemia bacterium. When the recipients developed symptoms, they were treated with antibiotics. This experiment demonstrated that aerosol vaccination was more effective in protecting against aerosol challenge than vaccination through the skin.[11]

Russian research on aerosol vaccines continued after the breakup of the Soviet Union. A 1999 review paper concluded that dry or rehydrated vaccines were safe and highly effective at conferring immunity in rabbits, sheep, monkeys, and humans, and that live vaccines against plague, tularemia, and anthrax could be developed for aerosol administration.[12] In 2008, a multinational team of investigators from European research institutions reported the development of an aerosol vaccine against smallpox, consisting of two highly attenuated strains of live vaccinia virus. After testing the candidate vaccine on six rhesus monkeys, the investigators concluded that the aerosol-delivered smallpox vaccine was safe and induced long-lasting systemic and mucosal immune responses. "Given the advantages of aerosol vaccine delivery, namely speed, simplicity, safety, and cost effectiveness," they wrote, "aerosol vaccination with recombinant poxvirus-based . . . vaccines could offer a viable solution for future mass vaccination campaigns against mucosally transmitted diseases."[13] Other recent reports describe the development of aerosol vaccines against measles and tuberculosis.[14]

In the early 2000s, the first successful live-virus vaccine designed for nasopharyngeal delivery became available to the general public: FluMist® influenza vaccine, manufactured by MedImmune LLC of Gaithersburg, Maryland. The U.S. Food and Drug Administration (FDA) approved this vaccine in 2003 as a nasal spray for use in healthy children and adults aged five through 49. The vaccine contains three live strains

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[11] R.B. Hornick and H.T. Eiglsbach, "Aerogenic immunization of man with live tularemia vaccine," *Bacteriological Reviews*, vol. 30 (1966), pp. 532-537.
[12] A.V. Stepanov, L.I. Marinin, and A.A. Vorobyev, "Aerosol vaccination against dangerous infectious diseases" [in Russian], *Vestnik Rossiiskoi Akademii Meditsinsikh Nauk*, no. 8 (1999), pp. 47-54.
[13] M. Corbett, W.M. Bogers, J.L. Heeney, et al., "Aerosol immunization with NYVAC and MVA vectored vaccines is safe, simple, and immunogenic," *Proceedings of the National Academy of Sciences*, vol. 105, no. 6 (2008), pp. 2046-2051.
[14] N. Low, S. Kraemer, M. Schneider, and A.M. Restrepo, "Immunogenicity and safety of aerosolized measles vaccine: systematic review and meta-analysis," *Vaccine*, vol. 26, no. 3 (2008), pp. 383-398; L. Garcia-Contreras, Yun-Ling Wong, P. Muttil, et al., "Immunization by a bacterial aerosol," *Proceedings of the National Academy of Sciences*, vol. 105 (2008), pp. 4656-4660.

of influenza virus in a formulation designed for delivery as a large-particle spray into the nasopharynx, where it stimulates both mucosal and systemic immunity.[15] FluMist is packaged in individual disposable sprayers, each containing a single dose. Several studies have demonstrated the safety and efficacy of FluMist.[16] At present, a dry formulation of influenza vaccine (using inactivated virus) is being developed that would make it unnecessary to continuously refrigerate the vaccine, as is now required for FluMist.[17] Before the dry vaccine is ready for clinical testing, however, numerous technical problems must be overcome pertaining to reproducible particle size, distribution, stability, and performance characteristics.[18]

Aerosol vaccines have also been prepared against a number of livestock diseases. During the 1960s, East German veterinary scientists developed aerosol vaccines against a bacterial infection of pigs called swine erysipelas.[19] Ten years later, another group of East German scientists developed an aerosol vaccine against erysipelas septicemia in ducks raised in large coops. The operators estimated that it took only 10 man-hours to vaccinate 10,000 ducks, significantly lowering production costs.[20] More recently, a team of U.S. Army scientists at Fort Detrick developed an aerosol vaccine to protect horses against glanders, a disease caused by the bacterium *Bacillus mallei*, a putative BW agent.[21]

At present, the most widely used veterinary aerosol vaccine is used to immunize chickens against Newcastle disease, a virus that affects poultry. Because factory farms

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[15] The manufacturer states: "Immune mechanisms conferring protection against influenza following receipt of FluMist vaccine are not fully understood." See MedImmune, "FluMist Influenza Vaccine, Live, Intranasal Spray," 2009-210 formula, Package Insert of June 2009, paragraph 12.1.

[16] M. J. Gagliani, "Direct and total effectiveness of the intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine against the 2000-2001 Influenza A(H1N1) and B epidemic in health children," *Archives of Pediatric and Adolescent Medicine*, vol. 158 (2004), pp. 65-73. See also, Z. Wang, et al., "Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel," *Journal of the American Medical Association*, vol. 301, no. 9 (2009), pp. 945-953.

[17] R. J. Garmise, K. Mar, T. M. Crowder, et al., "Formulation of a dry powder influenza vaccine for nasal delivery," *AAPS Pharmaceutical Science and Technology*, vol. 7, no. 1 (March 2006), online at: http://www.aapspharmscitech.org/articles/pt0701/pt070119/pt070119.pdf.

[18] Ibid.

[19] H. Möhlman, Margot Meese, P. Stohr, and V. Schultz, "Technology of aerogenic immunization against swine erysipelas under conditions of actual practice" [in German], *Monatshefte für Veterinärmedizin*, vol. 25, no. 21 (1970), pp. 829-832.

[20] H. Müller and G. Reetz, "Aerosol immunization of ducks with Spirovak erysipelas vaccine 'Dessau'" [in German], *Archiv für experimentelle Veterinärmedizin*, vol. 34, no. 1 (1980), pp. 55-57.

[21] R.L. Ulrich, Kei Amemiya, David M. Waag, et al., "Aerogenic vaccination with a *Burkholderia mallei* auxotroph protects against aerosol-initiated glanders in mice," *Vaccine*, vol. 23 (2005), pp. 1986-1992.

raise chickens in large coops containing up to 45,000 birds, it is impractical to vaccinate them individually. The Newcastle vaccine is administered twice, first when chicks are a day old and a second time when they are several weeks old. The V4 strain of the virus is nonpathogenic and highly immunogenic, so that half of the chickens acquire protective immunity within seven days.[22] Aerosol vaccination is particularly effective because it stimulates a two-fold immune response: the production of antibodies that circulate in the bloodstream and a local mucosal response in the respiratory tract.[23] Intervet/Schering-Plough Animal Health, the world's largest supplier of veterinary vaccines, offers seven vaccines that are diluted in distilled water and disseminated over poultry by a sprayer, creating aerosol particles in the 50 to 100 micron range.[24]

Utility of the Technology

Despite the success of FluMist, a review of alternative routes for the delivery of measles vaccine notes that several studies "highlight the unreliability of intranasal agent delivery, making it a less attractive choice when compared to other aerosol delivery systems. . . . Moreover, because of their inability to comply with proper operating procedures, using this method to administer drugs to infants, young children, and persons with certain disabilities can prove difficult."[25]

Aerosol vaccines for deep-lung delivery offer several advantages compared to both classical vaccines and nasopharyngeal aerosol vaccines. First, deep-lung aerosol vaccines are rapidly absorbed from the alveoli of the lung and have a greater stimulatory effect on the immune system.[26] Second, deep-lung aerosol vaccines protect better than traditional vaccines because they stimulate both mucosal and systemic immunity. Soviet studies found that deep-lung delivery induces a significantly higher increase in serum

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[22] D. Lu and A.J. Hickey, "Pulmonary vaccine delivery," *Expert Review of Vaccines*, vol. 6 (2007), pp. 213-226.
[23] P.W. Cargill and J. Johnston, "Vaccine Administration to Poultry Flocks," Merial Avian Business Unit, December 2006; <http://www.poutry-health.com/library/cargilljohnson0612.html> and DeKalb Veterinary Service Bulletin, "Vaccination by Spray," DeKalb University, undated, <http://www.dekalbpoultry.com/vetinfo/vsb%203030392.pdf>.
[24] Intervet/Schering-Plough Animal Health, "All Vaccines," 2009, <http://www.intervet.com/ipg/vaccines.aspx>.
[25] F.T. Cutts, C.J. Clements, and J.V. Bennett, "Alternative routes of measles immunization: a review," *Biologicals*, vol. 25 (1997), pp. 323-338.
[26] G. Scheuch, Martin J. Kohlhaeufl, Peter Brand, et al., "Clinical perspectives on pulmonary systemic and macromolecular delivery," *Advanced Drug Delivery Reviews*, vol. 58 (2006), pp. 996-1008.

antibodies, fewer negative reactions, and milder side effects than the intranasal method.[27] Another advantage of deep-lung aerosol delivery is that large groups of animals or persons can be immunized simultaneously with few support personnel.

Nevertheless, the drawbacks of deep-lung aerosol vaccines appear to outweigh the advantages. Major safety concerns exist about such vaccines because they have the potential to exacerbate respiratory diseases such as bronchitis, pneumonia, and allergic asthma, and because the excipients (carriers) used in aerosol vaccines may be allergenic or irritating to some individuals. People suffering from asthma, chronic obstructive pulmonary disease, and emphysema are at particular risk for adverse side effects. Other drawbacks are that aerosol vaccines for deep-lung delivery typically require higher concentrations of live microorganisms than conventional vaccines, and adjuvants are usually needed to enhance the recipients' immune response. Clinical testing of aerosol vaccines is more difficult and expensive than for other types of vaccines.

Another drawback of aerosol vaccines for deep-lung delivery is that even with efficient aerosol generators that disperse particles in the 1 to 5 micron range, fewer than 10 percent of the inhaled particles actually reach the lungs. Over 90 percent of the particles either stay in the delivery device or are retained in the back of the throat and swallowed.[28] Of the particles that reach the lungs, 50 percent are retained in the alveoli and the other 50 percent are exhaled.[29] To overcome these drawbacks, aerosol generators for large-scale immunization must be carefully standardized by a well-trained technician according to the vaccine formulation to be dispensed, the operating conditions, and the intended aerosol output. High-quality aerosol generators suitable for mass immunization are available at only a few locations, however. Finally, some liquid aerosol vaccines lose potency after sitting in an aerosol generator for more than a few minutes. For this reason, it may be necessary to keep the device and its contents at a near-freezing temperature with crushed ice, which may be hard to obtain.

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[27] V.M. Zhdanov, V.V. Ritova, N.Y. Gefen, et al., "A comparative study of the intranasal and aerosol methods of vaccination against influenza" [in Russian], *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii*, no. 11 (1962), pp. 63-67.

[28] John Rees, "ABC of asthma; methods of delivering drugs," *British Medical Journal*, vol. 331, no. 7515 (September 3, 2005), p. 504.

[29] S.A. Shoyele and A. Slowey, "Prospects of formulating proteins/peptides as aerosols for pulmonary drug delivery," *International Journal of Pharmaceutics*, vol. 314 (2006), pp. 1-8.

Today, the pharmaceutical industry is making a significant effort to develop small-molecule drugs for nasopharyngeal delivery but is doing little work on aerosol vaccines. Although the success of FluMist may inspire additional companies to develop aerosol vaccines against influenza (and possibly the common cold) for nasopharyngeal delivery, it is not clear whether other diseases could be prevented by this method. If, however, a safe and efficacious live vaccine for nasopharyngeal delivery is developed that can cross the blood-brain barrier, that would change the situation dramatically.

Potential for Misuse

Aerosol vaccine technology *per se* does not pose a significant threat of misuse for hostile purposes. In particular, the aerosol vaccines designed for nasopharyngeal delivery have several characteristics that minimize risk: they are packaged for individual use and dispersed in particles greater than 20 microns into the nasal cavity, usually with a hand-held inhaler. Such large-particle aerosols are not suitable for delivering BW agents because they are retained in the upper airways rather than traveling into the deep regions of the lungs, where maximum absorption occurs. Moreover, aerosol vaccines consisting of live attenuated virus, such as FluMist, are unstable above 4° Celsius (and thus quickly become inactive when exposed to the normal human body temperature of 37° Celsius) and are vulnerable to other environmental stresses, such as low humidity. Finally, individual inhalers are not capable of generating a large aerosol cloud that would expose many people simultaneously. All of these factors appear to exclude nasopharyngeal vaccine technology from the risk of misuse for hostile purposes.

As for deep-lung aerosol vaccines, microbiologist and policy analyst Kathryn Nixdorff has argued that "when advances in aerosol delivery technology are combined with improvements in specific targeting, gene transfer, and gene expression efficacy of viral vectors, the potential synergy effects raise the dual-use risk aspect to a new level."[30] In fact, viral vector technology does not pose an imminent threat. A virologist seeking to convert a viral vector into a biological weapon would have to embark on an arduous process of development. The candidate viral agent would have to be tested for infectivity

[30] Kathryn Nixdorff, "Advances in targeted delivery and the future of bioweapons," *Bulletin of the Atomic Scientists*, vol. 66, no. 1 (January/February 2010), p. 30.

and virulence in animal models or in humans before the developer could be certain of its pathogenicity. The agent would then have to undergo realistic field testing to determine its ability to survive storage at normal temperatures and delivery as an aerosol in the open air. If the candidate virus proved to be fragile, additional development and testing would be required to remove these unwanted characteristics while retaining its pathogenic properties. These technical hurdles make it unlikely that either state proliferators or would-be bioterrorists would go down this path.

Ease of Misuse (Explicit and Tacit Knowledge)

The development of aerosol vaccines requires an advanced research infrastructure and an interdisciplinary scientific team that has both the explicit and tacit knowledge to overcome complex technical problems before the product is finalized. Such a team must include trained scientists and engineers with years of practical experience in aerobiology, microbiology, biochemistry, fermentation processes, formulation, materials, and downstream industrial processing. In the past, development teams were assembled and supported by national BW programs, such as those of the United States and the Soviet Union. In more recent times, pharmaceutical companies intent on developing aerosol vaccines have presumably assembled scientific teams with a similar composition.

Accessibility of the Technology

The main biosecurity concern associated with aerosol vaccines does not involve the vaccine formulations *per se* but rather aerosol generators that can disperse particles small enough to reach the alveoli. These devices are of potential dual-use concern because they can deliver virulent bacteria or viruses just as easily as attenuated pathogens. Aerosol generators are far from a new threat, however. During the 1970s, Soviet scientist V. A. Belyakov and his colleagues developed an aerosol generator called the SPI-1 Atomizer to perform clinical studies on aerosol vaccines. This device delivered a uniform distribution of aerosol particles, of which 16.4 percent (by mass) were the 1 to 5 micron

range. The generator was small and lightweight (16 kilograms), quiet, and dispersed mist evenly throughout rooms ranging in size from one to 40 cubic meters.[31]

The dual-use potential of aerosol generators for the delivery of aerosol vaccines is limited because they are designed to disseminate small quantities of liquid under controlled circumstances, rather than in the open air. Although these devices might be modified to make them more useful for biological warfare or bioterrorism, such an effort appears unnecessary given the many other types of aerosol generators that are commercially available.[32] For example, equipment for the aerosol dispersal of biopesticides, such as formulations of *Bacillus thuringiensis* (Bt), is far more amenable to misuse for BW purposes than is aerosol vaccine technology.[33]

Imminence and Magnitude of Risk

In view of the considerations discussed above, the imminence and magnitude of the dual-use risk associated with aerosol vaccines *per se* appear low. Although the aerosol generators used to deliver deep-lung aerosol vaccines are potentially dual-use, similar devices of greater concern are readily available from uncontrolled sources such as the Internet. Today, anyone with an Internet connection and a search engine can type in terms such as "aerosol generator," "nebulizer," or "atomizer," and call up sites that sell a variety of new and used devices designed for medical, environmental, agricultural, and industrial purposes. For example, the Danish company GEA Niro manufactures an atomizer that is described as "particularly well suited for the production of particles with a sub-5 micron mean particle size, such as particles required for inhalation products within the pharmaceutical industry."[34] This aerosol generator, along with others available on the commercial market, appear more efficient, compact, and concealable than the Soviet SPI-1 Atomizer.

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[31] V.A. Belyakov, S.F. Fedyaev, and A.P. Drozdov, "Atomizer of dry biological preparations" [in Russian], *Meditsinskaya Tekhnica*, no. 5 (1972), pp. 18-20.
[32] Micron, "View our complete product range," 2010, <http://www.micron.co.uk/all_products>.
[33] David B. Levin and Giovana Valadares de Amorim, "Potential for Aerosol Dissemination of Biological Weapons: The Science of Biological Control," *Medscape Today*, 2003, <http://www.medscape.com/viewarticle/452339_2>.
[34] GEA Niro, "Atomizers," http://www.niro.com/niro/cmsdoc.nsf/WebDoc/webb7ezgp8, accessed October 17, 2009.

Characteristics of the Technology Relevant to Governance

Embodiment. Aerosol vaccines consist of a live agent, a formulation, and an aerosol generator and are thus a hybrid of hardware and intangible information.

Maturity. Only one human vaccine for nasopharyngeal delivery (FluMist) is commercially available, plus a few aerosol vaccines for veterinary purposes. Despite extensive research and development, no human aerosol vaccines for deep-lung delivery have yet been approved or marketed.

Convergence. The development of aerosol vaccines depends on innovations in microbiology and vaccinology. Aerobiology techniques are also required to deliver a sufficient number of living organisms into the oronasal cavity or the alveoli to stimulate the host's immune defenses.

Rate of advance. Ever since aerosol-vaccine technology was introduced in the 1950s, progress has been extremely slow. Methods for dispersing live microorganisms in aerosol form have changed little since Soviet times. MedImmune's development of FluMist in the early 2000s was a significant advance but hardly a paradigm shift.

International diffusion. At present, the development of aerosol vaccines appears to be limited to the United States, Europe, and Russia.

Susceptibility to Governance

Because aerosol vaccine technology is based on hardware as well as intangible information, and is advancing slowly, it is moderately susceptible to governance.

Past and Present Approaches to Governance

In the broad context of aerosol vaccine technology, only aerosol generators have been subject to regulation in the past. Significant gaps in the nonproliferation regime still exist, however, with respect to aerosol generators. Countries participating in the Australia Group (AG) restrict the export of "complete spraying or fogging systems, specially designed or modified for fitting to aircraft, lighter than air vehicles or UAVs [unmanned aerial vehicles], capable of delivering, from a liquid suspension, an initial droplet [with a median diameter] of less than 50 microns at a flow rate of greater than two liters per

minute."[35] Because of this narrow definition, the AG control list covers only a small fraction of the commercially available aerosol generators that are potentially suitable for BW use. Moreover, many manufacturers and suppliers of this equipment are located in countries outside the AG that lack strong national export controls on dual-use equipment.

Options for Future Governance

The low dual-use risk associated with aerosol vaccines *per se* does not warrant the development of dedicated governance measures. Although the aerosol generators that are used to deliver aerosol vaccines provide a more plausible target for regulation, the commercial availability of similar aerosol generators for other purposes would significantly reduce the benefits of such a governance measure. For this reason, the security community should concentrate on controlling access to aerosol generators that could be readily used for biowarfare purposes. To close this gap in the nonproliferation regime, the AG controls should be reviewed and strengthened. Once that goal has been accomplished, steps should be taken to curtail the trade in aerosol generators from uncontrolled (non-AG) suppliers, including companies that sell over the Internet or that specialize in marketing second-hand equipment.

Conclusions

For the foreseeable future, the commercial prospects of human aerosol vaccines for deep-lung delivery are limited. The difficulty and expense of conducting clinical trials and the unacceptably high risks to test subjects have led pharmaceutical companies to conclude that aerosol vaccines, despite their advantages, are not worth the cost and effort to develop. Given the lack of deep-lung aerosol vaccines on the market, there is little reason for concern that this technology could be misused. Moreover, aerosol generators designed for the delivery of aerosol vaccines pose no significant dual-use risk beyond that posed by devices that are widely marketed for other applications. Nevertheless, urgent steps are needed to reduce the risk that the aerosol generators currently available for purchase over the Internet could be exploited for biological warfare and terrorism.

[35] Australia Group, "Control List of Dual-use Biological Equipment and Related Technology and Software," September 2009, <http://www.australiagroup.net/en/dual_biological.html>.

Chapter 18: Neuropsychopharmacology

Malcolm R. Dando

Many neuroscientists working today believe that research over the next few decades will yield an integrated, mechanistic understanding of the human brain and behavior. Such an understanding could provide effective treatments for people suffering from schizophrenia, depression, and other mental illnesses, but it could also create new possibilities for misuse. Given the well-documented efforts by military scientists and intelligence agencies during the Cold War to develop and use psychoactive drugs as truth serums and incapacitating agents, it would be naïve to assume that such work has ended. Although top-down government regulation to prevent the hostile exploitation of neuroscience is unlikely anytime soon, improved governance may be possible through bottom-up initiatives.

Overview of the Technology

The standard textbook *Psychopharmacology: Drugs, the Brain, and Behavior* includes some useful definitions: "*Neuropharmacology* is concerned with drug-induced changes in the functioning of cells in the nervous system, while *psychopharmacology* emphasizes drug-induced changes in mood, thinking, and behavior. . . . In combination, the goal of *neuropsychopharmacology* is to identify chemical substances that act upon the nervous system to alter behavior that is disturbed due to injury, disease, or environmental factors."[1] For example, the antidepressant drug fluoxetine (Prozac) selectively inhibits the reuptake into nerve endings of the neurotransmitter chemical serotonin, increasing the availability of this messenger substance in the brain of depressed people and thereby improving mood. Neuropsychopharmacology can also be defined as the convergence of three disciplines: *medicinal chemistry* (the synthesis of new drugs), *pharmacology* (the study of the action of drugs on living systems), and *neuroscience* (the study of how genetics and the environment interact to produce variations in neuronal structure and neurotransmitter/receptor systems, and how these brain systems in turn affect behavior).

[1] Jerrold S. Meyer and Linda F. Quenzer, *Psychopharmacology: Drugs, the Brain, and Behavior* (Sunderland, Mass: Sinauer Associates, 2005), 4.

Despite considerable progress over the past few decades, the treatment of many mental illnesses remains rudimentary. Writing in 2001, at the turn of the new century, the psychiatrist Nancy Andreasen divided the major mental illnesses into four categories: dementias, schizophrenia, mood disorders, and anxiety disorders. For each category she assigned a grade of "A" through "D" for syndromal definition, understanding of the causes of the illness, and treatment. Only mood disorders received an "A," and in that case a detailed understanding of what goes wrong in the brain is still lacking.[2]

Contemporary neuroscience seeks to unravel brain function in health and disease by working at several levels of analysis. During the 1990s, the use of molecular biology techniques opened the way to rapid growth in the understanding of neurotransmitters and their receptors. At the same time, advanced imaging technologies such as functional magnetic resonance imaging (fMRI) have made it possible to observe directly the activity of the living human brain.[3] Over the next few decades, Andreasen believes, these different levels of analysis will converge. When that happens, she writes, "We will understand how the cells in our brains go bad when their molecules go bad, and we will understand how this is expressed at the level of systems such as attention and memory so that human beings develop diseases such as schizophrenia and depression."[4]

History of the Technology

The scientific study of the nervous system did not begin until the early twentieth century, when it became clear that the brain and spinal cord are made up of functional cells called neurons and supporting cells called glia. In the 1920s, the German physiologist Otto Loewi showed that information is transferred between neurons by chemical messenger substances called neurotransmitters, which travel across a gap called the "synapse" between the transmitting and the receiving cells. Loewi also identified the first neurotransmitter substance, acetylcholine.

In 1936, the same year that Loewi shared the Nobel Prize for his discovery, the German industrial chemist Gerhard Schrader was developing new insecticides when he

[2] Nancy C. Andreasen, *Brave New Brain: Conquering Mental Illness in the Era of the Genome* (Oxford: Oxford University Press, 2001), p. 173.
[3] Brain-imaging technologies include computerized tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and functional MRI.
[4] Andreasen, *Brave New Brain*, p. 173.

accidentally discovered an organophosphorus compound that was extraordinarily toxic to the nervous system. It is now known that this class of chemical blocks the enzyme that breaks down acetylcholine at the synapse after transmission has occurred. The excess neurotransmitter overstimulates the nervous system, resulting in convulsions, flaccid paralysis, and death. Schrader's compound later became the basis for a new generation of highly lethal chemical weapons: the nerve agents tabun, sarin, and soman.

After World War II, a series of serendipitous discoveries led to the first therapeutic drugs for people suffering from schizophrenia, greatly improving the prospects of those who previously had been treated only by incarceration. This breakthrough provided a strong incentive for additional basic and applied research in neuropsychopharmacology. At the time, a large gulf existed between psychiatrists exploring the behavioral aspects of mental illness and neuroscientists studying the chemistry and physiology of the nervous system. During the second half of the twentieth century, however, neuropsychopharmacology made significant strides and shed new light on the mode of action of many psychoactive drugs.

In one key advance, Arvid Carlsson of the University of Gothenburg in Sweden discovered that Parkinson's disease is associated with the degeneration of the neurons in the brain that release the neurotransmitter dopamine; the resulting low levels of dopamine disrupt the brain's ability to control movement. This finding led to the therapeutic use of the dopamine precursor L-DOPA to compensate for the degeneration of dopamine-producing neurons and increased the confidence of scientists that a fully mechanistic understanding of the brain was possible. At the same time, several countries developed new types of chemical weapons that targeted the brain. During the 1960s, the United States produced and stockpiled the hallucinogen BZ as an incapacitating agent, although it was never used in battle because of its unpredictable effects.[5]

Beginning in the 1990s, molecular biology led to major advances in the understanding of neurotransmitter receptors, which are large proteins embedded in the outer membrane of neurons. The binding of a neurotransmitter triggers a change in the shape of the receptor protein that in turn induces functional changes in the receiving cell.

[5] Malcolm R. Dando, *A New Form of Warfare: The Rise of Non-Lethal Weapons* (London: Brassey's, 1996).

Because the amino-acid sequence of each receptor protein is specified by the neuronal DNA, scientists began to use molecular-genetic techniques to elucidate the various classes of neurotransmitter receptors and the sub-types within each class. As a result of these studies, scientists have identified far more types of neurotransmitters in the brain than had previously been thought to exist.

Many of these messenger substances are not small molecules such as acetylcholine and dopamine but rather neuropeptides, which consist of short chains of amino acids. During the late 1990s, the study of narcolepsy, a serious sleep disorder, led to the discovery of two new peptide neurotransmitters, hypocretin and orexin, which are produced by cells in the hypothalamus.[6] One of the functions of hypocretin-containing neurons is to provide excitatory input to a brain region called the locus coeruleus, which is crucial for maintaining wakefulness. Research has shown that people with narcolepsy have low or non-existent brain levels of hypocretin.[7]

Several other important advances in brain science have occurred in recent years. The discovery that small-molecule neurotransmitters and neuropeptides can be co-located within individual neurons toppled the long-standing dogma that each neuron produces only one type of neurotransmitter. It was also found that certain brain chemicals called neuromodulators affect neuronal activity over relatively long time intervals, complementing rapid synaptic transmission. Moreover, electrical (rather than chemical) transmission between neurons is more important than previously believed, particularly in central pattern generators.[8] Finally, contrary to long-standing conventional wisdom, it is now known that new neurons can form in the adult brain, and neurogenesis has become an important area of research with numerous potential medical applications.[9] Further surprises and reorientations are to be expected as the vast complexity of the human brain is gradually elucidated.

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[6] Alexander Kelle, Kathryn Nixdorff, and Malcolm R. Dando, *Controlling Biochemical Weapons: Adapting Multilateral Arms Control for the 21st Century* (Basingstoke: Palgrave, 2006), Chapter 5: "Behaviour under Control: The Malign Misuse of Neuroscience."

[7] Craig W. Berridge, "Noradrenaline Modulation of Arousal," *Brain Research Reviews*, vol. 38 (2007), pp. 1–17.

[8] Steven Grillner, Henry Markram, Eric De Schutter *et al* "Microcircuits in Action – CPGs to Neocortex," *Trends in Neurosciences*, vol. 28, no. 10 (2005), pp. 525–533.

[9] U. Shivraj Sohur, Jason G. Emsley, Bartley D. Mitchell *et al*., "Adult Neurogenesis and Cellular Brain Repair with Neural Progenitors, Precursors and Stem Cells," *Philosophical Transactions of the Royal Society* B, vol. 261 (2006), pp. 1477–1497.

Utility of the Technology

Neuropsychopharmacology is an applied science whose goal is to develop drugs to treat mental illnesses with a minimum of side effects. To that end, the pharmaceutical industry seeks to identify compounds that act on specific receptor subtypes in the brain, where they can serve either as "agonists" to stimulate the receptors or "antagonists" to block them. For example, a class of neurotransmitter receptors known as "G protein-coupled receptors" (GPCRs) have become important targets for drug development.[10] Designing molecules that act selectively on particular GPCR subtypes has been difficult, however, because evolution has conserved the characteristics of the neurotransmitter binding site across a variety of receptor subtypes.[11] To get around this problem, scientists have synthesized drugs that bind to locations on the surface of GPCRs called "allosteric" sites, inducing changes in the shape of the receptor that modulate the action of the neurotransmitter. Because the allosteric sites are more variable than the neurotransmitter binding site itself, they provide greater opportunity for the development of tailored drugs. It is hoped that the discovery of allosteric modulators for certain types of acetylcholine receptors could lead to new treatments for Alzheimer's disease and other dementias.[12]

The study of neuropeptide systems in the brain is another current area of neuropsychopharmacology research. Oxytocin, for example, is a neuropeptide that for decades has been associated with social bonding behavior and reproduction. In 2005, researchers demonstrated experimentally that aerosolized oxytocin, administered through the nose, has a pronounced effect in increasing trust.[13] Another study using fMRI found that a whiff of oxytocin reduces the ability of threatening images to activate a brain

[10] Laren T. May, Katie Leach, Patrick M. Sexton *et al*., "Allosteric Modulation of G Protein-Coupled Receptors," *Annual Review of Pharmacology and Toxicology*, vol. 47 (2007), pp. 1–51.
[11] Christopher J. Longmead, Jennette Watson and Charlie Revill, "Muscarinic Acetylcholine Receptors as CNS Drug Targets," *Pharmacology and Therapeutics*, vol. 117 (2008), pp. 232–243.
[12] These receptor subtypes are known as muscarinic acetylcholine M_1 and M_4 receptors. See P. Jeffrey Conn, Carrie K. Jones and Crig W. Lindsley, "Subtype-selective Allosteric Modulators of Muscarinic Receptors for the Treatment of CNS Disorders," *Trends in the Pharmacological Sciences*, vol. 30, no. 3 (2008), pp. 148–155.
[13] Michael Kosfeld *et al*., "Oxyocin Increases Trust in Humans," *Nature*, vol. 435 (2005), pp. 673–676.

region called the amygdala, which generates fear in response to danger. This finding suggests that oxytocin regulates social anxiety.[14]

The structure of oxytocin and a related neuropeptide called vasopressin are highly conserved across a variety of mammals, and there is growing evidence that variations in the genes coding for these peptides and their receptors underlie variations in social behavior, both within and between species. For example, research has shown that mice whose oxytocin gene has been "knocked out" by genetic manipulation are unable to recognize other mice, even after repeated social encounters, although their sense of smell and general learning ability are unaffected. Injecting low doses of oxytocin into the amygdala, however, restores the capability for social recognition.[15] Based on this and other experiments, one paper concluded that "the molecular basis of social behavior is not beyond the realm of our understanding."[16]

The intimate relationship between brain and behavior is suggested by a bizarre phenomenon from the annals of parasitology. A protozoan parasite called *Toxoplasma gondii* reproduces in the gut of cats, which excrete the parasite eggs in their feces. Rats then eat the cat feces and become infected with the protozoa. The life-cycle of the parasite begins anew when a cat eats an infected rat. Normally, rats are afraid of cats and avoid the smell of cat urine. But research has shown that the *Toxoplasma* parasite forms cysts in the amygdala of the rat brain, altering the animal's behavior so that instead of avoiding cat urine, the rat finds it attractive. As a result, rats infected by the parasite are more likely to encounter cats and be eaten, to the parasite's advantage. The researchers found that "the loss of fear is remarkably specific."[17] Whether new psychoactive drugs will eventually be capable of manipulating human cognition and behavior with the same degree of precision remains to be seen.

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[14] Peter Kirsch, Christine Esslinger, Qiang Chen, et al., "Oxytoxin Modulates Neural Circuitry for Social Cognition and Fear in Humans," *Journal of Neuroscience*, vol. 25, no. 49 (December 7, 2005), pp. 11489-11493.
[15] J. T. Winslow and T. R. Insel, "The Social Deficits of the Oxytocin Knockout Mouse," *Neuropeptides*, vol. 36, nos. 2-3 (2002), pp. 221–229.
[16] Zoe R. Donaldson and Larry J. Young, "Oxytocin, Vasopressin, and the Neurogenetics of Sociality," *Science*, vol. 322 (2008), pp. 900–904.
[17] Ajai Vyas, Seon-Keyong Kim, and Nicholas Giacomini, "Behavioral Changes Induced by *Toxoplasma* Infection of Rodents are Highly Specific to Aversion of Cat Odors," *Proceedings of the National Academy of Sciences*, vol. 104 (2007), pp. 6442–6447.

Potential for Misuse

During the Cold War, the major powers devoted considerable effort to developing "improved" chemical warfare agents, both lethal and incapacitating.[18] Given that history, recent advances in neuroscience could lead to a renewed search for ways to assault the brain through pharmacological intervention. Indeed, the discovery of several classes of neurotransmitters and their receptors during the 1990s was not lost on those interested in developing so-called "non-lethal" chemical agents designed to incapacitate rather than kill. A study in 2000 by researchers at Pennsylvania State University listed several classes of drugs as potential "calmative" agents, along with the receptor types and sub-types affected by them.[19] Along similar lines, a U.S. National Academies report on cognitive neuroscience observed in 2008:

> [I]f agonists of a particular system enhance cognition, it is mechanistically plausible that antagonists might disrupt cognition; conversely, if antagonists of a particular neurotransmitter enhance, its agonists might disrupt. Examples of the former might include dopamine agonists, which enhance attention, and dopamine antagonists, which disrupt it; examples of the latter might include the suspected cognitive enhancing effects of cannabinoid antagonists and the disrupting effects of agonists like THC.[20]

A key indicator of the dual-use risks of neuropsychopharmacology is the extent to which the development of new drugs for cognitive manipulation has been assimilated into military forces, operations, and doctrines in various parts of the world. In fact, the signs are increasingly ominous. The most immediate danger comes from efforts by states to exploit the so-called "law enforcement exemption" in Article II.9 (d) of the Chemical

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[18] M. R. Dando and M. Furmanski, "Midspectrum Incapacitant Programs," in Mark L. Wheelis, Lajos Rózsa, and Malcolm R. Dando, eds., *Deadly Cultures: Biological Weapons Since 1945* (Cambridge, Mass.: Harvard University Press, 2006), pp. 236–251.

[19] Joan M. Lakoski, W. Bosseau Murray, and John M. Kenny, *The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique* (College Park, PA: Pennsylvania State University, College of Medicine and Applied Research Laboratory, October 3, 2000). See also, Neil Davison, *"Non-Lethal" Weapons* (Basingstoke, UK: Palgrave, 2009).

[20] Committee on Military and Intelligence Methodology for Emergent Neurophysiological and Cognitive/Neural Science Research in the Next Two Decades, *Emerging Cognitive Neuroscience and Related Technologies* (Washington D. C.: National Academies Press, 2008).

Weapons Convention (CWC), which states that toxic chemicals may be used for "law enforcement including domestic riot control purposes" and implies that certain chemicals other than standard riot-control agents may be permitted in such cases. In October 2002, for example, Russian security forces employed a derivative of the opiate anesthetic fentanyl to break the siege of a Moscow theatre by Chechen rebels, killing all of the hostage-takers and 130 of the roughly 800 hostages. Despite the fact that the incapacitating and lethal doses of fentanyl are so close that the term "non-lethal" is a misnomer, the reluctance of other CWC member states to challenge the legality of Russia's use of chemical agents in the Moscow theater incident could be an ominous harbinger of the future.[21] Indeed, it is not difficult to find Western military officers who advocate for the development of similar capabilities.[22]

Ease of Misuse (Explicit and Tacit Knowledge)

The ability to exploit scientific and technological advances in neuroscience for the development of new types of biochemical weapons that affect the brain would demand a great deal of explicit and tacit knowledge on the part of highly trained scientists. Accordingly, a program to develop novel incapacitating agents would probably require the technical and financial resources of a state rather than a non-state actor. If state use of psychoactive drugs for law enforcement and counterterrorism operations becomes widespread, however, the risk will increase that such agents could fall into the hands of terrorists and other non-state actors.

Accessibility of the Technology

The most immediate risk of misuse of neuropsychopharmacology involves efforts by technologically advanced states to acquire so-called "non-lethal" means of dealing with terrorism and insurgency. These countries could easily load existing delivery systems for riot-control agents (such as CS tear gas) with more potent incapacitating agents, which differ from tear gas in that they produce long-lasting effects on the central

[21] Julian Perry Robinson, "Difficulties Facing the Chemical Weapons Convention," *International Affairs*, vol. 84, no. 2 (2008), pp. 223-239.
[22] George N. T. Whitbred, Commander, U.S. Navy, *Offensive Use of Chemical Technologies by US Special Operational Forces in the Global War on Terror: The Nonlethal Option*, Maxwell Paper No. 37 (Alabama: Air War College, Maxwell Air Force Base, 2006).

nervous system. Indeed, a study for the European Defense Agency in 2007 suggested that "calmative" drugs were available to incapacitate individuals and to clear facilities, structures, and areas, indicating that a line may have already been crossed.[23] At present, a major obstacle to the use of incapacitants is the fact that police and troops have not been adequately trained to deal with the consequences.[24]

Imminence and Magnitude of Risk

Although future progress in the field of neuropsychopharmacology is likely to be incremental, the technology is sufficiently advanced that some of its products already pose a risk of misuse. It is also possible that an unexpected discovery in the field of brain chemistry could permit the development of a highly accessible means of incapacitation. As British chemical warfare expert Julian Perry Robinson has observed, "If a new molecule is discovered that can exert novel disabling effects on the human body at low dosage, attempts to weaponize it may well ensue." [25] Such a development would have serious consequences for international security.

Awareness of Dual-Use Potential

The misuse of advances in brain chemistry to develop new types of chemical incapacitating agents would undermine the international norm against the hostile use of the life sciences. Although the dual-use potential of neuropsychopharmacology is not widely recognized by the scientific community, some members of the national security establishment have grasped it with great clarity for at least half a century. These experts are increasingly aware that certain neuropeptides that exist naturally in the brain offer a potential means of manipulating consciousness, cognition, and emotion. In 1991, the U.S. contribution to a background paper on the implications of advances in science and technology for the Biological Weapons Convention (BWC) stated in the section on neuropeptides, "Even a small imbalance in these natural substances could have serious consequences, including fear, fatigue, depression or incapacitation. These substances are

[23] Michael J. A. Crowley, *Regulation of Riot Control Agents and Incapacitants under the Chemical Weapons Convention* (Bradford, UK: Non-Lethal Weapons Project, 2009).
[24] Ross Kirby, "Paradise Lost: The Psycho Agents," *CBW Conventions Bulletin*, no. 71 (2006), pp. 1-5.
[25] Robinson, "Difficulties Facing the Chemical Weapons Convention," pp. 223-239.

extremely difficult to detect but could cause serious consequences or even death if used improperly."[26] (See Chapter 8.)

Characteristics of the Technology Relevant to Governance

Embodiment. The field of neuropsychopharmacology consists primarily of intangible knowledge, although researchers utilize a variety of sophisticated tools, such as functional brain imaging and genetic engineering.

Maturity. Many psychoactive drugs are commercially available while others are still in research and development. Despite considerable progress over the past few decades, the efficacy of many drugs for the treatment of mental illness are controversial, and serious side effects are common.

Convergence. Neuropsychopharmacology is a convergent technology because advances are occurring simultaneously from the "bottom up" (molecular genetics) and from the "top down" (visualization of brain function).

Rate of advance. Indicative of the pace of progress in understanding the functional chemistry of the brain has been a rapid increase in the number of known neurotransmitter receptor systems and ion channels, of which some 50 different classes have been identified to date. In 1990, a standard listing of receptors and ion channels filled 30 pages, and structural information was available for about 25 percent. By 1999, the listing of receptors and channels filled 106 pages, and structural information was available for more than 99 percent.[27]

International diffusion. Mental illness is a major problem for all countries, leading to a strong interest on the part of the psychiatric profession and the pharmaceutical industry in creating more effective therapeutic drugs. Academic neuropsychopharmacologists publish in open scientific journals, and research and development in the field is increasingly international in scope.

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[26] United Nations, *Background Document on New Scientific and Technological Developments Relevant to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*, BWC/CONF.III/4 (Geneva: United Nations, August 26, 1991).

[27] Malcolm R. Dando, *The New Biological Weapons: Threat Proliferation and Control* (Boulder: Lynne Reinner, 2001), Chapter 6: Specificity of Receptors.

Susceptibility to Governance

Because the field of neuropsychopharmacology consists of intangible information that is widely available in the scientific literature, it is not readily susceptible to hard-law governance, although soft-law and normative measures (such as education and awareness-raising) may be of benefit in helping to prevent misuse.

Past and Present Approaches to Governance

Bottom-up governance measures, such as peer review, professional codes of conduct, oversight mechanisms, and pre-publication review of sensitive research findings all require an aware and engaged scientific community to operate them. Yet the large majority of life scientists are unaware of the potential for misuse of the materials, knowledge, and technologies they are developing.[28] Indeed, recent surveys of biosecurity education in Europe[29] and Japan[30] strongly suggest that the problem of dual-use research is rarely covered in university courses.

Options for Future Governance

Several experts have recommended limiting the law-enforcement exemption in the CWC to prevent the development of a new generation of chemical incapacitating agents. Nevertheless, given that the CWC review conferences in 2003 and 2008 failed even to address the issue, top-down governance measures will not be achieved quickly or easily. Although such efforts should be pursued, much can also be done from the bottom up. In particular, the lack of biosecurity awareness on the part of life scientists must be corrected by addressing these issues in the university curriculum, perhaps in the expanding number of bioethics courses. Greater awareness of dual-use concerns will help motivate scientists to develop workable codes of conduct, oversight mechanisms, and

[28] Malcolm R. Dando, "Dual-Use Education for Life Scientists," *Disarmament Forum*, vol. 2, pp. 41-44.
[29] Giulio Mancini and James Revill, *Fostering the Biosecurity Norm: Biosecurity Education for the Next Generation of Life Scientists* (Italy: Landau Network–Centro Volta and UK: University of Bradford, 2008), available at <http://www.dual-usebioethics.net>.
[30] Masamichi Minehata and Naryoshi Shinomiya, *Biosecurity Education: Dual-Use Education in Life-Science Degree Courses at Universities in Japan* (Japan: National Defense Medical College and UK: University of Bradford, 2009), available at <http://www.dual-usebioethics.net>.

other control measures. The Federation of American Scientists (FAS) has posted several biosecurity modules on the Web that lecturers can use as they see fit.[31]

Left to non-governmental action alone, however, the biosecurity awareness and education gap will close very slowly. It is therefore notable that the member states of the BWC, during their 2008 annual meetings in Geneva, agreed that "formal requirements for seminars, modules or courses" on biosecurity could include the possibility of "mandatory components."[32] In the United States, a federal advisory committee, the National Science Advisory Board for Biosecurity (NSABB), has developed a strategic plan for raising awareness of dual-use issues among life scientists.[33] Combined governmental and non-governmental action on biosecurity education could contribute to improving many areas of governance.

It is often argued that "soft-law" and normative measures, such as awareness-raising, education, and codes of conduct, will not prevent states, terrorist groups, or determined individuals from seeking biological weapons. Yet Igor Domaradsky's personal account of his experiences working in the Soviet offensive biological warfare program includes several references to scientists who avoided having anything to do with the program, despite the cost to their careers.[34] The British experience with medical ethics during the Cold War is also instructive. A history of the volunteer program at the Chemical and Biological Defence Establishment at Porton Down describes an ethical debate that took place in 1965 over whether Porton medical officers were justified in "deliberately dosing healthy men with drugs specifically designed to induce some malfunction, either physiological or psychological." When the head of the medical division admitted that the purpose of the testing program was not strictly defensive and also sought to identify agents for offensive development, "this admission 'changed the complexion very considerably' and it was thought that Porton were being asked to do things that 'went far beyond the Medical Research Council rules for human

[31] For the FAS case studies, see: http://www.fas.org/biosecurity/education/dualuse/index.html.
[32] Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, *Report of the Meeting of States Parties*, BWC/MSP/2008/5 (Geneva: United Nations, 2008).
[33] National Science Advisory Board for Biosecurity, *Strategic Plan for Outreach and Education on Dual Use Issues* (Washington, D.C.: NSABB, 2008).
[34] Igor V. Domaradsky and Wendy Orent, *Biowarrior: Inside the Soviet/Russian Biological War Machine* (Amherst: Prometheus Books, 2003), pp. 145, 150, 185.

experiments.’’’[35] These ethical concerns negatively affected the research and caused several of the participating medical doctors to become ill from stress or leave the program.

Conclusions

There is every reason to believe that in the coming decades, neuroscience will provide an increasingly mechanistic and integrated understanding of the human brain and behavior. It is also likely that this new knowledge will be misused for hostile purposes unless strong preventive measures are taken. Because there is no “silver bullet” for effective governance, an integrated web of preventive policies should be developed, including the effective use of education and training to inculcate researchers in the field with the ethos of personal responsibility. At present, the field of dual-use bioethics is underdeveloped compared to medical ethics, but that situation is likely to change in the future. [36]

[35] United Kingdom, Ministry of Defence, *Historical Survey of the Porton Down Volunteer Programme* (London: Ministry of Defence, June 2006).
[36] Malcolm R. Dando, “Bioethicists enter the dual-use debate,” *Bulletin of the Atomic Scientists*, web edition, April 20, 2009.

Chapter 19: Transcranial Magnetic Stimulation

Jonathan D. Moreno[1]

Transcranial magnetic stimulation (TMS), invented in 1985, uses electromagnetic induction to penetrate the skull and affect the human brain by modulating the electrical activity of the cerebral cortex.[2] Because TMS is a relatively inexpensive technology that can modify cognition and behavior, it is certain to attract attention in the coming years for a variety of applications. As a therapeutic technique, TMS offers hope for individuals suffering from major depression, Parkinson's disease, and treatment-resistant migraine headaches, and it is also under investigation for the treatment of post-traumatic stress disorder (PTSD). As a mind-enhancement technique, TMS may suppress the effects of sleep deprivation and enable individuals to perform above their baseline capabilities at specialized tasks.[3] Although TMS has some potential for deliberate misuse by state and non-state actors, the scale and scope of the resulting harm would be limited. For this reason, TMS does not warrant hard-law governance measures, although soft-law and normative measures could be beneficial.

Overview of the Technology

TMS is a painless form of neurostimulation that employs magnetic fields to induce electrical currents in brain tissue.[4] Originally developed as a diagnostic aid for neurologists, TMS has helped to map brain circuitry and connectivity, and it offers therapeutic benefits as well.[5] To conduct TMS, a technician holds an iron-core insulate coil on one side of the patient's head while a large, brief current is passed through the

[1] The author is grateful to Amanda Foote, a former intern at the University of Pennsylvania Center for Bioethics, for her assistance in preparing this paper. Anna C. Merzagora of Drexel University provided valuable technical comments on an earlier draft.

[2] Vincent Walsh and Alvaro Pascual-Leone, with John E. Desmond, "Editorial: Manipulating Brains," *Behavioral Neurology*, vol. 17 (2006), p. 132.

[3] National Research Council, Committee on Opportunities in Neuroscience for Future Army Applications, Board on Army Science and Technology, and Division on Engineering and Physical Sciences, *Opportunities in Neuroscience for Future Army Applications* (Washington, DC: National Academies Press, 2009).

[4] Alan Cowey and Vincent Walsh, "Tickling the brain: studying visual sensation, perception and cognition by transcranial magnetic stimulation," in C. Casanova and M. Ptito, eds., *Progress in Brain Research*, vol. 134 (Amsterdam: Elsevier Science, 2001), pp. 411-425.

[5] "Transcranial Magnetic Stimulation: Safety," *Brookhaven National Laboratories*, February 1, 2008, www.bnl.gov/medical/TMS/safety.asp.

coil. This current generates a magnetic pulse that penetrates the layers of skin, muscle, and bone covering the brain and induces weak, localized electrical currents in the underlying cerebral cortex. Although the mechanisms by which the localized currents modulate neuronal activity are not fully understood, it is believed that the induced electrical field triggers the flow of ions across neuronal membranes and thereby causes the cells to discharge, resulting in a chain-reaction of neuronal interactions.[6]

History of the Technology

The idea of treating ailments with electricity dates back to antiquity. Around 50 BC, Scribonius Largus, the physician to the Roman emperor Claudius, advised that "to immediately remove and permanently cure a headache, however long-lasting and intolerable, a live black torpedo [electric eel] is put on the place which is in pain, until the pain ceases and the part grows numb."[7]

The first attempt to stimulate the brain through the skull occurred in 1755, when Charles Le Roy tried to cure a 21-year old man of his blindness by applying electrical impulses to his head.[8] The impulses generated phosphenes (glowing spots) on the patient's retina but were not strong enough to permanently affect the brain. Although Le Roy failed to cure blindness, he proved that nervous tissue responds to electricity.[9] His work, together with the study of electromagnetism, raised the possibility that strong magnetic fields could stimulate brain tissue.

In 1831 the renowned English chemist and physicist Michael Faraday demonstrated that when an electric current is passed through a primary coil of wire, the fluctuating magnetic field created around the first coil will induce a current in a neighboring coil.[10] By the beginning of the twentieth century, it was known that magnetic fields could modify neural activity, but it was not yet possible to generate large electrical

[6] Cowey and Walsh, "Tickling the brain," p. 411.
[7] Amanda Schaffer, "It May Come as a Shock: Can Electricity Block Migraines?" *New York Times*, November 7, 2006, p. F1.
[8] Vincent Walsh and Alvaro Pascual-Leone, with John E. Desmond, "Editorial: Manipulating Brains," *Behavioral Neurology*, vol. 17 (2006), p. 132.
[9] Ibid.
[10] Cowey and Walsh, "Tickling the brain," p. 411.

currents using a magnet.[11] In 1980 the British neurophysiologists P. A. Merton and H. B. Morton reported stimulating the cerebral cortex of an intact human subject with "brief but very high voltage shocks . . . without undue discomfort."[12]

In 1985 Anthony Barker and colleagues at the University of Sheffield in England succeeded in using transcranial electromagnetic induction to stimulate the human motor cortex, thereby inventing TMS. In some ways TMS is similar to functional magnetic resonance imaging (fMRI) in that both employ intense magnetic fields, but there are important differences. First, fMRI is an imaging technique, whereas TMS is a stimulation and therapeutic technique. Second, the magnetic field plays a central role in fMRI, while the induced electrical current is paramount in TMS. Third, fMRI machines are expensive, bulky, and require extensive technical knowledge for safe and effective operation, while TMS equipment is much smaller and can easily be performed in a doctor's office.

Utility of the Technology

There are two basic types of TMS. In single-pulse TMS, which is employed for diagnostic purposes, the magnetic pulse that induces electrical currents in the cerebral cortex is delivered in a non-repetitive way and the induced currents do not persist beyond the period of stimulation.[13] For therapeutic applications, an improved method called repetitive TMS (rTMS) was developed. It involves the use of a high-speed magnetic stimulator to produce short magnetic pulses of an appropriate frequency. The repetitive pulses induce longer-lasting electrical currents that result in enduring cognitive effects.

[11] Several other researchers made important contributions, including the Germans Gustav Fritsch (1838-1927) and Eduard Hitzig (1838-1907), the Scotsman Sir David Ferrier (1843-1928), the Briton Sir Charles Scott Sherrington (1856-1952), and the Canadian Wilder Penfield (1891-1976). See Roland Sparing and Felix Mottaghy, "Noninvasive brain stimulation with transcranial magnetic or direct stimulation (TMS/tDCS)—From insights into human memory to therapy of its dysfunction," *Methods*, vol. 44, no. 4 (2008), pp. 329-337.

[12] P.A. Merton and H. B. Morton, "Stimulation of the cerebral cortex in the intact human subject," *Nature*, vol. 285, no. 227 (May 22, 1980), http://www.nature.com/nature/journal/v285/n5762/abs/285227a0.html.

[13] Dhwani B. Shah, Laurel Weaver, and John P. O'Reardon, "Transcranial Magnetic Stimulation: A device intended for the psychiatrist's office, but what is its future clinical role?" *Expert Reviews*, vol. 5 (2008), p. 559.

As a therapeutic tool, rTMS can be customized to treat different illnesses.[14] In most stroke victims, one brain hemisphere is retarded while the other is largely unaffected. This asymmetry causes decreased motor-cortex activity in the affected hemisphere and increased activity in the unaffected hemisphere. Restoring function in both hemispheres is essential if the stroke victim is to recover. Using localized magnetic pulses, TMS can help to balance the neurological activity of the two hemispheres by enhancing the excitability of the cortical neurons on the injured side of the brain and suppressing the activity on the unaffected side.[15]

Repetitive TMS (rTMS) is often compared to electro-convulsive therapy (ECT), another neurostimulation technique that delivers a direct electrical shock to the brain rather than a magnetic pulse. ECT, developed before rTMS, is still the standard treatment for adults suffering from treatment-resistant major depressive disorder, but there are indications that this situation could soon change.[16] On January 26, 2007, the U.S. Food and Drug Administration (FDA) convened an expert panel to determine the risk-benefit profile of the Neurostar Transcranial Magnetic Stimulator (manufactured by Neuronetics, Inc.) compared to standard ECT therapy. In a letter to the FDA panel, a psychiatrist stated that in her practice, ECT presented a number of drawbacks for the treatment of major depressive disorder because of its lingering side effects. Patients were unable to work or drive for two or three weeks after an ECT session, and individuals of modest means could not afford to take off that amount of time. The psychiatrist found that rTMS produced the same therapeutic benefit as ECT with fewer long-term side effects.[17] In addition, the Department of Psychiatry at Rush University Medical Center in Chicago reported that it had been "contacted by thousands of patients interested in rTMS." Many of those who enrolled in clinical trials of rTMS "had often failed multiple antidepressant trials, had few treatment options remaining, and were hesitant to risk the cognitive side effects

[14] Felipe Fregni and Alvaro Pascual-Leone, "Technology Insight: noninvasive brain stimulation in neurology – perspectives on the therapeutic potential of rTMS and tDCS," *Nature Clinical Practice Neurology*, vol. 3, no. 4 (2007), www.nature.com/clinicalpractice/neuro.
[15] Ibid.
[16] Jeffery Rado, et al, "To the FDA Neurological Devices Panel," January 19, 2007, <http://www.fda.gov/ohrms/dockets>
[17] Ibid.

associated with ECT." After rTMS treatment, "many subjects reported feeling like themselves for the first time in years."[18]

On October 8, 2008, the FDA gave Neuronetics approval to manufacture an rTMS device for the therapy of treatment-resistant major depressive disorder in adult patients.[19] Although the FDA has not yet approved rTMS for other medical purposes, several academic institutions are using the technique experimentally in clinical research settings for the "off-label" treatment of other brain disorders. For example, researchers at Columbia University have studied the effect of rTMS on the memory of students after an extended period of sleep deprivation.[20] Some evidence also suggests that rTMS could be employed clinically to suppress traumatic memories. According to a U.S. Army survey in 2004 of the mental health of troops who had fought in the Iraq War, about one in eight veterans reported symptoms of post-traumatic stress disorder (PTSD) but less than half of them had sought help.[21] It is tempting to speculate that rTMS may provide an effective treatment for PTSD by helping to suppress negative memories and the emotions that go with them, or by preventing memory formation in the first place. If rTMS turns out to be useful for memory suppression, however, there is a risk that soldiers could be returned to combat too quickly after suffering psychological trauma. Such treatments may also have unintended long-term consequences that are not immediately apparent.

Finally, a few studies have explored the use of fMRI and TMS together for the purpose of lie detection, as an alternative to polygraph use. Scientific evidence for the validity of polygraph data is lacking, and much evidence suggests that the predictive value of the technique is poor in many screening and investigative situations. According to a patent application for a fMRI/TMS "deception inhibitor," an fMRI scan would first indicate whether or not an individual was attempting to deceive the interrogator, after

[18] Ibid.
[19] U.S. Food and Drug Administration, "510(k) Premarket Notification Database. NeuroStar® TMS Therapy System," No. K083538 (Rockville, MD: FDA, December 16, 2008).
[20] B. Luber, A. D. Stanford, P. Bulow, et al., "Remediation of Sleep-Deprivation–Induced Working Memory Impairment with fMRI-Guided Transcranial Magnetic Stimulation," *Cerebral Cortex*, vol. 18, no. 9 (2008), pp. 2077-2085.
[21] Associated Press, "1 in 8 returning soldiers suffers from PTSD; but less than half with problems seek help, report finds," *MSNBC: Health*, June 30, 2004, www.msnbc.msn.com.

which rTMS would be used to block the deception by inhibiting the associated part of the cerebral cortex.[22]

Because of its relatively noninvasive nature, rTMS is generally considered to be a low-risk technology.[23] In fact, safety studies in "normal" subjects show few if any side effects, but rTMS has been employed clinically to treat individuals suffering from Parkinson's disease and major depressive disorder. A bioethical analysis concluded, "While it may be safe to stimulate healthy brain tissue, we have less information about the effects of TMS on abnormal brain tissue."[24] Among the risks associated with rTMS, the most troubling is the potential induction of seizures. Seizure activity may occur when the induced neuronal excitability spreads beyond the localized site, and it typically involves involuntary hand or arm movements.[25] The most important risk factor for seizures is the overall health of the subject's brain. One study found that "seizures are far less likely to occur in normal, healthy subjects than in subjects with neurological diseases such as stroke, brain tumor, or multiple sclerosis."[26]

From 1985 to 1995, seven cases of unintentionally induced seizures occurred during rTMS research protocols.[27] In 1996 the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation reviewed these cases and developed safety guidelines for the use of rTMS. Ever since the guidelines were introduced in 1998, the risks associated with the therapeutic use of rTMS have diminished considerably. Even so, the risks of non-therapeutic use remain substantial. Absent appropriate screening to test the state of an individual's brain before rTMS is performed, there is a possibility of serious side effects, including seizures. Sustained sessions of rTMS could also pose longer-term risks that are not well understood. Like other applied medical technologies, rTMS should be studied under controlled conditions with full informed consent.

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[22] WO/2004/006750, FUNCTIONAL MAGNETIC RESONANCE IMAGING GUIDED TRANSCRANIAL MAGNETIC STIMULATION DECEPTION INHIBITOR, Publication Date 22/01/2004. (The author is grateful to Nita Farahany for informing him of this patent application.)
[23] Cowey and Walsh, "Tickling the brain," p. 416.
[24] Judy Illes and Marisa Gallo, with Matthew P. Kirschen, "An ethics perspective on Transcranial Magnetic Stimulation (TMS) and human neuromodulation," *Behavioral Neurology*, vol. 17 (2006), p. 151.
[25] H. Branch Coslett, "Transcranial Magnetic Stimulation: Safety Considerations," Department of Neurology, University of Pennsylvania, www.ncrrn.org/papers/methodology_papers/tms.pdf.
[26] Ibid.
[27] "Transcranial Magnetic Stimulation: Safety," *Brookhaven National Laboratories*, February 1, 2008, www.bnl.gov/medical/TMS/safety.asp.

Potential for Misuse

Repetitive TMS is a clear case of a dual-use technology. Under strictly controlled conditions, it offers a promising and apparently safe intervention for persons suffering from serious mental illnesses. Given the limited expertise needed to employ the technique, however, states or terrorist organizations could potentially misuse it for harmful purposes. Aside from the obvious misuse of rTMS to induce permanent brain damage, other misapplications may warrant more nuanced ethical scrutiny. Some malign applications would be *intrinsically* unethical, such as "erasing" the memory of a highly trained operative who carried out a sensitive operation, such as a rendition or an assassination. This procedure would shield the individual from PTSD and also render him immune to interrogation in the event of capture or compromise. Other applications of rTMS could be *extrinsically* unethical, depending on the larger context and purpose for which the technique is used. For example, it would be unethical to enhance the ability of a terrorist to carry out an attack in a highly stressful environment.

Although TMS has existed since 1985, the U.S. Department of Defense has only recently recognized its potential for "warfighter enhancement" over some baseline of normalcy. A 2009 report by the U.S. National Academies titled *Opportunities in Neuroscience for Future Army Applications* recommended that the Army increase its investment in TMS research. According to the report,

> It is possible that TMS can be employed to enhance rather than suppress activation. One recent study showed enhancement of top-down visuospatial attention using combined fMRI/TMS stimulation (Blankenburg et al., 2008). The ability to target smaller areas is an objective sought by the TMS research community in general, but making such a device deployable in the field would require Army investment. Making this technology available in-vehicle is achievable in the medium term. The committee believes that in-helmet TMS technology would not

> be a useful investment until definitive applications, enhancing or inhibiting, are identified in the laboratory.[28]

The committee estimated the research and development timeframe for enhancing attention with rTMS at five to 10 years, and for in-vehicle deployment at 10 to 20 years. Repetitive TMS might also be used to improve learning and memory, such as increasing the ability of an operative to speak a native dialect or to recall complicated instructions.[29] Nevertheless, human experimentation with rTMS in the national security context poses significant ethical challenges.[30] If any of the proposed military applications prove to be successful and cost-effective, they could lead to an "arms race" in the neural enhancement of combat troops. In that case, how much and what types of cognitive modification would individual soldiers be required to accept? Although neural enhancement through rTMS might improve their combat performance and ability to protect one another, it might not provide as clear a benefit as a superior weapon.

Recent evidence also suggests that repetitive TMS might be misapplied to manipulate moral judgment, or beliefs about right and wrong. In a laboratory simulation in which subjects were told about a failed attempt to kill an intended victim, subjects in whom rTMS was used to disrupt the activity of a small region of the brain called the right temporo-parietal junction (TPJ) were more likely to forgive an unsuccessful murder attempt than those subjects in whom the right TPJ was not stimulated. Thus, the right TPJ appears to be involved in the application of moral principles; when its activity is disrupted with rTMS, the brain relies more on actual outcomes. [31]

This experiment suggests that while studies of rTMS could be important for elucidating the role of the brain in moral development, there is a real potential for abuse. For example, it is often alleged that suicide bombers are drugged, yet a precisely targetable technology that caused people to suspend their moral judgment without

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[28] National Research Council, *Opportunities in Neuroscience for Future Army Applications*, p. 85.
[29] Ibid.
[30] Jonathan D. Moreno, *Undue Risk: Secret State Experiments on Humans* (New York: W.H. Freeman, 1999).
[31] Liane Young, Joan Albert Camprodon, Marc Hauser, Alvaro Pascual-Leone, and Rebecca Saxe, "Disruption of the right temporo-parietal junction with transcranial magnetic stimulation reduces the role of beliefs in moral judgments," *Proceedings of the National Academy of Sciences*, vol. 107, no. 15 (April 27, 2010), pp. 6753-6758.

suffering debilitating side effects might offer a more desirable alternative. It is possible, for example, that applying TMS to the appropriate brain region could cause subjects to suspend their moral beliefs and behave according to some grossly utilitarian calculus, such as, "If you carry out a suicide attack, you will send a message to our foes and save the lives of many others."

Ease of Misuse (Explicit and Tacit Knowledge)

Given the relatively modest equipment and training required, non-state actors and terrorists might be able to exploit repetitive TMS for its actual or perceived effects. Nevertheless, although the technology may seem straightforward, using it safely involves some technical expertise and experience. The angle at which the coil is held against the head, and which side of the coil is closer to the skull, can substantially affect the outcome of the stimulation. Without proper training to pinpoint the intended region of the brain to be activated, there is a risk of causing significant and potentially irreversible brain damage.

Accessibility of the Technology

The basic components of TMS technology—an iron-core coil and a magnetic stimulator—are commercially available at reasonable cost and thus are relatively easy to obtain. Major manufacturers of TMS equipment exist in Canada, China, Germany, Israel, South Korea, Switzerland, and the United States. Although the current pool of manufacturers is limited, the relative simplicity of the technology will enable the number to increase rapidly in response to demand.

Imminence and Magnitude of Risk

The misuse of rTMS could be extremely detrimental to individual subjects by suppressing the neuronal activity of localized brain regions. The technology might therefore be misused for hostile purposes, such as disabling enemy combatants. Because rTMS can be applied to only one individual at a time, however, it cannot harm entire groups or populations and thus poses a lower magnitude of potential risk than many other dual-use technologies discussed in this volume.

Characteristics of the Technology Relevant to Governance

Embodiment. TMS is primarily a hardware-based technology, although it requires functional know-how to operate.

Maturity. Over the past 20 years, repetitive TMS has evolved from an experimental diagnostic technique into a mature technology that has been approved for the treatment of major depressive disorder and has other promising clinical applications.

Convergence. TMS is a convergent technology to the extent that it can be used in conjunction with functional MRI and other brain-imaging techniques.

Rate of advance. Repetitive TMS is in advanced development for the treatment of several mental and neurological disorders for which standard therapies are ineffective, such as Parkinson's disease, stroke, and post-traumatic stress disorder.

International diffusion. Therapeutic use of rTMS is spreading rapidly among the advanced industrialized countries, mostly in academic settings such as medical schools and research institutes. Several countries outside the United States have approved TMS for the treatment of major depression, including Australia, Canada, China, and Israel. Once the safety and efficacy of rTMS have been demonstrated, it is likely to spread to many more countries.

Susceptibility to Governance

Governance of TMS could mean two things: (1) regulating experiments with and legitimate applications of the technology, and (2) regulating the sale of TMS equipment. The first approach would seek to prevent the development of hostile applications of TMS, while the second would try to prevent TMS equipment from falling into the wrong hands. The feasibility of the two strategies differs. Because TMS not yet diffused widely, it can still be controlled at the national level through the existing regulatory approval process. With respect to sales of TMS equipment to various customers overseas, verifying that the technology was being used for legitimate therapeutic purposes—or, alternatively, for state-sponsored experiments aimed at harmful applications—would be a difficult task. For this reason, the susceptibility to governance of TMS appears to be fairly low, particularly in the long-term. It is also important to weigh the potential costs of overly

stringent governance, which could impede the wider use of TMS for treating a variety of neuropsychiatric disorders.

Past and Present Approaches to Governance

At present, treatment-resistant major depressive disorder is the only application of rTMS that has been approved by the FDA, providing a time window for the regulation of other medical applications.

Options for Future Governance

Possible governance options for rTMS include control through the regulatory approval process for medical devices, as well as regulations on experimentation with human subjects. Beginning in 1996, the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation adopted safety regulations to limit the risks of rTMS to patients.[32] These and other rules for experimentation on human subjects may provide an opportunity to regulate the military applications of rTMS at an early stage. A key factor will be how the first soldiers equipped with this technology are treated: as human subjects in an experiment or, alternatively, as trainees such as test pilots, for whom a different calculus of risk and benefit applies.

At least for the near future, the limited number of manufacturers and vendors of TMS machines could make it possible to track international sales. Even so, it is difficult to determine the end-use of a TMS device after it has been exported, particularly in countries that, for whatever reason, are not transparent in their laboratory practices. Other options for governance include normative measures, such as voluntary awareness-raising and education about the dual-use risks of TMS.

Conclusions

In little more than a quarter-century, TMS has evolved from a diagnostic tool into a therapeutic technology with the potential to improve the quality of life of patients with

[32] Eric M. Wassermann, "Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996," *Electroencephalography and Clinical Neurophysiology,* vol. 108 (1998), pp. 1-16.

neuropsychiatric disorders such as treatment-resistant major depression. In addition, repetitive TMS can suppress the operation of a specific brain region to block unwanted memories or activities, and it could potentially erase traumatic memories from the psyche of patients suffering from PTSD. In conjunction with other neurotechnologies, rTMS may enhance brain networks associated with attention, learning, and other cognitive processes. Although rTMS could be misused to manipulate or harm individual human subjects, it has no capacity to harm large numbers of people. As researchers continue to explore the applications of TMS technology, governance measures to prevent misuse will need to evolve as well.

PART III: FINDINGS AND CONCLUSIONS

Chapter 20: Comparative Analysis of the Case Studies

Jonathan B. Tucker

The 14 case studies of emerging dual-use technologies included in the previous section were chosen to be illustrative rather than comprehensive, while attempting to capture the full range of variability in several key characteristics. Taking an inductive approach, this chapter attempts to distill the voluminous information in the case studies into an analytical framework that can be applied to both current and future dual-use technologies. Although efforts to develop a reasonably parsimonious model inevitably require some loss of nuance and detail, that drawback is more than offset by the virtue of identifying general principles.

Monitoring Technological Developments

A prerequisite for the assessment of emerging dual-use technologies is the existence of a "technology-watch" program that monitors innovations in the biological and chemical fields and identifies those with a potential for misuse. At present, the regular five-year review conferences of the Biological Weapons Convention (BWC) and the Chemical Weapons Convention (CWC) include a review of advances in science and technology relevant to the two treaties. In the case of the BWC, individual member states prepare national papers on scientific and technological developments during the five-year period since the last review conference, and these contributions are merged into a single document by the BWC Implementation Support Unit (ISU) in Geneva. For the CWC, prior to each review conference the Scientific Advisory Board (SAB) of the Organization for the Prohibition of Chemical Weapons (OPCW) conducts an assessment of advances in science and technology relevant to the Convention, with significant input from an independent technical panel under the auspices of the International Union of Pure and Applied Chemistry (IUPAC). Unfortunately, the SAB suffers from an uneven level of expertise and a lack of travel money to support regular meetings, which have undermined its effectiveness. Some analysts have also argued that given the rapid rate of advance in the

biological and chemical fields, the five-year reviews of advances in science and technology relevant to the BWC are not sufficient and that an ongoing monitoring process is warranted. According to Nicholas Sims, for example,

> The BWC exists in a scientific context which has altered drastically from the assumptions of the 1972 text and is still changing fast. . . . Science and technology input to review conferences has been spasmodic, and never systematically considered. In any case, in view of the pace of development and innovation in the biosciences, five years is too long an interval for S&T reviews. . . . These collective S&T reviews need to be undertaken every year in an expert forum. Whether organized as an appointed panel or as a looser network of scientific advisers, a forum of this kind would enable different specialisms, as well as different governments, to feed in their assessments of what is happening in the life sciences and elsewhere in the S&T universe that has a bearing on the health of the BWC.[1]

A few other entities also conduct periodic assessments of emerging dual-use technologies in the biological and chemical fields. The Australia Group has created ad hoc committees to review certain technologies of concern, such as microreactors and gene synthesis, in order to decide whether or not they should be added to the harmonized export control lists. Supplementing the activities of governments are the technology-monitoring efforts of independent advisory bodies, such as the U.S. National Academies and the British Royal Society. Both organizations assess emerging technologies when asked to do so, but they do not have an ongoing mandate to perform this function. Finally, a small number of scholars in academia and various think-tanks monitor emerging biotechnologies and assess their dual-use risks, including groups at the Massachusetts Institute of Technology, the University of California at Berkeley, Arizona State University, the Woodrow Wilson International Center for Scholars, and the Center for Policy on Emerging Technologies.

[1] Nicholas Sims, "Midpoint Between Review Conferences: Next Steps to Strengthen the BWC," *Disarmament Diplomacy*, No. 91 (Summer 2009), http://www.acronym.org.uk/dd/dd91/91bwc.htm.

Assessing Dual-Use Risk

Once emerging dual-use technologies have been identified, it is important to assess their risks in a systematic manner. As was discussed earlier in Chapter 5 ("Case Study Template"), the analysis of the case studies focused on two key dimensions, the risk of misuse and the susceptibility to governance, each of which was measured with a set of specific parameters. **Table 20.1** summarizes the level of dual-use concern for the 14 technologies included in this volume. For each case study, the risk of misuse was assessed on the basis of four parameters: (1) *ease of misuse*, including the extent to which both explicit and tacit knowledge are required to exploit the technology for harmful purposes; (2) *accessibility*, meaning the commercial or other availability of the technology and the amount of capital needed to acquire it; (3) the *magnitude of potential harm* that could result from misuse, including fatalities, injuries, economic costs, and social disruption; and (4) the *imminence of potential misuse*, ranging from near-term to long-term. For each of the case studies, the four parameters were ranked on a simple ordinal scale (HIGH, MEDIUM, or LOW) and then averaged to yield an "overall level of concern" for the technology in question.

Chemical micro process devices, for example, have a MEDIUM *ease of misuse* because considerable explicit and tacit knowledge are needed to adapt the technology to the production of chemical warfare (CW) agents. The *accessibility* of the technology is HIGH because micro process devices are commercially available and generally within the financial means of both state and non-state actors. The *severity of potential harm* is HIGH because microreactors could allow the large-scale production of CW agents in small, easily concealable facilities. Finally, the *imminence of potential misuse* is HIGH because current forms of the technology could be exploited for covert chemical weapons production. Thus, averaging the four parameters, the overall risk of misuse associated with this technology is HIGH.

An emerging technology at the opposite end of the dual-use risk spectrum is gene therapy. The *ease of misuse* of this technology is LOW because using viral vectors to deliver harmful genes to a target population would require expertise and tacit knowledge that currently do not exist. The *accessibility* of the technology to scientists in industrialized countries is MEDIUM, but the severity and imminence of potential misuse are LOW because the technology is not at the point at which it would be feasible to carry out a covert, large-scale attack. Thus, the

overall dual-use risk associated with this technology is currently judged to be LOW, although that assessment might change at some point in the future.

In general, to meet the criteria for a MEDIUM or HIGH overall level of risk, an emerging dual-use technology must have characteristics that provide a significant qualitative or quantitative advantage over established technologies in the ability to cause harm. For example, because micro process devices are potentially capable of synthesizing large quantities of toxic chemicals in small, easily concealed facilities, they represent a significant increase in dual-use risk over conventional chemical batch reactors. The same is true of gene-synthesis technology, which provides the capability to create infectious viruses from scratch, including those that have become extinct or have been eradicated from nature. Thus, both of these emerging technologies are associated with a new and salient threat of misuse that warrants an appropriate set of governance measures. In contrast, whenever the overall dual-use risk associated with an emerging technology is judged to be LOW and is unlikely to materialize for some time, policymakers should put the technology on a "watch list" and monitor its further development so that governance measures can be introduced later on, should they be considered necessary.

Assessing Governability

The second key variable associated with emerging dual-use technologies is susceptibility to governance. **Table 20.2** assesses the governability of the 14 emerging technologies included in this volume according to five parameters: (1) the *embodiment* of the technology, meaning whether it takes the form of hardware, intangible information, or a combination of the two; (2) the *maturity* of the technology, referring to its position in the development pipeline that extends from basic research to widespread commercialization; (3) the *convergence* of the technology, meaning the number of different disciplines that were brought together to create the new capability; (4) the *rate of advance* of the technology, namely whether its speed, throughput, and accuracy are increasing exponentially or linearly over time or have reached a plateau; and (5) the *international diffusion* of the technology, as measured by the number of countries that have acquired it.

For each of the 14 technologies studied, the five parameters of governability were ranked on an ordinal scale of HIGH, MEDIUM, or LOW and then averaged to give a rough assessment

of the technology's overall susceptibility to governance. As noted in Chapter 5, three of the parameters—convergence, rate of advance, and international diffusion—are inversely related to governability, while for the other two—embodiment and maturity—the relationship to governability is complex. In general, the parameters of an emerging technology that make it most susceptible to governance include the following:

- *Embodiment*. Technologies embodied in the form of hardware are relatively easy to govern through measures such as registration and export controls. In contrast, technologies embodied in the form of intangible information are less governable because information can be transmitted easily and undetectably in written or electronic form. Formal regulation is particularly difficult in the case of "enabling" technologies that are largely intangible and widely employed in research laboratories, such as the polymerase chain reaction (PCR) or RNA interference.
- *Maturity*. A technology in the prototyping or early-commercial stage of development is most governable because it is neither too early to assess the risk of misuse nor too late to impose effective governance measures.
- *Rate of advance.* A slow or incremental rate of technological progress is best because it is possible for governance measures to keep pace.
- *Convergence*. Technologies that draw on only one or at most a few disciplines are more governable because of the limited number of different professional communities that must be engaged.
- *International diffusion*. The limited geographical spread of a technology facilitates governance by reducing the need for international coordination and harmonization.

Categorizing the Case Studies

To develop a generic model for the governance of emerging dual-use technologies, the study used an inductive approach based on examining patterns across the 14 case studies. The three-by-three matrix in **Table 20.3** classifies the emerging technologies included in this volume according to the two dimensions of risk of misuse and susceptibility to governance. One goal of this analysis was to identify the subset of technologies for which it is most urgent and productive for policymakers to develop governance measures.

Table 20.3: Typology of the 14 Case Studies

Governability

Risk of Misuse	**LOW**	**MEDIUM**	**HIGH**	
HIGH	DNA shuffling and directed evolution Neuropsycho-pharmacology	Combinatorial chemistry and high-throughput screening	Viral genome synthesis Chemical micro process devices	**HIGH**
MEDIUM	RNA interference Rational vaccine design	Protein engineering Bioregulators and peptide synthesis		**MEDIUM**
LOW	Synthetic biology with standardized parts	Personal genomics Aerosol vaccines	Gene therapy Transcranial magnetic stimulation	**LOW**
	LOW	**MEDIUM**	**HIGH**	

The technologies that fall within the shaded area in the upper right-hand corner of the matrix are judged to have a HIGH or MEDIUM overall risk of misuse *and* a HIGH or MEDIUM overall level of governability. Two emerging technologies—viral genome synthesis and chemical micro process devices—rank HIGH in both dimensions of dual-use risk and governability. Three additional technologies within the shaded portion—combinatorial chemistry and high-throughput screening, protein engineering, and bioregulators and peptide synthesis—have a combination of HIGH and MEDIUM scores. Only for the technologies in the shaded area does the development of specific risk-management strategies appear both necessary and feasible in the immediate term.

The technologies in the upper left-hand corner of the matrix, DNA shuffling and neuropsychopharmacology, pose a HIGH risk of misuse but a LOW susceptibility to governance, either because they are based on intangible knowledge that makes them more difficult to control or because they draw on materials, equipment, and know-how that are widely available in

laboratories around the world. Although these technologies pose a significant risk of misuse, they are not amenable to formal, legally binding regulations, putting effective governance beyond the direct control of policymakers. Nevertheless, the significant dual-use risk associated with these technologies means that they should not simply be ignored. Instead, they should be carefully monitored and, to the extent possible, subjected to normative measures such as education and awareness campaigns.

The technologies in the lower right-hand corner of the matrix, gene therapy and transcranial magnetic stimulation (TMS), pose a LOW risk of deliberate misuse because they can be applied only to one individual at a time rather than to a large group or population. At the same time, these technologies provide a HIGH level of governability because their clinical use is already regulated on biosafety or ethical grounds. TMS is also relatively governable because it is embodied in the form of hardware.

Finally, the one technology in the lower left-hand corner of the matrix, synthetic biology with standardized parts, currently has a LOW risk of misuse and a LOW susceptibility to governance. With respect to the risk of misuse, the limited availability of biological parts with known functionality and reliability, and the current need for a high level of expertise and tacit knowledge to assemble these parts into functional genetic circuits, make it difficult at present to exploit this technology for harmful purposes. The governability of parts-based synthetic biology is also assessed to be LOW because the technology is currently at an embryonic stage of development and its practitioners are pursuing an "open source" approach in which all legitimate researchers are granted unrestricted access to the Registry of Standard Biological Parts. In principle, however, more stringent governance mechanisms could be imposed—for example, by limiting access to the Registry and by requiring all who are granted access to undergo some type of personal security vetting.

Because the field of synthetic biology is evolving so rapidly, the current assessments of risk and governability should be viewed as a snapshot in time and should therefore be revisited periodically in the coming years as the technology evolves and its potential for misuse becomes more apparent. Over the next decade, it is likely that the design and synthesis of artificial genomes will become increasingly "de-skilled" through the commercial availability of easy-to-

use kits and manuals. If these expected developments do in fact materialize, then the dual-use risk of synthetic biology will increase and its governability will decline further.

Selection of Governance Measures

Once the analysis described above has identified the subset of emerging dual-use technologies that pose a significant risk of misuse *and* are reasonably susceptible to governance, the next step is to select a tailored package of control measures, as shown in **Figure 20.1**. As a first step, it is important to identify any laws, regulations, or guidelines governing the technology that already exist before proposing new ones. It is also important to determine whether the existing governance measures apply to the technology itself (e.g., registration of DNA synthesizers) or products resulting from its use (e.g., screening of gene synthesis orders). Finally, the analysis of possible governance measures should start at the national level and, if the technology has spread to other countries, extend to the development of international measures.

In addition to identifying existing laws and regulations, it is important to assess how well they are being implemented. Just because a law is on the books does not mean it is effective. An important factor is what agency is responsible for its enforcement and whether it has inefficiencies or conflicts of interest that impede its utility. Edward Hammond has shown, for example, that the U.S. system of Institutional Biosafety Committees (IBCs) is deeply flawed and that the effectiveness and rigor of IBCs varies widely from institution to institution.[2] Gregory Koblentz has also argued that the National Science Advisory Board for Biosecurity (NSABB) has a conflict of interest because it is administered by the National Institutes of Health, which is charged with promoting biomedical research and thus has a strong bias against governance measures that could reduce scientific productivity, raise the costs of research, or hamper innovation.[3]

As noted in Chapter 3, there are three broad categories of technology governance measures. The first category is *hard law* or legally binding measures, including arms control treaties, national laws, formal regulations, and statute-based export controls. Multilateral treaties such as the BWC and the CWC prohibit member states from engaging in the hostile use of

[2] Margaret S. Race and Edward Hammond, "An Evaluation of the Role and Effectiveness of Institutional Biosafety Committees in Providing Oversight and Security at Biocontainment Laboratories," *Biosecurity and Bioterrorism*, ol. 6, no. 1 (March 2008), pp. 19-35.
[3] Gregory Koblentz, personal communication to author, May 27, 2010.

poison and disease and also require them to adopt national implementing legislation making these prohibitions binding on their citizens, both at home and abroad. Synergies exist between the norm-reinforcing role of treaties and the national laws and regulations that are devised to implement those norms in a practical manner. At the domestic level, hard-law measures can run the gamut from a simple requirement to declare certain information to stringent regulations (such as the Select Agent Rules) that are enforced with audits, on-site inspections, and penal sanctions for violations.

The second category of technology governance involves *soft law* measures that are not legally binding. Such measures include voluntary guidelines promulgated by governments, self-regulatory mechanisms devised by industry associations and non-governmental organizations, and international standards such as those established by the International Standards Organization (ISO). Finally, the third category of technology governance involves *normative* measures, which are less formal than soft-law measures and generally apply to individuals and groups rather than to institutions. Examples include consensus best practices, professional codes of conduct, dual-use education and awareness-building efforts, and the creation of secure channels through which whistleblowers can report misuse without risk of retaliation. Normative measures generally seek to build a culture of security and responsibility within a relevant professional community, such as research scientists or the suppliers and customers of dual-use equipment and services.

Because emerging technologies entail varying levels of dual-use risk and governability, they are best managed by tailored packages of hard-law, soft-law, and normative measures. In general, the more a technology is susceptible to governance, the greater the utility of hard-law approaches, such as national legislation and formal regulation. For technologies that are not readily susceptible to governance because they are pervasive, intangible, enabling, or widely accessible, the only workable governance options may be normative measures, such as awareness-raising and codes of conduct. Although normative measures are generally less effective than more formal measures, they may still be useful for preventing misuse. Wherever possible, it is desirable to pursue synergies among the three modes of governance by combining them in mutually reinforcing ways to create a "web of prevention."

Intervention Points and Targets

For best effect, the various types of governance measures (hard law, soft law, and normative) can be introduced at different points along the technology development pipeline. In thinking about the timing of policy interventions, it is useful to visualize technology development as a stream, with intervention points at various points along its bank. In the case of synthetic genomics, for example, one can intervene "upstream" by requiring the registration of all new DNA synthesizers, "midstream" by licensing commercial suppliers who use DNA synthesizers to produce custom synthetic genes to order, and "downstream" by screening DNA synthesis orders to ensure that they do not contain pathogenic sequences.[4]

Another important variable is the target of the policy intervention, which may be the federal or state government, a company or institution, an individual, a product or piece of hardware, or a piece of intangible knowledge. Technology research and development (R&D) takes place in four different settings: (1) private industry, (2) government research laboratories, (3) universities or non-profit research institutes, and (4) outside the formal institutional context, as in the case of hobbyist organizations such as Do-It-Yourself Biology (*DIYbio*). In most of these settings, the R&D process proceeds in secret until the technology is formally disclosed. Such disclosure may take various forms: a patent application or the launch of a commercial product in the case of private industry, the declassification or licensing of a technology in the case of the federal government, and the publication or presentation of research findings at a professional conference in the case of an academic or nonprofit research institution.

Although most governance measures are relevant to the post-disclosure phase, pre-disclosure R&D may be a suitable target for intervention in some cases. For example, it is possible to imagine a regulatory framework that would require both government and non-government laboratories to report any emerging technology that poses potential dual-use risks before it is publicly released.[5] Indeed, the U.S. Patent and Trademark Office reviews patent applications for innovations that may have implications for national security, and it has the

[4] Another type of upstream intervention would be to design DNA synthesizers that are "proliferation-resistant" because they are technically incapable of synthesizing pathogenic sequences. See Ali Nouri and Christopher F. Chyba, "Proliferation-resistant biotechnology: An approach to improve biological security," *Nature Biotechnology*, vol. 27 (2009), pp. 234-236.

[5] Leonard S. Spector, James Martin Center for Nonproliferation Studies, personal communication.

power to classify patents in exceptional cases.[6] **Table 20.4** provides a menu of governance measures according to the mode of governance and the target of the policy intervention.

Table 20.4: Menu of Possible Governance Measures

	MODE OF GOVERNANCE		
INTERVENTION TARGET	**HARD LAW (civil and criminal statues, binding regulations)**	**SOFT LAW (voluntary guidelines and self-governance mechanisms)**	**NORMATIVE (codes of conduct, education and training, etc.)**
STATE	Multilateral treaty Framework convention National export controls End-user certificates Economic sanctions	Voluntary guidelines and best practices Multilateral export-control regimes Oversight mechanisms Recombinant DNA Advisory Committee	International norms Economic pressure from customers
INSTITUTION	Registration, accreditation, or certification Mandatory data declarations Onsite inspections Institutional Review Boards (IRBs) Conditions on funding	Informal oversight mechanisms Industry best practices and voluntary standards Institutional Biosafety Committees (IBCs)	Economic pressure from customers Economic boycotts Outreach and awareness-raising
INDIVIDUAL	Security vetting or screening Registration, accreditation, or certification	Voluntary guidelines and best practices	Hippocratic Oath, professional codes of conduct Dissent and whistle-blowing channels Education and awareness-building
PRODUCT	Licensing or registration Select Agent Rules	ISO standards Screening of DNA synthesis orders	Sales awareness training ("know thy customer")
KNOWLEDGE	Classification Deemed exports	Pre-publication review	Information-sharing Transparency

[6] The Invention and Secrecy Act of 1952 (35 U.S.C. 181) empowers the U.S. Patent and Trademark Office to prevent the release of information contained in a patent on security grounds. The statute specifies that "whenever publication or disclosure by the grant of a patent on an invention in which the Government has a property interest might, in the opinion of the head of the interested Government agency, be detrimental to the national security, the Commissioner upon being so notified shall order that the invention be kept secret and shall withhold the grant of a patent therefor."

International Governance

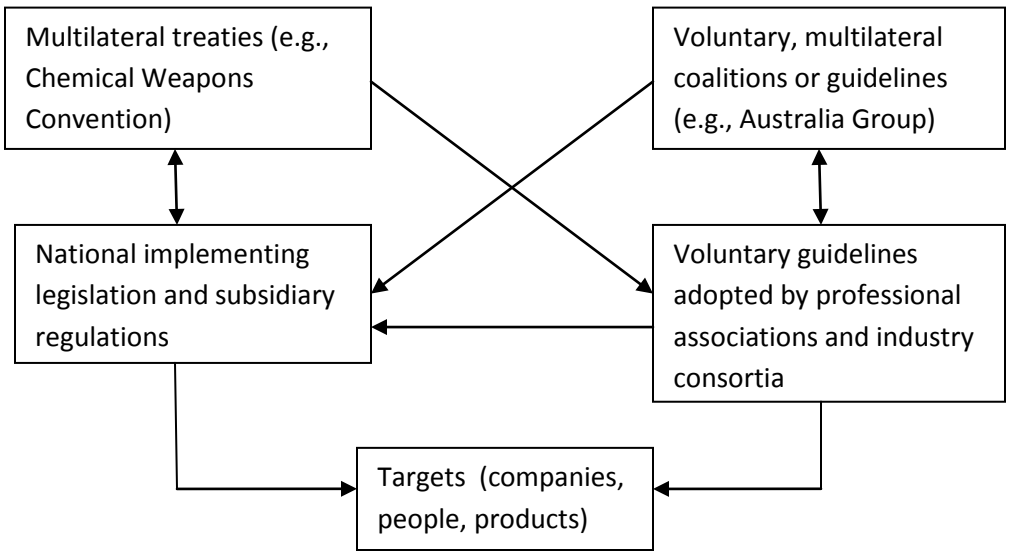
Today, as a consequence of economic globalization, many dual-use biological and chemical technologies have diffused internationally, making it necessary to govern them at the regional or global level. In such cases, the selection of domestic measures should take into account whether or not they can be implemented by all relevant countries. International measures for the governance of dual-use technologies may be developed and promulgated through four different mechanisms, the first two top-down and the second two bottom-up:

1. *A group of states come together to negotiate a multilateral treaty* ab initio*, that is, without any previous activity at the national level.* If the treaty is not self-executing, it will mandate each member state to adopt domestic implementing legislation that imposes new obligations on its citizens and private companies. Such legislation may either supersede or complement existing laws. For example, the CWC, the BWC, and UN Security Council Resolution 1540 require member states to adopt export controls and penal legislation. Additional countries wishing to accede to a treaty after its entry into force must comply with the mandate to adopt domestic implementing legislation.
2. *An informal coalition of like-minded states jointly develops a set of common guidelines or other soft-law measures to regulate a dual-use technology of concern.* For example, the nations participating in the Australia Group meet each year to update and harmonize their national export controls on dual-use materials and equipment related to the production of chemical and biological weapons.
3. *Domestic legislation developed by one or more country serves as a model for others, leading over time to the emergence of a harmonized international regime.* For example, several countries have emulated the U.S. Select Agent Rules, which impose stringent access controls on a list of pathogens and toxins of bioterrorism concern.
4. *An association of private companies or a coalition of non-governmental organizations work together to establish a set of voluntary guidelines or norms, which they then promote to similar non-state entities from other countries.* In the case of synthetic genomics, for example, two groups of commercial gene-synthesis firms have proactively developed their own sets of guidelines to verify the bona fides of

customers and to screen gene synthesis orders to prevent the acquisition of pathogenic DNA sequences by criminals or terrorists. These industry initiatives subsequently inspired the U.S. government to propose its own set of voluntary guidelines, which may eventually be extended to other countries.[7]

Figure 20.2 depicts the four approaches to international governance, demonstrating how national-level and international-level measures can operate in both directions.

Figure 20.2 – Relationships among national and international governance measures



Cost-Benefit Analysis

After identifying a set of potentially suitable governance measures, it is necessary to perform a cost-benefit analysis to make a final selection. This task involves weighing the security benefits of each measure against the direct and indirect economic costs, including which benefits of the technology (health and safety, economic, or environmental) must be foregone as a result of the proposed governance measure. Criteria to consider when conducting a cost-benefit analysis include the magnitude of risk to be mitigated, the likely effectiveness of the proposed

[77] Jonathan B. Tucker, "Double-Edged DNA: Preventing the Misuse of Gene Synthesis," *Issues in Science and Technology*, vol. 26, no. 3 (Spring 2010), pp. 23-32.

measure at reducing risk, the extent to which the measure diminishes the expected benefits of the technology, and any direct and indirect costs of implementation, such as decreased international competitiveness.

In fast-moving fields such as synthetic genomics, which are potentially governable by hard-law means, the costs of formal regulations may outweigh the risk of misuse. Legally binding treaties, for example, have a number of drawbacks. They usually take several years to negotiate and, once concluded, may be too inflexible to keep pace with rapid technological change. In addition, treaties rarely apply to specific technologies, making them ill-suited to tailored approaches to governance. For these reasons, more flexible measures may be preferable at the international level. Possible alternatives may include the development of internationally harmonized guidelines on a voluntary basis, or the negotiation of a framework convention that can be easily modified over time as a technology matures.

The cost-benefit analysis of various governance measures should be conducted in an iterative manner, with the goal of identifying the "package" of hard-law, soft-law, and/or normative measures that provides the greatest overall benefit and the lowest cost. An optimal governance package for a given technology may also involve a combination of several different targets and intervention points, which ideally should reinforce one another. For example, governance measures for the synthesis of bioactive peptides might target the companies that can manufacture peptides to order in significant quantities, the firms that manufacture and sell peptide synthesizers, and the companies and scientists who work with bioactive peptides in the research, medical, and pharmaceutical communities.

Although synergies among governance measures are highly desirable, tradeoffs are inevitable. In some cases, only partial measures to lower the risk of misuse may be feasible because more stringent measures would impose excessive costs. If the dual-use risks of a technology are particularly large and imminent, however, policymakers may be prepared to tolerate high governance costs in order to ensure an adequate level of security. Another factor influencing the cost-benefit analysis of specific governance measures is the perception of risk. As noted in Chapter 2, a large literature in psychology and behavioral economics describes how non-rational factors such as cognitive biases distort risk judgments and influence government action to regulate new technologies. In general, the developers of a new technology tend to

emphasize its tangible benefits, both immediate and hypothetical, while downplaying any distant or abstract risks it may pose in the future. Conversely, certain stakeholders may exaggerate risk because of the potentially catastrophic consequences that could result from misuse, no matter how unlikely the scenario in question. Such perceptual biases often create an uneven playing field in which the burden of proof falls disproportionately on the regulator.

Another real-world constraint on cost-benefit analysis is the fact that any governance mechanism, whether or not it is legally binding, must exist in a political environment in which various stakeholders and interest groups will have their say. Thus, when devising a package of governance measures, policymakers generally consider the views of major stakeholders, such as the willingness of an affected industry to accept a particular regulatory scheme. These competing interests are balanced through a process of negotiation and compromise, ideally resulting in a governance strategy that is not only effective and benefits the public good but is acceptable to all of the major players. In the real world, of course, suboptimal outcomes are common.

Conclusion

The aim of this book is not simply to characterize current dual-use technologies in the biological and chemical fields but to develop a general decision algorithm that policymakers can apply to future emerging technologies to minimize the risk of misuse. Based on the foregoing analysis, such an algorithm—in broad strokes—might consist of the following steps:

(1) Monitor technology development in academia, government, and private industry with the goal of identifying emerging technologies in the biological and chemical fields that have a potential for misuse.

(2) Assess the *risk of misuse* of an emerging technology according to the four parameters in the analytical framework (ease of misuse, accessibility, magnitude of potential harm, and imminence of potential misuse).

(3) If the overall risk of misuse is LOW, there is no urgent need to devise governance options, but the technology should be monitored in case its potential for misuse increases over time.

(4) If the risk of misuse of an emerging technology is MEDIUM or HIGH, proceed to assess its governability according to the five parameters in the analytical framework (embodiment, maturity, convergence, rate of advance, and international diffusion).
(5) If the governability of the technology is LOW, focus primarily on normative governance measures.
(6) If the governability of the technology is MEDIUM, consider soft-law and normative measures.
(7) If the governability of the technology is HIGH, consider the full spectrum of governance measures, from hard-law to normative.
(8) Based on a cost-benefit analysis of various governance measures, identify a tailored package of measures that reduces risk at acceptable cost and in a manner that is acceptable to all major stakeholders.

Because emerging technologies are "moving targets" that are undergoing a continual process of evolution and refinement, governance strategies must be flexible enough to permit frequent modification and adaptation at various points in the research and development cycle. Yet even if the effectiveness of early governance measures declines over time as the technology evolves, such measures can help to establish and reinforce enduring behavioral norms.

In conclusion, this book has sought to address the dual-use dilemma that characterizes many technological innovations in the biological and chemical fields. Beyond seeking to elucidate the nature of the problem, the study has proposed a systematic approach to technology governance that is designed to reduce the risk that innovations will be misused for harmful purposes but without smothering them in the cradle or foregoing their substantial benefits. Ultimately, however, strategies of technology governance can only be as effective as the policymakers who select them, the companies, institutions, and researchers who comply with them, and the members of the public who—in a democratic system—must hold all of these actors politically accountable. As we move forward into an uncertain future, a technologically literate and aware citizenry must do its part to ensure that double-edged innovations enrich and enhance human welfare rather than threatening or degrading it.

Figure 20.1: Selection of Governance Options and Cost-Benefit Analysis

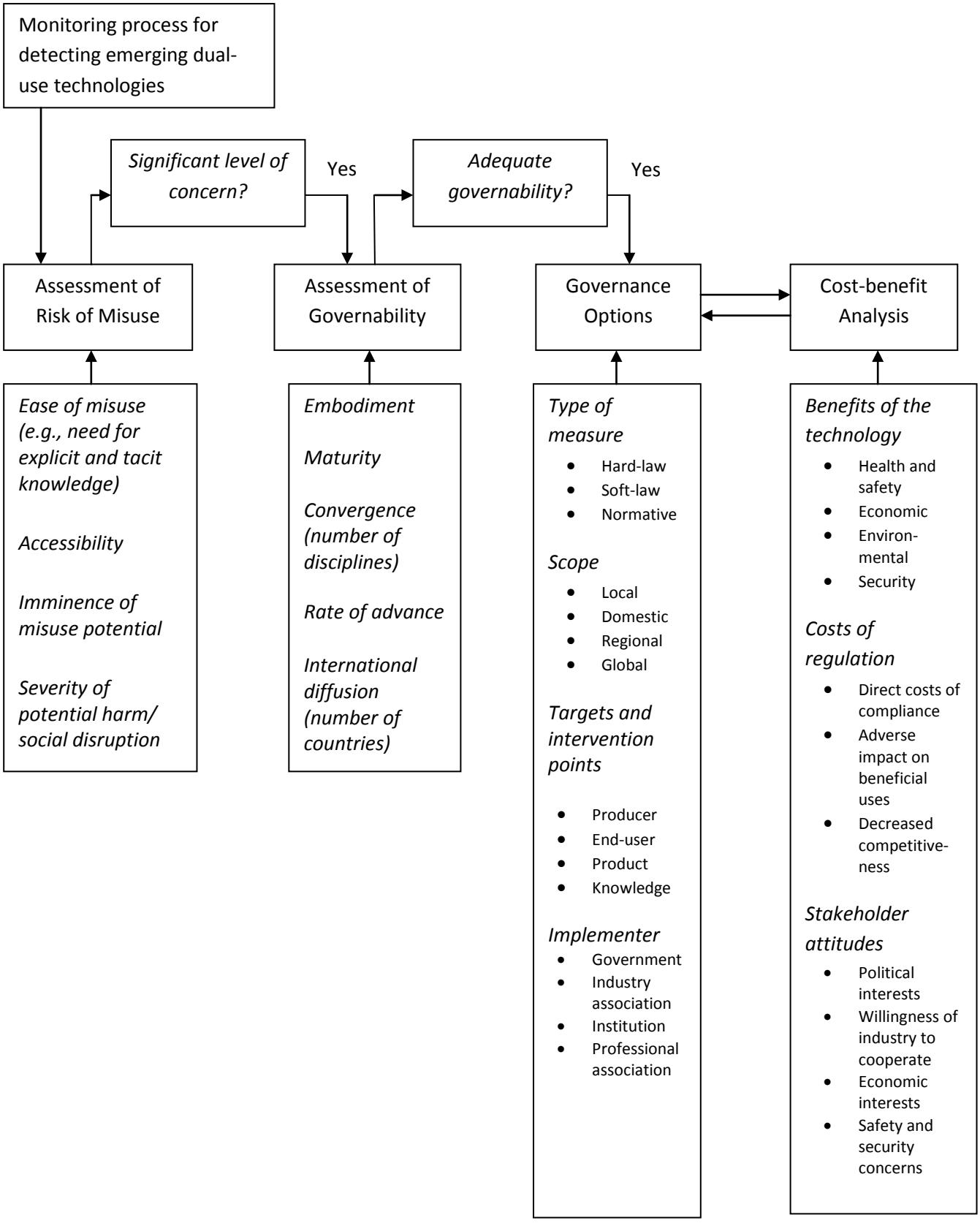


Table 20.1: Assessing the Risk of Misuse

PARAMETERS	Ease of misuse (including need for explicit and tacit knowledge)	Accessibility (including commercial availability and capital requirement)	Magnitude of potential harm (in fatalities, injuries, economic cost, and social disruption)	Imminence of potential misuse (near-term, medium-term, long-term)
Relationship between parameter and level of concern	*Direct correlation* (i.e., high ease of misuse = high level of concern; and vice versa)	*Direct correlation*	*Direct correlation*	*Direct correlation*

CASE STUDIES	Level of concern based on **Ease of Misuse**	Level of concern based on **Accessibility**	Level of concern based on **Magnitude of potential harm**	Level of concern based on **Imminence of potential misuse**	OVERALL LEVEL OF CONCERN
Combinatorial chemistry and high-throughput screening (HTS)	MEDIUM – effective use of the technology requires Ph.D.-level expertise to design experimental system and mine the resulting compound library to identify highly toxic agents	HIGH – commercially available, within the financial means of a state or a sophisticated terrorist group	HIGH – could facilitate the development of new types of chemical warfare agents by a state program	HIGH – immediate, given the current availability of this technology to states	**HIGH**
Chemical micro process technology	MEDIUM – deskilled for proven applications, but explicit and tacit knowledge are needed to adapt the process of chemical synthesis to micro devices	HIGH – commercially available; within the financial means of a state or a sophisticated terrorist group	HIGH – could allow the covert, large-scale production of known chemical warfare agents and facilitate development of novel agents	HIGH – immediate, given the commercial availability of the hardware and software	**HIGH**
Bioregulators	MEDIUM – misuse not easy unless diverted from established medical or other applications; requires knowledge, experience, and technical skills	HIGH – accessible for established medical and other applications	MEDIUM – could lead to new agents for military use, and possibly terrorist use, coercion, interrogation or torture	MEDIUM – short to medium-term risk given the current interest in "non-lethal" weapons and rapid advances in bioregulator research	**MEDIUM**
Peptide synthesis	MEDIUM – custom peptides can be ordered from suppliers over the Internet or made in automated desktop synthesizers currently on the market, but that is only the first step in a chain of development and weaponization hurdles	MEDIUM – widely accessible in gram to kilogram scale, and a few suppliers can produce ton quantities	MEDIUM – could provide a supply of biopeptides for R&D and CW agent production	HIGH – if a peptide bioregulator was selected as a chemical warfare agent, production could start on relatively short notice	**MEDIUM**
Protein engineering	MEDIUM – rational design requires a high level of expertise, but directed evolution is moderately easy	MEDIUM – depends on R&D infrastructure and expertise	MEDIUM – could lead to development of novel toxin agents	LOW – risk is long-term because a high level of expertise is needed	**MEDIUM**
Synthesis of viral genomes	MEDIUM – synthesizing sequences greater than 180 base pairs remains somewhat of an art, and technical hurdles to virus construction exist	HIGH – genetic sequences needed for the synthesis of many viruses can be ordered from suppliers over the Internet	HIGH – could recreate dangerous pathogens and possibly engineer pathogens that do not exist	HIGH – technical barriers still exist but are likely to diminish as the technology advances	**HIGH**
Synthetic biology with standardized biological parts	LOW – misuse is difficult because of the current absence of weaponizable parts and devices	MEDIUM – the field is still embryonic but may become increasingly accessible due to emergence of do-it-yourself biology and commercially available BioBrick kits	LOW – over the long term, could potentially permit the development of novel and highly dangerous synthetic organisms	LOW – long-term, but could be medium-term in the event of unexpected scientific breakthroughs	**LOW**
RNA interference	LOW – specific applications of the technique require tacit knowledge from a variety of fields	MEDIUM – most molecular biology research labs can perform the technique, but it requires a substantial investment of resources	HIGH – by combining RNAi with viral pathogens, it might be possible to develop highly infectious and virulent infectious agents and even ethnically targetable weapons	LOW – long-term because several years of R&D would be required to create and optimize an RNAi-based weapon	**MEDIUM**

Table 20.1: Assessing the Risk of Misuse

CASE STUDIES	Level of concern based on **Ease of Misuse**	Level of concern based on **Accessibility**	Level of concern based on **Magnitude of potential harm**	Level of concern based on **Imminence of potential misuse**	**OVERALL LEVEL OF CONCERN**
DNA shuffling and directed evolution	HIGH – performing the technique requires only basic molecular biology skills, without the need to understand the underlying biological mechanisms. Even so, applying the results demands specialized knowledge. Misuse also depends on developing screening methodologies to identify harmful organisms	HIGH – readily available either from patented or unpatented methods	HIGH – technique could permit the development of highly dangerous microorganisms and toxins	MEDIUM – risk of misuse depends on the development of a screening procedure for harmful pathogens, which would not arise from legitimate R&D	**HIGH**
Gene therapy	LOW – the field requires substantial amount of tacit knowledge; until viral vector technology is perfected, would be difficult to introduce genes into populations without being detected	MEDIUM – viral vector technology is accessible, especially to scientists in industrialized nations	LOW – potentially high if "stealth" viral vector technology can be perfected	LOW – long-term risk of misuse of viral vector technology	**LOW**
Personal genomics	LOW – the capacity for weaponization does not yet exist, nor do the aggregated databases that could be exploited for misuse (e.g., development of ethnic weapons)	LOW – the aggregate data and scientific knowledge that would be necessary for misuse/harm are not yet available	MEDIUM – if genetically targetable agents could be developed, consequences could be high	LOW – large genomics databases do not yet exist but will in the next five years; scientific knowledge relevant for weaponization will take much longer	**LOW**
Rational vaccine design	LOW – moderate to difficult due to the challenges of weaponization and delivery, the requirement for tacit knowledge in a variety of fields, and the need for animal and clinical testing	MEDIUM – accessible to those with Ph.D.-level skills	MEDIUM – potential for both covert and mass operations; knowledge produced could identify new vulnerabilities	MEDIUM – medium-term	**MEDIUM**
Aerosol vaccines	LOW – requires technical skills and knowledge of aerosol behavior in the environment and respiratory systems, knowledge of formulations, and favorable atmospheric conditions	MEDIUM – classic aerosol vaccines are described extensively in the scientific literature	LOW – potential for mass casualties but no particular advantage over existing delivery systems for biowarfare agents	LOW – long-term	**LOW**
Neuropsycho-pharmacology	LOW – Ph.D.-level technical skills are required for drug development	HIGH – neuroactive agents are available and employed therapeutically and experimentally; purchasing such drugs is within the means of an individual, group, or state	HIGH – could lead to new agents for military use, and possibly terrorist use, coercion, interrogation, or torture	HIGH – near-term	**HIGH**
Transcranial magnetic stimulation (TMS)	MEDIUM – potential misuse to erase memories and otherwise influence human behavior in a coercive manner; moderate deskilling, with substantial risk to subjects if operator is poorly trained	HIGH – TMS devices can be purchased on the commercial market and are within the means of an individual, group, or state	LOW – no identifiable risk for mass casualties; for individual subjects, there is a risk of seizures and disruption of neural networks	LOW – the technology is available but has no potential use for causing mass casualties	**LOW**

Table 20.2: Assessing Governability

PARAMETERS	Embodiment	Maturity	Convergence	Rate of advance	International diffusion
Relationship between parameter and governability	Intangible = LOW governability Hybrid = MEDIUM governability Hardware = HIGH governability	Not mature = LOW governability Very mature = MEDIUM governability Moderately mature = HIGH governability	*Inverse relationship* (i.e., high level of convergence = LOW governability, and vice versa)	*Inverse relationship* (i.e., Rapid rate of advance = LOW governability)	*Inverse relationship* (i.e., high rate of international diffusion = LOW governability)

CASE STUDIES	Susceptibility to governance based on **Embodiment**	Susceptibility to governance based on **Maturity**	Susceptibility to governance based on **Convergence**	Susceptibility to governance based on **Rate of advance**	Susceptibility to governance based on **International diffusion**	**OVERALL GOVERNABILITY**
Combinatorial chemistry and high-throughput screening (HTS)	MEDIUM – hybrid of hardware and integrated software	MEDIUM – commercially available	MEDIUM – miniaturization, laboratory robotics, drug screening	MEDIUM – exponential in 1988-92 but has since plateaued	MEDIUM – major vendors in USA, Europe, and Japan	**MEDIUM**
Chemical micro process technology	HIGH – primarily hardware	HIGH – commercially available but with a limited number of manufacturers	MEDIUM – advanced machining, specialized materials, theory of nanoreactions	HIGH – increasing number of applications and types of devices	MEDIUM – about 20 vendors in Europe, USA, Japan, and China	**HIGH**
Bioregulators	LOW – mainly Intangible, includes some wetware and materials	HIGH – in advanced development	MEDIUM – brain research, receptor research, systems biology	LOW – rapid growth of pharmaceutical R&D	LOW – all countries with pharmaceutical R&D capability	**MEDIUM**
Peptide synthesis	LOW – mainly intangible but includes wetware & materials	MEDIUM – commercially available	MEDIUM – use of peptides in pharma R&D, similarity to DNA synthesis	MEDIUM – incremental	MEDIUM – available in Canada, China, Europe, India, Japan, South Korea, USA	**MEDIUM**
Protein engineering	LOW – mostly a technique, but with some upstream hardware	HIGH – advanced development of technique; some fusion toxins are commercially available	MEDIUM – chemical synthesis of DNA, protein biochemistry, molecular modeling software	MEDIUM – was rapid from mid-1980s to mid-1990s but is now incremental	LOW – largely global, coincident with modern molecular biological capabilities	**MEDIUM**
Synthesis of viral genomes	HIGH – hybrid of DNA synthesizers plus advanced know-how	MEDIUM – commercially available from private suppliers, many of which screen customers and orders	MEDIUM – integrates biotech, engineering, nanotech, bioinformatics	LOW—rapid advance in speed, accuracy, and cost	MEDIUM – approximately 50 companies worldwide produce gene-length sequences	**HIGH**
Synthetic biology with standardized parts	LOW – materials-based, with a vital information-technology element	LOW – still in development, now emerging from proof-of-principle phase	MEDIUM – chemical DNA synthesis, molecular biology, engineering, bioinformatics	LOW – each application still requires extensive R&D and refinement	MEDIUM – increasing numbers of iGEM team from a growing number of countries around the world	**LOW**
RNA interference	LOW – an intangible technique that relies on a natural phenomenon	MEDIUM – reagents are commercially available; drug applications are in clinical trials	LOW – human genomics, small-molecule biochemistry, genetic engineering, RNA synthesis	LOW – but each application still requires extensive R&D and refinement	MEDIUM – about 20 firms with global distribution operations offer custom reagents	**LOW**

Table 20.2: Assessing Governability

CASE STUDIES	Susceptibility to governance based on **Embodiment**	Susceptibility to governance based on **Maturity**	Susceptibility to governance based on **Convergence**	Susceptibility to governance based on **Rate of advance**	Susceptibility to governance based on **International diffusion**	**OVERALL GOVERNABILITY**
DNA shuffling and directed evolution	LOW – a technique that is an extension of existing biotechnology	MEDIUM – widely used in research and industry for protein engineering; not available for sale but can be created by those seeking its benefits	HIGH – not convergent; squarely within mainstream molecular biology	LOW – seminal advances were made in 1990s but the technique is now being applied to new situations	LOW – technology is largely global, coincident with modern molecular biological capabilities	**LOW**
Gene therapy	LOW – a technique with some wetware	HIGH – still in clinical testing	MEDIUM – recombinant DNA, virology, immunology	HIGH – incremental, with some major setbacks	MEDIUM – 28 countries conducting clinical trials	**HIGH**
Personal genomics	MEDIUM – based on information technology, but databases might be subject to regulation	MEDIUM – commercially available	MEDIUM – DNA sequencing, systems biology, bioinformatics	LOW—field advancing rapidly since 2008, was slow before then	MEDIUM – more than 10 companies and institutions in North America and Europe	**MEDIUM**
Rational vaccine design	LOW – involves a confluence of science and technology	MEDIUM – advanced development, some commercial availability	LOW – general biotechnology and immunology; animal and human testing	LOW – a range of rates depending on methods, but generally rapid	LOW – accessible to all countries with pharmaceutical R&D capability	**LOW**
Aerosol vaccines	MEDIUM – based predominantly on know-how (intangible) but requires access to aerosol generators	MEDIUM – a few veterinary vaccines commercially available, plus one new human vaccine (FluMist); past government-sponsored development	HIGH – limited extent of convergence (vaccinology, aerobiology, formulation techniques)	MEDIUM – rapid from 1970 to 1980; the field plateaued until the early 2000s but has increased slowly since then	HIGH – limited to a few advanced industrial countries	**MEDIUM**
Neuropsycho-pharmacology	LOW – an intangible technology with some role for brain imaging machines	MEDIUM – many psychoactive drugs are commercially available	MEDIUM – neuroscience, neuroimaging, genomics	LOW – with continuing discovery of new neurotransmitter/receptor systems in the brain	LOW – accessible to any country with a pharmaceutical R&D capability	**LOW**
Transcranial magnetic stimulation (TMS)	HIGH – mainly hardware with some need for functional know-how	MEDIUM – advanced development for various applications; FDA-approved for major depression	MEDIUM – transcranial electrical stimulation, functional MRI, other imaging technologies	MEDIUM – incremental, but growing interest in clinical use of TMS among neurologists and psychiatrists	HIGH – at least nine U.S. and European companies offer versions of TMS	**HIGH**

APPENDIX: HISTORICAL CASE STUDIES

Appendix A: Development of the V-series Nerve Agents

Caitríona McLeish and Brian Balmer

During the twentieth century, many beneficial dual-use technologies were transferred from the military to the civilian sector, including atomic energy, microelectronic chips, FM radio frequencies, and systems analysis techniques. Less well known and understood are historical transfers of technology in the opposite direction, from the civilian to the military sector. Such civil-to-military transfers are particularly relevant when discussing chemical warfare (CW) because the production of chemical weapons requires access to a "civilian chemical industry capable of manufacturing organic chemicals on a substantial scale."[1] Thus, a CW capability is inherently characterized by dual-use technologies.

Drawing on recently released documents from The National Archives in Britain, this historical case study explains how technology transfer from civilian pesticide research to the British army during the Cold War resulted in a new generation of chemical weapons called the "V-agents." By tracing the process through which a particular technology moved from peaceful to military application, the case study makes clear that the weapons application did not arise automatically from the inherent properties of the artifact itself (e.g., its high toxicity) but required the active intervention of military officials. Using science-policy terminology, the technology transfer resulted as much from "pull" on the part of the military customer as "push" on the part of the civilian developer. This observation suggests that the governance of dual-use technologies requires a nuanced and historically informed understanding of dual-use technology transfer.

Characteristics of the Technology

The V-series compounds are a subset of the chemical warfare agents known as "nerve agents" because they interfere with the transmission of nerve signals at synapses—the microscopic gaps between nerve cells (neurons) in the central nervous system or between a neuron and an effector organ such as a muscle or gland. The arrival of an electrical nerve impulse at a nerve ending triggers the release of neurotransmitter molecules, which diffuse

across the synapse and bind to receptor sites on the post-synaptic cell to initiate a physiological response. Acetylcholine is a major neurotransmitter at synapses in the brain and the peripheral nervous system. Under normal conditions, an enzyme called cholinesterase breaks down acetylcholine after its release into the synapse, rapidly resetting the electrochemical switch to the "off" position so that a new chemical signal can be transmitted.

The class of chemicals known as organophosphorus nerve agents (so-called because they contain both carbon and phosphorus atoms) work by blocking the action of cholinesterase, preventing the enzyme from breaking down acetylcholine and resetting the electrochemical switch.[2] The result is an excessive buildup of acetylcholine in the synapse that causes the postsynaptic cell to remain in a state of continual excitement until it seizes up. Thus, the symptoms of nerve-agent poisoning include major convulsions followed by a flaccid paralysis in which the breathing muscles cease to function, leading to death by asphyxiation within several minutes.

In the civilian sector, organophosphorus compounds are used primarily as pesticides that attack the cholinesterase of insects, as well as flame retardants and lubricants. During the Cold War, pesticide manufacturers and CW establishments both became interested in organophosphorus chemistry because of the benefits it offered to their respective pursuits. Whereas a successful pesticide is highly toxic to insects but much less so to humans, a successful CW agent is the reverse.

Once the mechanism of nerve-gas poisoning had been elucidated for the first-generation of nerve agents developed in Germany before and during World War II (the so-called "G-agents" tabun, sarin, and soman), it was a short step to increase the potency of these molecules by adding a choline group, which binds tightly to the active site of cholinesterase and thus strengthens the nerve agent's inhibition of the enzyme.[3] Between 1952 and 1953, at least three companies independently discovered a new family of organophosphate esters with strong anticholinergic activity that proved to be effective insecticides, especially against mites.[4] One such compound was called Amiton.[5] In the early

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[1]Julian Perry Robinson, "Supply-Side Control of the Spread of Chemical Weapons," in Jean-Francois Rioux, ed., *Limiting the Proliferation of Weapons: The Role of Supply-Side Strategies* (Ottawa, Canada: Carlton University Press, 1992), p. 63.

[2] Most organophosphorus pesticides are organophosphate esters, which contain a carbon-oxygen-phosphorus bond. In the most potent nerve agents, however, the carbon atom is bound directly to the phosphorus atom.

[3]Julian Perry Robinson, director, Harvard Sussex Program on Chemical and Biological Weapons, personal correspondence with Caitríona McLeish, August 10, 1997.

[4]Julian Perry Robinson, "V-Agent Nerve Gases," in Stockholm International Peace Research Institute (SIPRI), *The Problem of Chemical and Biological Warfare, Vol. 1: The Rise of CB Weapons* (New York: Humanities Press, 1971), p. 74.

1950s, Amiton was transferred from the pesticide industry to the British Chemical Defence Experimental Establishment (CDEE), where it led to the development of a new generation of nerve agents, the V-series.

The Policy Context

For a short period after the end of World War II, British defense policy gave equal priority to chemical, biological and atomic weapons. Even before the 1947 decision to build an atomic bomb, the Labour government of Prime Minister Clement Atlee decided that it was imperative that Britain be "in a position to wage chemical warfare from the start of hostilities."[6] Scientists at the Defence Research Policy Committee (DRPC), which advised the Minister of Defence and the Chiefs of Staff on defense research priorities, supported this policy, as did the Chiefs of Staff.[7] Whitehall's enthusiasm for CW research and development was relatively short-lived, however, and the prioritization of the nuclear program soon drew attention away from chemical warfare.[8] The interest of British military planners in chemical warfare also waned when they realized that the 1925 Geneva Protocol, to which Britain was a party, banned the first use of these weapons.[9]

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[5] Christa Fest and Karl-Julius Schmidt**,** *The Chemistry of Organophosphate Pesticides* (Berlin: Springer Verlag, 1982), p. 128.

[6] The National Archives, Kew [TNA], CAB [Cabinet Office papers] 131/1. Minutes of Defence Committee of the Cabinet, June 20, 1946.

[7]DRPC chemist and radar scientist Henry Tizard suggested in 1947 that the post-war chemical and biological weapons programs should "be given priority effectively equal to that of atomic energy." TNA DEFE [Defence Ministry papers] 10/18 DRP(47)53 Defence Research Policy Committee, *Future Defence Policy* May 1, 1947. Just months after Tizard's statement, the Chiefs of Staff, referring explicitly to atomic, biological, and chemical weapons, agreed on "a cardinal principle of policy to be prepared to use weapons of mass destruction. The knowledge of this preparedness is the best deterrent to war in peacetime." TNA DEFE 10/19, DRPC. Final Version of Paper on Future of Defence Research Policy, July 30, 1947. See also, Jon Agar and Brian Balmer, "British Scientists and the Cold War: The Defence Research Policy Committee and Information Networks, 1947-1963," *Historical Studies in the Physical Sciences*, vol. 28 (1998), pp. 209-252.

[8] In October 1952, Britain tested its first atomic bomb, elevating nuclear weapons above the other types of unconventional weapons, and soon after, the defense budget was cut in the wake of rearmament for the Korean War. At the 1953 Tripartite Conference with Canada and the United States, one of a regular series to share CW research results among the three countries, attendees acknowledged that a lack of money for British CW research was slowing the effort of building a retaliatory capability. See Gradon Carter and Graham Pearson, "North Atlantic Chemical and Biological Research Collaboration: 1916-1995," *Journal of Strategic Studies*, vol. 19 (March 1996), pp. 74-103.

[9]In 1954, the DRPC, which had previously endorsed the expansion of the CW research program, stated, "Reliance on chemical weapons is . . . at present impracticable. Our international commitments and the political objections to initiating chemical warfare mean that . . . the effort devoted to chemical warfare research and development will never be as great as it would be if military and scientific factors alone were taken into account." The phrase "international commitments" was a reference to British ratification of the 1925 Geneva Protocol, which meant that the nation had renounced first use of chemical and biological weapons. TNA DEFE 10/33, Defence Research Policy Committee, 10th Memo, Review of Defence Research and Development, *Trends in Scientific and Technical Development. Weapons of Mass Destruction*, March 10, 1954, p. 27.

For a brief period, however, the discovery of the German nerve agents, which were far more toxic and fast-acting than any previously known chemical weapons, revived the British government's interest in CW research.[10] The staff of the Chemical Defence Experimental Station at Porton Down, Wiltshire—renamed in 1948 the Chemical Defence Experimental Establishment (CDEE) —considered the German nerve agents to be a development of major importance that had to be properly assessed. Adding to the sense of urgency were intelligence reports that the Soviet Union had dismantled one of the German nerve-agent factories and rebuilt it in Stalingrad.[11] Britain confiscated substantial stocks of German nerve agents and weapons after World War II until it could build its own production capacity.[12]

The technological opportunities offered by the German nerve agents gave Porton Down a new mission and probably saved it from closure in the post-World War II environment of financial austerity. Much of the work at Porton focused on assessing the properties and effectiveness of tabun and sarin as lethal weapons. Scientists also determined that low-dose exposures caused a severe blurring and darkening of vision that could incapacitate soldiers temporarily.[13] A 1947 Porton report concluded that "the advent of the nerve gases makes obsolete the previous lethal gases CG [phosgene], AC [hydrogen cyanide] and CK [cyanogen chloride] except for very special purposes."[14] The R&D effort also yielded a number of new candidate CW agents, including some that were comparable in potency to the German nerve agents.[15]

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[10]The new agents had been discovered in the course of pesticide research a few years before the outbreak of World War II, initially by Dr. Gerhard Schrader at the IG Farben Company. Although the German Army produced 12,000 tonnes of tabun nerve agent, the secret weapons remained unused and became known to the Allies only in the closing stages of the war, when they stumbled across German tabun-filled munitions. See Julian Perry Robinson, "V-Agent Nerve Gases," in Stockholm International Peace Research Institute (SIPRI), *The Problem of Chemical and Biological Warfare, Vol. 1: The Rise of CB Weapons* (New York: Humanities Press, 1971), p. 73.

[11]Gradon Carter and Graham Pearson, "Past British Chemical Warfare Capabilities," *RUSI Journal*, vol. 141 (February 1996), p. 61.

[12]Gradon Carter and Brian Balmer, "Chemical and Biological Warfare and Defence, 1945-90," in Robert Bud and Philip Gummett, eds., *Cold War, Hot Science: Applied Research in Britain's Defence Laboratories 1945-1990* (Amsterdam: Harwood, 1999). The Ministry of Supply was responsible for the military research establishments, such as the CDEE. See David Edgerton, "Whatever Happened to the British Warfare State? The Ministry of Supply 1946-1951," in Helen Mercer, Neil Rollings and Jim D. Tomlinson, eds, *Labour Governments and Private Industry: The Experience 1945-1951* (Edinburgh: Edinburgh University Press, 1992).

[13]Gradon Carter and Graham Pearson, "Past British Chemical Warfare Capabilities" *RUSI Journal*, vol. 141 (February 1996), p. 62.

[14]TNA W[ar] O[ffice papers], 195/9236 Porton Report No. 2747, *Preliminary Report on the Potential Value of Nerve Gases as CW Agents*, January 18, 1947. Mustard gas continued to rank highly in the chemical arsenal. See TNA WO 195/12063 CDAB, 21st Meeting of the Board, November 6, 1953.

[15] Julian Perry Robinson, director, Harvard-Sussex Program on Chemical and Biological Weapons, personal correspondence with authors, August 6, 2009.

By the early 1950s, however, there were growing indications that the development of the G agents had come to a turning point. Rudolph Peters, the Whitley Professor of Biochemistry at Oxford University, reported in November 1951 that nerve-agent research at Porton "had reached a transition stage with past work largely finalized and new fields envisaged."[16] A few months later, in a discussion entitled "further work on G agents," the Chemical Defence Advisory Board (CDAB), a technical advisory committee to Porton Down, concluded that "little of value was likely to arise from investigation of further changes in the groupings of known nerve gases."[17]

The Civil-Military Overlap

The dwindling returns from G-agent research stimulated a quest for novel CW agents. As early as November 1950, the members of the CDAB, including A.E. Childs, the director of the Chemical Defence Research Department in the Ministry of Supply, discussed how to proceed. The CDAB minutes quoted below are notable because they indicate that the chemical industry was seen as a possible—but by no means guaranteed—source of new directions:

> The chairman [Prof. Alexander R. Todd] remarked that it could not be expected that extra-mural workers would be found who were prepared to proceed along speculative lines in a search for new toxic compounds and it was, therefore, necessary for all concerned to watch the literature carefully for any guidance. Dr Barrett [CDEE] agreed that, in the absence of sufficient information on structure/toxicity relationships, the only possible approach was empirical but he wondered if it were possible for industry to submit all likely compounds for test. Mr. Childs [Ministry of Supply] said that a scheme of this nature had been started in regard to antibiotics but had produced no worthwhile results; nothing was lost, however, in trying to get information this way.[18]

The difficulty of predicting toxicity from chemical structure had led to a process of trial and error. In a letter, Childs noted the shortcomings of this "empirical" technique:

[16]TNA, WO195/11648 CDAB, 18th Meeting of the Board, November 1, 1951.
[17]TNA, WO195/11754 CDAB, 19th Meeting of the Board, February 7, 1952.
[18] TNA, WO195/11216. CDAB, 15th Meeting of the Board, November 9, 1950.

> The methods of approach at the moment are mainly empirical and, in short of a staff out of all proportion greater than we can afford, only the fringes can be touched. In consequence, success depends largely on a stroke of luck. This state of affairs is regarded by all concerned as dangerous and unsatisfactory.[19]

The advisers considered two alternatives: literature scanning or soliciting assistance from private industry. CDEE Porton Down had had a long relationship with representatives of the chemical industry. During World War I, the British government had contracted with chemical companies to produce poison gases and had called on academic chemists to aid in the military research and development effort. The links among government, industry, and academia continued after the war.[20] Several companies that the British government had contracted to produce chemical weapons during World War I merged to form Imperial Chemical Industries (ICI).[21] In 1937, the government turned to ICI to build and operate factories that would produce and fill the next generation of chemical munitions.[22]

Childs and his assistant Dr. J. McAulay led Porton Down's effort to seek assistance from the chemical industry. Childs drew on his personal contacts, and in January 1951 he wrote to James Davidson-Pratt at the Association of British Chemical Manufacturers.[23] During World War II, Davidson-Pratt had worked in the Ministry of Supply, where he had dealt with biological warfare research, and he was currently a member of the ministry's biological equivalent of the CDAB, the Biological Research Advisory Board.[24] Childs's letter outlined the haphazard and inefficient search for new toxic compounds at Porton and mentioned that the United States had established a Chemical and Biological Coordination Center in Washington, D.C. to collate information provided by industry.[25] Childs then requested that the British association circulate to its members a request for information on new toxic compounds.

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[19] TNA WO 188/2716, Letter to James Davidson Pratt, Association of British Chemical Manufacturers from A.E. Childs, DCDRD, Ministry of Supply, January 4, 1951.
[20] In 1920, *Nature* ran a series of Letters to the Editor commenting on the Government's proposal to continue the relationship forged with universities during the inter-war years. Letters to the Editor, *Nature,* vol. 106, nos. 2662/3, November 4, 11, and 18, 1920.
[21] Gradon Carter and Graham Pearson, "Past British Warfare Capabilities," *RUSI* Journal, vol. 141, no. 1 (1996), p. 60.
[22] Carter and Pearson, "Past British Chemical Warfare Capabilities," p. 60.
[23] The Association of British Chemical Manufacturers (ABCM) was founded in 1916 as a trade association for the chemical industry. It is currently called the Chemical Industries Association.
[24] Brian Balmer, *Britain and Biological Warfare: Expert Advice and Science Policy 1930-65* (Basingstoke: Palgrave, 2001) , pp. 45, 101.
[25] TNA WO 188/2716, Letter to James Davidson Pratt, Association of British Chemical Manufacturers from A.E. Childs, DCDRD, Ministry of Supply, January 4, 1951.

Davidson-Pratt responded immediately, offering to send out a confidential letter to member companies asking them to communicate "anything which appears unusually toxic or novel" to the Ministry of Supply. On a less optimistic note, he pointed out that a proposal two years earlier to create a center similar to the one in the United States had not been well received. "The general view of British industry was to express grave doubts as to whether the results to be obtained would ever be commensurate with the efforts involved," he said. "I.C.I. felt particularly strongly on this point in the light of their past research experience."[26] Thus, although industry was a potentially useful ally, its cooperation or utility could not be taken for granted.

Plant Protection Limited

One industrial field of particular interest to researchers at Porton Down was pesticide research and manufacture. After World War II, the pesticide and insecticide industries expanded rapidly, and many companies began working on organophosphorus compounds. Between 1952 and 1953, at least three firms identified a group of organophosphate esters with potent insecticidal activity, especially against mites.[27] After these substances were patented and their properties published in open literature, some of them were marketed as insecticides.

One such compound was a candidate miticide, later named Amiton.[28] It was discovered by the chemists Ranajit Ghosh and J. F. Newman, working at Plant Protection Limited (PPL) in Yalding, Kent. PPL was a subsidiary of ICI and another company called Cooper, McDougall and Robertson (CMR) that had been established in 1937 to end the competition in pesticide production between the two firms.[29] Ghosh probably synthesized Amiton in early 1952, although one source claims it was synthesized as early as 1948.[30] PPL did not apply for a patent on the compound until November 1952 and the details were not published until 1955, when Amiton was protected by several patents covering its synthesis.[31]

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[26] WO 188/2716, Letter J. Davidson Pratt (ABCM) to A.E. Childs (Ministry of Supply), January 5, 1951.
[27] Robinson, "V-Agent Nerve Gases," p. 74.
[28] Amiton has the chemical formula O, O-diethyl-S-2-diethylaminoethyl phosphorothiolate.
[29] From early 1953, CMR began to reduce its investment in PPL and the partnership between ICI and CMR ended in 1958. See William J. Reader, *ICI: A History, Volume 2: The First Quarter Century 1927--52* (London: Oxford University Press, 1975) pp. 335, 455-456. See also, Wellcome Trust Archives, London, Wellcome Foundation, Cooper McDougall & Robertson Ltd, WF/C/6/1/302, WF/C/6/1/303, WF/C/M/PC/07.
[30] A. Calderbank (1978), 'Organophosphorus instecticides' in F.C. Peacock (ed) *Jealott's Hill: Fifty Years of Agricultural Research, 1928-1978*, Bracknell: ICI Ltd, p50; the earlier date is given in Fest and Schmidt, *Chemistry of Organophosphate Pesticides*, p. 128.
[31] Patents protecting Amiton and its synthesis are: For the substance: Ranajit Ghosh, *New Basic Esters of Phosphorus-Containing Acids*, British Patent Number 738839, Application Date: November 19, 1952, Complete

In 1954, ICI marketed a form of Amiton (the hydrogen-oxalate salt) as an insecticide under the trade name Tetram®.[32] Three years later, *Nature* reported that PPL was manufacturing a "new" pesticide under the trade names Tetram® and ICI Amiton that "has a high toxicity to man, but as an insecticide it is claimed to be largely specific for red spider and other mites and for scale insects, and to have little effect on insect predators." [33] Significantly in view of the civil-military links, in 1955 ICI placed a production contract for Amiton with the Chemical Defence Establishment (CDE) Nancekuke, a British government facility in Cornwall that manufactured nerve agents for the military.[34]

Amiton did not turn out to be a successful insecticide. It was not only highly toxic to humans but was readily absorbed through the skin into the blood circulation, making it too dangerous for agricultural use. According to an unpublished document, "Although [Amiton] showed great promise as a systemic insecticide against sucking arthropods such as mites and scale insects, and despite the absence of accidents during trial, it was eventually decided that the intrinsic toxicity of the material was too high for commercial exploitation."[35] As a result, the product was withdrawn from the market around 1958.[36] But while high percutaneous toxicity is not a quality that lends itself to a successful agrochemical, it is a great asset in a CW agent.

Technology Transfer

Current restrictions on the availability of primary documents make it difficult to trace the exact process by which Amiton was transferred from PPL to Porton Down. Porton's initial request in 1951 for industry assistance yielded little of interest.[37] The Ministry of Supply began a renewed effort in July 1953, when it sent a series of letters directly to chemical and medical firms (19 were named on one list) and through the Association of

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Specification Published: October 19, 1955; Ranajit Ghosh, *Manufacture of Basic Esters of Phosphorothiolic Acid*, British Patent Number 763,516, Application Date: July 16, 1954, Complete Specification Published: December 12, 1956; Ranajit Ghosh, *New Pesticidal Basic Esters of Phosphorothiolothionic Acid* British Patent Number 763,516 Application Date: July 16, 1954, Complete Specification Published: December 12, 1956.

[32] Stockholm International Peace Research Institute, *The Problem of Chemical and Biological Warfare. A Study of the Historical Technical, Military, Legal, and Political Aspects of CBW and Possible Disarmament Measures. Vol. 1. The Rise of CB Weapons*, Humanities Press: New York, 1971, pp. 70-75, 280-282).

[33] Anonymous, "A New Organophosphorus Insecticide," *Nature*, no.4563 (13 April 13, 1957), p. 763.

[34] Graham Pearson, reply to a question by the Countess of Mar, *Hansard* (House of Lords), April 11, 1994, p. 2

[35] Unpublished document, Ministry of Defence, Annex C *Properties of the insecticide "Amiton" and its salts R6199 and R 6200*, Sussex Harvard Information Bank (SHIB), Harvard-Sussex Program, University of Sussex.

[36] Robinson, "V-Agent Nerve Gases," p. 74. The termination of the contract with Nancekuke to manufacture Amiton in 1958 suggests this as the date of withdrawal from the market.

[37] TNA WO 188/2716, F. Savage, Assistant Managing Director for Anchor Chemical Company (Manchester) to Ministry of Supply, Chemical Defence Research Department, January 16, 1951.

British Chemical Manufacturers, which contacted 25 firms.[38] Although some of the letters were individually tailored, the main circular is worth quoting at length:

> The main duty of this Directorate is to plan protective measures against any toxic materials which might be used in war.
>
> The rapid growth of research and development in chemistry, and particularly in the fields of biochemistry, chemotherapy and insecticides, greatly increases the chance that new and unexpected types of toxic materials may be brought to light. Some of these compounds might prove to be effective as war chemical agents against which a method of protection will be needed.
>
> We should therefore appreciate the co-operation of industrial and other research organisations in providing us with data on the synthesis and properties of any new compounds which you prepare (or extract from natural products) and which show high toxicity or toxicity associated with new molecular structures or toxicity of a novel type.[39]

The suggestion that new toxic chemicals were required for protective purposes was clearly disingenuous, unless the retaliation-in-kind policy was interpreted at the time as a form of protection. The letter from the Ministry of Supply to the research controller of ICI, dated July 16, 1953, was more personalized and contained an intriguing addendum:

> We have been very grateful for the co-operation of the I.C.I in the past and hope very much that we can count on it in the future. For your own private information the last item received from you has now been put well within the barbed wire fence and is receiving much attention.[40]

[38]TNA, WO 188/2721 TA 9002, Firms Asked to Co-Operate in Providing Data on New Toxic Compounds (not dated but with 1953 papers); Letter Davidson-Pratt to McAulay, July 22, 1953.
[39]TNA, WO 188/2721, Ministry of Supply, Directorate of Chemical Defence Research and Development. New Compounds Prepared in Industrial and in other research laboratories and found to be too toxic for medical or industrial use. July 1953.
[40]TNA, WO 188/2721, Letter from J. McAulay to R.M. Winter, Research Controller, Messrs ICI Ltd, Nobel House, Buckingham Gate, July 15, 1953.

The items provoking "much attention" in the search for new toxic compounds at the time were related to Amiton, suggesting that PPL had passed the compound to Porton Down through its parent company ICI.

An important feature of the military-industry relationship was secrecy. In their correspondence with industry, British government officials expressed the hope that their requests for information would be held in confidence.[41] Yet the need for confidentiality operated in both directions. Porton's initial outreach efforts in 1951, rather than provoking a flood of information from industry, had met a significant barrier in companies' need to protect commercial secrets. Thus, before sending out the second set of letters to industry in 1953, the Ministry of Supply established a system of commercial (C) codes to identify each compound that was submitted. A memo from CDEE explained, "In the hope of inducing firms etc to bring forward toxic compounds for test more freely, it has been decided to restrict knowledge of the origin of such compounds as much as possible."[42]

Instead of revealing the names of the originating firms, the ministry merely passed to Porton the C number of each compound, along with information about its composition and properties. This system was explained in the letter-writing campaign and flagged as a means of protecting commercial interests. In correspondence dated April 29, 1953, the first compound dealt with under the new system, R5158, was given the code number C11.[43] One year later, Dr. McAulay reported to the Chemical Defence Advisory Board that the ongoing outreach efforts to industry were "an extension of our previous vigorous efforts to maintain contact with all important industrial and academic research laboratories on matters which might have a CW interest. (Compound C11 . . . resulted.)"[44]

Compound C11 was described as a compound that was "notified to the Ministry by a commercial firm, [and] was proving to be of great importance."[45] Scientists originally considered C11 to be closely related to compound T2274 (the internal codename assigned to

[41]TNA WO 188/2721, Letter from J. McAulay (CDR1) to Prof. Bergel, Chester Beatty Research Institute, July 15, 1953, and similar correspondence in this file.
[42]TNA, WO 188/2721, Code Numbers for Toxic Compounds Received from Firms etc by Superintendent Research Division, CD Experimental Establishment, May 27, 1953.
[43]TNA, WO188/2721, Letter from Superintendent Research Division, CD Experimental Establishment, Porton [signature unclear but same as on following letter] to Dr J McAulay (Ministry of Supply) (April 29, 1953); Code Numbers for Toxic Compounds Received from Firms etc by Superintendent Research Division, CD Experimental Establishment, May 27, 1953.
[44]TNA, WO188/2721, From J, McAulay, Copy to Sir Rudolph Peters. Chemical Defence Advisory Board. Minutes of 26th Meeting, Action 1, Minute 257(d). Liaison with commercial interests. 28 July 28, 1954.
[45]TNA, WO195/12549, Ministry of Supply, Chemical Defence Advisory Board, Minutes 24th Meeting of the Board, November 5, 1953.

Amiton), but they soon realized that the two molecules had the same structure.[46] CDAB member Professor Ewart Jones, an organic chemist from Manchester University, summed up the excitement generated by compound C11:

> There had, thus, appeared an entirely new lead in the nerve gas field, when it was thought to have been completely circumscribed, and it was inevitable that new light would be thrown on the structure/activity relationships. The compounds could be seen on inspection to be a remarkable combination of the nerve gases, mustard gas and the nitrogen mustards, and it was natural that the Committee had been able to put forward many suggestions for further work.[47]

Once C11 or Amiton had been transferred to Porton Down, it was given the military code-name VG. (The "V" apparently stood for "venomous" because of the compound's skin-penetrating characteristics.) The members of the Chemical Defence Advisory Board noted that C11 and another related compound designated T2290 (later code-named Agent VE) were "by far the most dangerous of all for attack through the bare skin." Porton was therefore aware of the properties of Agent VE by the end of 1953. Although VE had powerful insecticidal properties, it was even more toxic than Amiton to warm-blooded animals. As a result, VE superseded Amiton (VG) as a candidate agent for weaponization. PPL continued its development work in this area and, in June 1955, Ghosh applied for a patent on VE.[48] What remains unclear is whether military scientists at CDEE synthesized VE independently by modifying Amiton, or whether PPL discovered VE and transferred it to Porton Down.[49] Subsequently, Porton scientists identified substances that were even more toxic than VE by making modifications to the Amiton-type molecular structure.

The historical documents that are currently available leave many important questions unanswered about the nature of the civil-to-military technology transfer. In particular,

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[46] A structural isomer is composed of exactly the same elements, arranged into a different three-dimensional structure. C11 might even have been a mixture. A later report noted , "It has been established that the occasionally erratic behaviour of these compounds [organic-phosophorus-sulphur compounds] is due to their tendency to undergo internal structure change (isomerisation), one form being highly toxic and the other non-toxic." WO195/13005. CDAB Annual Review of the work of the Board for 1954 (11 November 1954)

[47] TNA, WO195/12549, Ministry of Supply, Chemical Defence Advisory Board, Minutes 24th Meeting of the Board, November 5, 1953.

[48] Rajanit Ghosh (ICI Ltd), "New basic ester of thiophosphonic acids and salts thereof," British Patent no. 797603 (applied June 1955).

[49] Amiton was converted into the far more toxic Agent VE by replacing one of its two ethoxyl groups with an ethyl group. This modification created a direct carbon-phosphorus bond (rather than carbon-oxygen-phosphorus

ambiguities remain concerning how much information about Amiton and Agent VE was transferred by PPL to Porton Down, and how much Porton acquired on its own.[50] Based on the available historical record, all that can be stated with confidence is that the dual-use chemical C11 (closely related if not identical to Amiton) was transferred from PPL to Porton Down sometime between 1951 and 1953, and probably in late 1952 or early 1953.

By May 1954, the British government passed information about Amiton and VE to allied chemical-weapons scientists at Edgewood Arsenal in the United States and Suffield Experimental Station in Canada. Members of the Chemical Defence Advisory Board were told that it was not known if the Soviet Union possessed similar knowledge.[51] As with the G agents, British military chemists sought to develop more potent forms of the new Amiton-based agents. The CDAB report for 1954 noted that "a number of new phosphorus-sulphur compounds have been synthesised and much effort has been devoted to preparing each structural form in a pure state."[52] This report also noted that "many of the fascinating problems presented by these new compounds could not have been solved without the up-to-date infra-red spectrometric equipment recently purchased; even so these dangerous investigations are still impeded by lack of standard analytical techniques."[53] Porton scientists reported synthesizing over 200 organophosphorus compounds with anticholinesterase activity, and noted that "at Edgewood probably more have been examined."[54]

In July 1956, the Cabinet Defence Committee, in a bid to reduce defense spending, decided not to proceed with the planned large-scale production of nerve agents and to destroy all of the remaining stocks. By this time, however, U.S. military scientists had created about

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bond), a transformation that was already known to convert the chemical DFP into the far more toxic sarin. The formula of VE is O-ethyl S-2-diethylaminoethyl ethylphosphonothioate.

[50] Some of the still-unanswered questions include: Did PPL tell Porton about Amiton before or after the first patent application was filed in 1952? Was the compound C11, originally postulated to have a different structure to Amiton, transferred at the same time as Amiton? A further possibility is that PPL passed C11 but not Amiton to Porton via ICI, believing the two compounds to be different substances. In this case, it could be conjectured that Porton synthesised T2274, and PPL synthesised Amiton, independently. Further uncertainties remain. Was further information passed to Porton in 1954, when Ghosh discovered Agent VE, or had CDEE independently synthesized VE? Was PPL's role in the technology transfer limited to information concerning the existence of the V agents, or did it provide practical details about how Amiton or VE could be synthesized in high yields?

[51] TNA, WO195/12802, Ministry of Supply, Chemical Defence Advisory Board., 26th Meeting of the Board, May 13, 1954.

[52] TNA WO195/13005, CDAB, Annual Review of the Work of the Board for 1954, November 11, 1954.

[53] Ibid..

[54] TNA, WO 188/2716, A Memorandum on Possible Increases in Intrinsic Toxicity of Organo-Phosphorus Compounds and the Case for a Search for New Agents, D. R. Davies and A. L. Green. CDEE Porton. December 9, 1957.

50 different V-series agents, and in February 1957 the U.S. Army Research and Development Command selected Agent VX for large-scale production.[55]

The Porton report from 1957 estimated that there was a limit to the toxicity of V agents, and that VX approached that limit.[56] Concurrently, the twelfth Tripartite Conference of U.S., British, and Canadian chemical weapons experts issued a call to "divert the maximum possible effort to research for new agents and recommended that the field of natural products should receive particular attention."[57] ("Natural products" was a reference to toxins, highly toxic chemicals produced by living organisms.) In parallel with the new emphasis on toxins, the conference participants recommended seeking help with the search from industry and academic research institutions.

Further Outreach to Industry

Although an overlap existed between the requirements of the commercial pesticide industry and the military, their agendas were not perfectly aligned. This discrepancy was highlighted in May 1957, when the Ministry of Supply sent out a fresh round of letters, both directly to individual firms and indirectly through the Association of British Chemical Manufacturers. CDEE scientists followed up the letter campaign with visits to a small number of companies. Although the industry responses to the letters generally offered cooperation, some expressed reservations. For instance, the reply from Fisons Pest Control Ltd read:

> We do of course occasionally find compounds which are exceptionally toxic to mammals, in the course of our search for the other thing, but as you appreciate this is the signal for doing no further work on the subject and usually our information at this stage is meagre. . . . I feel that a little more exchange of information between people concerned with organo phosphorus compounds as insecticides and people concerned with them as war gases would be helpful to both parties.[58]

[55] Jonathan B. Tucker, *War of Nerves: Chemical Warfare from World War I to Al-Qaeda* (New York: Anchor Books, 2007), p. 158.
[56] TNA, WO 188/2716, A Memorandum on Possible Increases in Intrinsic Toxicity of Organo-Phosphorus Compounds and the Case for a Search for New Agents.
[57] TNA, WO 188/2716, The Search for New Agents, T.F. Watkins, December 12, 1957.
[58] TNA WO 188/2716, G.S. Hartley (Director of Research) to E.E. Haddon, Director of Chemical Defence Research & Development, Ministry of Supply, June 4, 1957.

The goal of the pesticide industry was to develop chemicals that were highly toxic to insects but not to mammals, whereas the military sought the opposite. Porton scientists noted optimistically after a visit to the Glaxo Research Laboratories, "It would seem that the possibility exists of mutual benefit in that Glaxo's failures may be Porton's successes and vice versa."[59] But Glaxo responded to the CDEE request by noting, "Generally our aim is to find substances with low mammalian toxicity and high activity as therapeutic agents, insecticides, etc. It is very unusual for us, therefore, to prepare substances of very high toxicity."[60]

This response underlines the point that private firms would not, in the normal course of events, get as far as synthesizing or characterizing the highly toxic materials sought by the Porton scientists. The same point was made by Shell: "We regret we have no products of this kind, mainly by reason of the fact that the type of chemical compounds which we are synthesising as potential agricultural chemicals are based on structures which might reasonably be supposed to possess low mammalian toxicity."[61] Similarly, a pharmaceutical research director stated that time pressures prevented him from following up on the properties of toxic agents that surfaced from time to time in the company's research laboratories.[62]

More fine-grained examples gleaned from the historical record underline the mismatch between the agendas of the military and the civilian chemical industry. Porton scientists visited a company that used acute oral toxicity in rats to determine the suitability of a compound for its research program. The firm did not test toxicity by routes such as the skin, which were of greater interest to the CDEE.[63] For their part, Porton staff resisted industry proposals for a two-way flow of information by discouraging companies from making reciprocal visits.[64]

Although the British chemical industry and Porton Down operated under conditions of strict secrecy—the former to protect proprietary information, the latter to safeguard

[59] TNA WO188/2721, Visit by Mr.Watkins and Mr. Callaway (CDEE) to Glaxo Research Laboratories, Greenford, Middlesex, to see Mr. Toothill and Dr. Child, April 14, 1958.
[60] TNA WO188/2721, From TG Maccrae, Executive Director of Research and Development, Glaxo Laboratories Ltd, January 1, 1958.
[61] TNA WO188/2721, From CG Williams, Shell Research Limited, to D.E.Woods, Minstry of Supply, June 13, 1957.
[62] TNA WO188/2721, Consultation Report of visit by R.W. Brimblecomb (CDEE) to Glaxo (Sefton Park, Stoke Poges, Bucks) to meet Dr. Campbell (Director of Research) and Dr. Ball, March 24, 1958.
[63] TNA WO188/2721, ASG Hill (for Director), Porton Down to DCDRD, "Search for New Toxic Compounds. Visits to Firms," February 18, 1958, "Appendix: Visit to Murphy Chemical Co. Ltd (T.F. Watkins)," February 12, 1958.
[64] TNA WO188/2721, ASG Hill (for Director), Porton Down to DCDRD. Search for New Toxic Compounds. Visits to Firms," February 18, 1958, Appendix: Visit to Murphy Chemical Co. Ltd (TF Watkins, February 12, 1958.

national security—the secret of the V-agents managed to leak out. By the late 1950s it had spread to the Soviet Union and France.[65] Between 1960 and 1972, chemists in seven countries (the United States, Sweden, West Germany, the Netherlands, Yugoslavia, the United Kingdom, and Czechoslovakia) published information on V-agents in the scientific literature.[66] Other countries known or suspected to have synthesized V-agents include Iraq, Israel, and Syria. In 1975, British journalists discovered the previously secret patent for VX in a public library, raising concerns about the possible acquisition of V-agents by terrorists.[67] Indeed, the Japanese Aum Shinrikyo cult produced small quantities of VX for assassination purposes in the mid-1990s.[68] Ever since the entry into force in 1997 of the Chemical Weapons Convention (CWC), which prohibits the development, production, stockpiling, transfer, and use of chemical weapons, any offensive development work on nerve agents has been banned. The CWC also obligates member states that possess stockpiles of chemical weapons to declare and destroy them.[69]

Conclusions

Although military research and development laboratories achieved incremental improvements in chemical warfare, the major breakthroughs—such as the discovery of the G- and V-agents—were spin-offs of civilian technologies. The transfer of Amiton (C11) from civil industry to Porton Down demonstrates how the British military interacted with the domestic chemical industry to develop a new family of nerve agents. Even so, it was not preordained that "Amiton the pesticide" would become "VG the nerve gas." Despite a degree of civil-military overlap, forging the conditions for technology transfer from the chemical industry to the military sector required an active process of outreach. The British military authorities mounted repeated letter-writing campaigns to industry in search of new toxic compounds, arranged for secrecy measures to protect industrial trade secrets, and sought to translate the goals of the pesticide industry into those of the chemical warfare laboratory.[70] Even so, these efforts failed to generate a flood of new research leads. Instead, the solicited

[65] Tucker, *War of Nerves*, pp. 181, 169.
[66] TNA, DEFE 13/823, Security Classification and Production of VX, R. Holmes. January 8, 1975..
[67] Brian Balmer, "A Secret Formula, a Rogue Patent and Public Knowledge about Nerve Gas: Secrecy as a Spatial-Epistemic Tool," *Social Studies of Science*, vol. 36 (2006), pp. 691-722.
[68] David E. Kaplan, "Aum Shinrikyo (1995)," in Jonathan B. Tucker, ed., *Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons* (Cambridge, MA: MIT Press, 2000), p. 214.
[69] In 1997, Russia declared 15,558 metric tons of a V-agent termed R-33 and the United States declared 4,032 metric tons of VX, all of which must be destroyed under the terms of the CWC.
[70] Bruno Latour, *Science in Action* (Cambridge, MA: Harvard University Press, 1987).

chemical companies stated repeatedly that they would not, in the normal course of events, be interested in the same things as the military scientists.

Focusing narrowly on technology alone gives rise to the "dual-use dilemma," in which both benign and malign applications are construed as being inherent in the technological artifact itself.[71] Examining the historical context, however, reveals that the military's efforts to transform a pesticide into a chemical weapon, coupled with a policy environment that encouraged the search for new toxic compounds, involved an active network of artifacts and people. Although Amiton and VG shared the same molecular structure, "Amiton the pesticide" was not identical to "VG the nerve gas." Instead, Amiton had to be *translated* into VG through an active network of artifacts and people, including a policy environment that encouraged the search for new toxic compounds.

The concept of "translation" comes from research in the sociology of science. Because the interests of different groups crucial to the success of a research project will not always align, in order for the work to move forward and succeed, the interests of one actor must be "translated" into the interests of the other. The metaphor is of linguistic translation, which involves more than a mechanical word-by-word substitution to preserve the original meaning of a phrase. In this case study, the military actively intervened to influence the goal of the pesticide industry to pursue compounds with low mammalian toxicity.

Lessons for Policy

Although the historical documents released to date provide evidence of the intentions of key historical actors, the exact details of the process by which Amiton was transferred to Porton remain obscure. Overall, however, the history of the V-series nerve agents suggests that effective governance of dual-use technologies requires policies that address the context in which innovation and technology transfer occur.[72] To that end, the governance architecture should seek to direct technological change along socially beneficial trajectories by influencing the "socio-technical networks" that are involved. [73]

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[71] See Caitríona McLeish, "Reflecting on the Dual-Use Problem," in Brian Rappert and Caitríona McLeish, eds., *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research* (London: Earthscan, 2007).

[72] See Paul Nightingale, "Technological capabilities, invisible infrastructure and the un-social construction of predictability: the overlooked fixed costs of useful research," *Research Policy*, vol. 33, no. 9 (2004), pp. 1259–1284.

[73] Giovanni Dosi, "Technological paradigms and technological trajectories: a suggested interpretation of the determinants and directions of technical change," *Research Policy*, vol. 11, no. 3 (1982), pp. 147–162. See also, Donald MacKenzie and Judy Wacjman, eds, *The Social Shaping of Technology* (Milton Keynes: Open University Press, 1999).

This historical case study also reminds us that static lists of artifacts can be innovated around or rendered obsolete by advances in science and technology, changing industrial practices, or the rise of new military utilities. Accordingly, the effective governance of dual-use technologies must accommodate change and innovation by moving away from governance measures based on lists of artifacts or technical characteristics and towards those that focus on intent and purpose. The CWC, for example, bans the development, production, stockpiling, transfer, and use of *all* toxic chemicals and their precursors regardless of their origin or method of production, *except* for "purposes not prohibited under this Convention," as long as the "types and quantities . . . are consistent with such purposes." The comprehensive nature of this prohibition means that as soon as a new chemical agent is developed for hostile purposes, it immediately falls under the scope of the treaty.

The Amiton case study suggests that the governance of dual-use technologies must look beyond the particular technological artifact under consideration and understand the social context in which innovation and technology transfer occur. Although intent is often viewed as ineffable and difficult to regulate, the V-agents case suggests that it may be more susceptible to governance than a static list of compounds.

Appendix B: The Use and Misuse of LSD by the U.S. Army and the CIA

Mark Wheelis

Introduction

The use of chemicals to modify brain function is an ancient practice. For millennia, humans have employed alcohol, marijuana, coca leaf, psychedelic fungi, and other plant extracts for ritual, therapeutic, and recreational purposes. There have also been sporadic reports of the use of psychoactive drugs for hostile ends, such as chemical warfare (CW) and covert operations. A wide variety of drugs have been examined for their potential to incapacitate enemy soldiers, enhance the capabilities of friendly troops, assist in interrogation, and induce psychosis in enemy leaders. Chemicals studied for these purposes have been drawn largely from recreational or ritual drugs, as well as known categories of pharmaceuticals (the two categories overlap). This historical case study examines the efforts by the U.S. Army and the Central Intelligence Agency (CIA) during the 1950s to develop lysergic acid diethylamide (LSD) as an incapacitating chemical weapon, an interrogation aid, and a mind-control agent.[1]

The Army and the CIA were attracted to LSD because of its extraordinary potency, dramatic disturbance of cognitive function, and low lethality, which gave the drug potential as a military incapacitant and as an agent for covert intelligence use. Although the mechanism of action of LSD was unknown when the programs took place, such understanding was not required for its empirical use. The Army's attempt to develop LSD into a battlefield weapon did not involve scientific innovation but simply extended traditional CW technology to a new agent. The effort failed for the same reasons that have prevented many other chemicals from becoming effective weapons, namely the instability of the drug when dispersed as an aerosol and the difficulty and high cost of its synthesis.

Similarly, the CIA's efforts to develop LSD as a mind-control agent, an interrogation aid, and a weapon to induce psychosis in enemy leaders were simply an extension of previous development efforts with other psychoactive chemicals such as mescaline, tetrahydrocannabinol

[1] Adrienne Mayor, *Greek Fire, Poison Arrows, and Scorpion Bombs: Biological and Chemical Warfare in the Ancient World* (New York: Overlook Duckworth, 2003).

(THC), scopolamine, and barbiturates. LSD was usually administered by adding it to a drink offered to an unwitting subject, an extremely low-tech delivery method. The CIA development program failed because the drug did not produce desirable effects in a reproducible manner, and because of belated concerns about the legality of the program.

Although U.S. experimentation with LSD as an agent for hostile purposes ended in the 1960s, military and intelligence agencies around the world continue to be interested in the development of other drugs for riot control, counterterrorism, interrogation, and troop enhancement. The potential use of such chemicals raises serious ethical and legal issues about manipulating the mental function of individuals without their informed consent. Broader themes addressed in this case study include the interpretation of misuse, the importance of oversight, the role of individuals, normative dynamics, and human rights issues.

Background on LSD

LSD disrupts the perceptual and cognitive systems in the brain, leading to powerful visions and hallucinations. These effects are sometimes experienced as profoundly meaningful, creating a sense of cosmic unity. Alternatively, the hallucinations induced by LSD can be terrifying, particularly if the subject is unaware of having been drugged. It is now understood that LSD is structurally similar to the neurotransmitter serotonin and mimics its excitatory action on a set of receptor sites in the cerebral cortex called 5-HT_{2A} receptors. LSD is therefore termed a serotonin receptor "agonist." (A serotonin "antagonist" is a drug that blocks rather than stimulates the receptor.) Because other 5-HT_{2A} agonists do not all produce hallucinations, it is clear that some aspects of the mechanism of action of LSD are not fully understood. Recent research has begun to identify the specific cortical pathways that are responsible for the drug's hallucinogenic effects.[2]

LSD was first synthesized in 1934 by Albert Hoffmann, a chemist at the Swiss pharmaceutical company Sandoz who was investigating derivatives of compounds isolated from ergot (a fungus that grows on rye and related plants) as possible drugs. Because lysergic acid is present in significant amounts in ergot-infected grains, Hoffmann extracted it and systematically

[2] J. Gonzáles-Maeso et al., "Hallucinogens recruit specific cortical 5-HT_{2A} receptor-mediated signaling pathways to affect behavior," *Neuron*, vol. 53 (2007), pp. 439-452.

synthesized derivatives of the molecule, including LSD. Several years later, in 1943, Hoffmann was renewing work with some of these derivatives when he suddenly felt dizzy and intoxicated in a way he had never experienced before. He left work early, bicycled home, and lay down. Several hours of vivid hallucinations followed before he gradually returned to normal. Hoffmann suspected that he had accidentally absorbed one of the experimental compounds he was handling. To determine if that was the case, he deliberately ingested a tiny amount of LSD—250 micrograms, a dose so small that no other drug known at that time would have had a noticeable effect. His plan was to gradually take more of the drug throughout the day until he reached a dose at which the first symptoms appeared. In fact, he had already ingested taken an amount that was several times the ED_{50} ("effective dose 50"), or quantity that causes a specified effect in 50 percent of the people taking it. Thus, Albert Hoffmann experienced the first deliberately induced "acid trip."[3]

LSD remained a curiosity until the early 1950s, when the psychiatric community became interested in it as a "psychotomimetic" agent—a drug that mimicked mental illness, especially schizophrenia. The hope was that LSD intoxication and schizophrenia shared a common biochemical basis and that the drug would provide a reversible clinical model for the study and eventual cure of schizophrenia. It was also believed that LSD would provide effective therapies for a number of mental illnesses by disrupting entrenched patterns of thought. Numerous studies of the drug were carried out in academic laboratories, psychiatric hospitals, and prisons, mostly with financial support from the Army and the CIA that was funneled through front organizations to conceal the source. These studies continued through the 1960s, but it gradually became clear that LSD intoxication was not a valid model of schizophrenia and provided no clinical benefit for any mental illness studied. In recent years, however, there has been a resurgence of interest in LSD for treating mental illnesses involving serotonin pathways, and it is possible that legitimate clinical uses may yet be discovered.[4]

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[3] John Marks, *The Search for the "Manchurian Candidate": The CIA and Mind Control* (New York: W. W. Norton, 1991), pp. 3-4.

[4] D. E. Nichols, "Hallucinogens," *Pharmacology and Therapeutics*, vol. 101 (2004), pp. 131-181; John Tierney, "Hallucinogens Have Doctors Tuning In Again," *New York Times*, April 11, 2010, p. A1.

The Army LSD Program

In May 1955 the U.S. Army officially launched Project M-1605, which sought to develop a psychochemical agent as a military weapon. The requirements were for a chemical that was as potent as sarin nerve agent, produced effects in less than an hour, was stable in storage, and was capable of dissemination from aircraft under all weather conditions. An absence of long-term effects was considered useful but not essential. About 45 compounds—including mescaline, LSD, THC, and related compounds—were tested in animals. In 1956, the Army approved testing by the Chemical Corps of psychochemicals in human subjects. Over the next two decades until 1975, more than 250 different chemical compounds were tested in over 2,000 experiments involving some 6,700 soldier volunteers and 1,000 civilians, mostly prisoner volunteers. In addition, the experimenters regularly subjected themselves to the agents they were testing. Most of the tests were conducted at Edgewood Arsenal, the Chemical Corps's research and development facility near Aberdeen, Maryland, on Chesapeake Bay. This facility was already involved in human experimentation because the Chemical Corps had long conducted tests of low doses of CW agents, such as mustard gas and nerve agents, on human volunteers. [5]

LSD was one of the most promising candidates for a new incapacitating weapon. Human testing showed it to be highly potent and demonstrated its ability to disorganize small military units performing routine tasks. By 1958, the Army was sufficiently enthusiastic about the potential of psychochemical agents that it mounted a major public relations campaign, including testimony to Congress to solicit additional funding. The campaign included a movie showing a cat on LSD cringing in terror before a mouse. In fact, however, the Army researchers encountered problems when trying to move LSD out of the laboratory and onto the battlefield. The compound was unstable in sunlight, limiting the ability to disseminate it as an aerosol cloud, the standard delivery method for military chemical weapons. LSD was also a highly complex molecule that was costly to produce. Initially the drug was prepared by chemically modifying lysergic acid extracted from ergot and was available only in small quantities from Sandoz. Even after Eli Lilly achieved the complete chemical synthesis of LSD in 1953, the multi-ton quantities needed for a chemical weapon stockpile would have been prohibitively expensive to produce.

[5] Martin Furmanski and Malcolm Dando, "Midspectrum Incapacitant Programs," in Mark Wheelis, Lajos Rózsa, and Malcolm Dando, eds., *Deadly Cultures: Biological Weapons Since 1945* (Cambridge, MA: Harvard University Press, 2006), pp. 236-251.

For these reasons the Army's interest in LSD waned, and the research effort ended in the early 1960s. Instead, the Chemical Corps turned its attention to another hallucinogenic agent called quinuclidinyl benzylate (BZ), a plant glycollate related to atropine and scopolamine. BZ was eventually weaponized and stockpiled, although it was never used on the battlefield or even deployed to forward bases.[6]

Despite this setback, the Army continued a research program to investigate the utility of LSD as an aid to interrogation, similar to what the CIA was doing but on a much smaller scale. As part of this program, 95 volunteers were dosed with LSD and subjected to mock interrogations. This effort was followed in 1961-62 by two programs, code-named THIRD CHANCE and DERBY HAT, which involved the administration of LSD during interrogations in Europe and the Far East. The Army interrogation programs, which ended in 1963, involved many of the same legal and ethical issues as the CIA program and are not discussed further in this case study.[7]

The CIA's LSD Program

The U.S. Office of Strategic Services (OSS), the predecessor to the CIA, tested several drugs as aids to interrogation during World War II. A "truth drug" committee studied mescaline, scopolamine, and barbiturates before turning to marijuana in 1943. Human testing was done on employees of the Manhattan Project (the atomic bomb program), presumably because it was subject to intense secrecy. When the subjects were given cigarettes injected with an extract of marijuana, the results were encouraging: they became talkative and freely disclosed information. The OSS then tested the technique on an unwitting subject, a gangster who was cooperating with the U.S. government to recruit Mafia support for the Allied forces preparing to invade Sicily. Again, this experiment was considered a success because the subject volunteered sensitive details about the mob's involvement in the drug trade. Additional trials on suspected Communist sympathizers were also considered successful. Ultimately, however, the OSS concluded that the

[6] Ibid.

[7] U.S. Senate, *Final Report of the Select Committee to Study Governmental Operations with Respect to Intelligence Activities* (hereafter the Church Committee report), (Washington, DC: U.S. Government Printing Office, 1976), pp. 392, 412.

drug treatment only worked on people who were predisposed to talk and not on resistant subjects.[8]

After the creation of the CIA in 1947, there was a renewed interest in enhanced interrogation techniques and the use of drugs to destroy a subject's will or to induce amnesia. These interests were inspired in part by two incidents that occurred in Hungary in 1949: the show trial of Cardinal József Mindszenty, who acted drugged and confessed to absurd charges, and the arrest later that year of Robert Vogeler, an executive with the International Telephone and Telegraph company who was charged with spying and given unknown drugs during his interrogation and trial. Although Vogeler was convicted and sentenced to 15 years in prison, he was released and repatriated after 17 months. Shortly after the outbreak of the Korean War in 1950, captured U.S. Air Force pilots began confessing to fictitious activities, such as waging biological warfare. These events convinced the CIA that the Soviet Union and its allies had developed techniques for "mind control" and that the United States had to catch up, both to understand the interrogation methods being used against U.S. soldiers and spies and to employ them against the Communist enemy.[9]

In response to these concerns, the CIA approved in April 1950 a program code-named BLUEBIRD, directed by Morse Allen, a polygraph expert from the agency's Office of Security. The purpose of BLUEBIRD was to explore various methods of enhanced interrogation, including drugs, electroconvulsive shock treatment, lobotomy, and hypnotism. The drug component of BLUEBIRD involved giving subjects a mixture of sedatives (the barbiturates amytal, seconal, or pentothal) and stimulants (amphetamines, caffeine, atropine, or scopolamine), together with hypnosis and occasionally marijuana, and subjecting them to a polygraph. In July 1950, a CIA team went to Japan for a few months to test these techniques on suspected Communist agents and North Korean prisoners-of-war. Although the results of these studies are unknown, they were apparently not encouraging because the search for new drugs continued.

In August 1951, BLUEBIRD was renamed ARTICHOKE for security reasons. Beginning in 1952, the CIA sent teams of interrogators to several countries, including Germany, France, Japan, and Korea, where they set up safe houses to conduct their activities. At least one safe

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[8] Marks, *Search*, pp. 6-9.

[9] H. P. Albarelli, Jr., *A Terrible Mistake: The Murder of Frank Olson and the CIA's Secret Cold War Experiments* (Walterville, Oregon: Trine Day, 2009), pp. 187-206.

house was established in Washington, DC. For several years, the ARTICHOKE teams used the new techniques to interrogate known or suspected double agents and defectors. The results were inconsistent: sometimes the interrogations produced useful information but often the results were disappointing. Furthermore, there was growing concern about releasing subjects who had been interrogated with ARTICHOKE methods, for fear that they would talk about their experiences. This concern led to studies of chemical or physical ways to induce amnesia, which ultimately failed. ARTICHOKE also investigated whether drugs, hypnosis, or other techniques could enable the CIA to control a subject's mind and force him to carry out a command, such as to assassinate a specified target. This effort appears to have been unsuccessful, although some have claimed that the CIA had limited success in controlling the minds of a small number of subjects who had pre-existing mental conditions such as multiple personality disorder.[10]

Given this background and the prior use of LSD as a model for schizophrenia, it is not surprising that CIA officials leapt at the drug when they became aware of it in the early 1950s. Much of the voluminous experimental work on LSD under project ARTICHOKE was supported by the CIA but performed in universities, prisons, and mental hospitals. To conceal the source of the funds, the money was channeled through front companies or other government agencies. In some cases, the investigators failed to obtain informed consent and administered LSD to unwitting people, such as adult or pediatric mental patients, but they usually informed the subjects in general terms about the nature of the experiments. Even so, many ethically marginal experiments took place.[11]

The CIA wanted to administer LSD to unwitting, mentally healthy, resistant individuals, which meant that informing subjects that they were participating in a drug trial would limit the value of the information being gathered. Because the experiments that the CIA wished to conduct were clearly illegal and unethical, they could not be performed by outside agencies. In 1953, CIA scientists began a series of projects, including one code-named MKULTRA, in which they gave LSD to unwitting subjects.[12] MKULTRA had two sister projects. MKNAOMI was a

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[10] Marks, *Search*, pp. 24-29, 31-47; Albarelli, *Terrible Mistake*, pp. 207-250; Colin A. Ross, *The CIA Doctors: Human Rights Violations by American Psychiatrists* (Richardson, Texas: Manitou Communications, 2006).

[11] Marks, *Search*, pp. 63-73; Ross, *CIA Doctors*, pp. 81-83.

[12] The MK prefix denotes projects run by the CIA's Technical Services Staff, a unit within the clandestine Directorate of Operations that was also responsible for developing new weapons, disguises, and false papers.

joint program with the U.S. Army Chemical Corps's Special Operations Division (SOD) at Fort Detrick, Maryland, to develop delivery devices and tactics for the covert use of chemical and biological products, including LSD. In addition, MKDELTA was a project to use MKULTRA products in field trials overseas, taking over from ARTICHOKE. All three projects were run by Sidney Gottlieb, a Ph.D. chemist who headed the Chemical Division of the CIA's Technical Services Staff.

In April 1953, Director of Central Intelligence Allen Dulles approved MKULTRA, and Richard Helms, the head of the CIA's Directorate of Operations, assigned the project an initial budget of $300,000. Due to its sensitivity, MKULTRA was exempted from the usual internal financial controls and requirements for written contracts. The initial project team consisted of six Technical Services Staff professionals. At first, the subjects were CIA agents who knew that they might be dosed with LSD at any time, but did not know when. Yet even these experiments did not necessarily provide useful information about the response of completely unwitting subjects.[13]

Beginning in May 1953, MKULTRA began testing LSD and other drugs on naïve subjects. This field program, MKULTRA Subproject 3, was run by George White, a narcotics agent who had been seconded part-time to the CIA from the Federal Bureau of Narcotics. White had previously worked for the Office of Strategic Services and had been part of the truth drug program during World War II. The testing of LSD on unwitting subjects began in a CIA-rented safe house in New York, but because of concerns that the location was vulnerable to exposure, the program was moved to San Francisco in 1955. The CIA opened a second safe house in Marin County, across the Golden Gate Bridge from San Francisco, and a third in New York in 1961. At all three locations, CIA operatives picked up prostitutes, petty criminals, and drug dealers in bars and on the streets and lured them to the safe house, or used prostitutes to lure clients there. Once at the safe house, the unwitting subjects were given drinks spiked with LSD or other drugs, and CIA scientists monitored their reactions by observing them through one-way mirrors. George White also administered LSD to suspects that he had arrested as a narcotics agent, to serve as an interrogation aid.

The logic behind the choice of subjects was that the individuals selected for the experiments, because of their illicit professions and marginal social status, would be unlikely to

[13] Marks, *Search*, pp. 59-62.

talk or protest afterwards, and this assumption proved to be correct. It is unclear whether or not the safe-house experiments provided any useful information about drugs and interrogations, but they did yield a great deal of information about the practices of prostitutes and the proclivities of their clients. Although LSD was the focus of much of MKULTRA's efforts, many other drugs were tested on unwitting subjects in the safe houses, including drugs considered too dangerous for CIA staff to experiment with on themselves. Deaths resulting from such experiments were rumored within the agency, and at least one hospitalization occurred. There were also claims of long-term mental health consequences, although such cases were not well documented.[14]

Another incident later proved to be highly controversial. In late 1953, near the start of the MKULTRA project, LSD was administered to a group of CIA agents and members of the Army Chemical Corps' SOD unit who collaborated with the agency on the covert use of chemical and biological agents. The individuals given LSD had gathered for a periodic retreat of SOD and MKULTRA staff at Deep Creek Lake in rural Maryland to discuss the programs. One SOD member, Frank Olson, had a bad LSD trip that left him suffering from severe depression, paranoia, and anxiety. About a week later, during a visit to New York City to consult with a CIA psychiatrist, Olson crashed through the tenth floor window of a hotel and fell to his death. Another CIA agent, who was acting as his escort, was the only other person known to have been in the room at the time. Although Olson's death was ruled a suicide, there have been persistent suspicions that it was murder. In any event, the CIA covered up the incident's connection to the LSD program until a congressional investigation in 1975.[15]

After Olson's death, the CIA briefly suspended the testing of LSD on unwitting suspects, but the experiments soon resumed. The testing continued until a 1963 oversight investigation of the Technical Services Staff by the CIA's Inspector General uncovered MKULTRA Subproject 3, raising serious concerns within the senior CIA leadership. The use of unwitting subjects was discontinued, although the program remained officially in existence. In 1973, Gottlieb destroyed

[14] Marks, *Search*, pp. 76-78, 94-109; Albarelli, *Terrible Mistake*, pp. 242-243, 280-281; John Ranelagh, *The Agency: The Rise and Decline of the CIA* (London: Weidenfeld and Nicolson, 1986), pp. 202-216; Church Committee, *Final Report*, pp. 385-422.

[15] Albarelli, *Terrible Mistake*, pp. 689-694. Albarelli argues that Olson was drugged not as part of an experiment on unwitting LSD intoxication but in order to interrogate him with ARTICHOKE methods because he had been talking loosely about CIA/SOD activities.

most of the records of MKULTRA, MKNAOMI, and MKDELTA with the permission of CIA Director Helms.[16]

Despite the CIA's failure to identify a drug that could serve as a truth serum, a 1957 report suggests that at least six drugs were moved out of the experimental category and into operational use against at least 33 targets. The goals of these operations are unclear, but in some cases the objective may have been to induce symptoms of mental illness so that the subject would be committed to a psychiatric hospital. Apparently some of these efforts were successful. It is not known if the drugs employed for this purpose included LSD, but it is likely.[17]

Use or Misuse?

At the time that the U.S. Army attempted to develop LSD as a battlefield chemical weapon, there were no legal barriers to the development, production, or stockpiling of chemical weapons. Thus, the Army program did not violate any treaties and was not considered misuse in the context of its time, although the release forms for human experimentation were later judged inadequate by a Senate investigative committee.[18]

In contrast to the Army CW program, the CIA efforts clearly went beyond the bounds of what was legal or ethical at the time and thus constitute a case of misuse of pharmacological technology. The principle of "informed consent" had been firmly established by the trials of Nazi doctors at the Nuremberg War Crimes Tribunal after World War II. These principles include the requirement that human subjects be fully informed of the nature of an experiment and its potential risks. Participation must be voluntary and cannot be coerced. The CIA routinely ignored these restrictions and the abuses grew progressively worse over time. The agency's willingness to violate the Nuremberg Code repeatedly is a major blot on its history. Further, the use of LSD to augment the interrogation of enemy POWs during the Korean War was a violation

[16] Marks, *Search*, pp. 79-93; Church Committee, *Final Report*, pp. 394-399.

[17] Marks, *Search*, pp. 110-111; Church Committee, *Final Report*, pp. 391-392.

[18] Church Committee, *Final Report*, pp. 417-418; James S. Ketchum, *Chemical Warfare Secrets Almost Forgotten: A Personal Story of Medical Testing of Army Volunteers with Incapacitating Chemical Agents During the Cold War (1955-1975)*, (Santa Rosa, California: ChemBooks, 2006), pp. 29-34.

of the Geneva Conventions[19] and the CIA's experiments with LSD on unwitting civilians and enemy defectors were violations of criminal law. Finally, the physicians who participated in classified projects involving LSD, and probably in some unclassified academic studies as well, were guilty of gross violations of medical ethics.[20]

Indeed, the very goals of the CIA's LSD program were illegal and unethical. Exerting control over the mind of an autonomous human being without his or her consent is a form of assault, as is the deliberate induction of psychosis. Thus, the misuse of pharmacology by the CIA was embedded deeply within the goals of the program. Although this account focuses on U.S. efforts to develop LSD for hostile purposes, it is likely that several other countries had similar programs, perhaps involving abuses that equaled or exceeded those of the CIA program.

Governance

The abuses committed by the CIA in its efforts to develop LSD and other drugs as an aid to interrogation, for "mind control," and to induce psychosis were a product of the intense paranoia of the times and the lack of effective internal and external oversight at the agency. Throughout the programs, the United States and its allies saw themselves as engaged in an existential struggle with the Soviet Union, and the overheated political rhetoric on both sides of the superpower confrontation encouraged that view. The perception that the United States faced an acute threat to its survival undoubtedly made it easier to condone violations of legal and ethical norms as permissible or necessary.[21] Even in extraordinary times, however, many individuals and organizations behave with integrity, and it is not entirely clear why the CIA programs were so egregiously abusive.

A few individuals within the agency did raise moral or legal concerns. For instance, in 1953 a member of the informal advisory committee to ARTICHOKE wrote:

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[19] *Convention Relative to the Treatment of Prisoners of War*, Geneva, July 27 1929 (entered into force on June 19, 1931); *Convention (III) Relative to the Treatment of Prisoners of War*. Geneva, August 12, 1949 (entered into force on October 21, 1950).

[20] Germany (Territory under Allied Occupation, 1945-1955: U. S. Zone), *Trials of War Criminals before the Nuremberg Military Tribunals under Law No. 10, Nuremberg, October 1946-April 1949* (Washington, DC: U.S. Government Printing Office, 1949-1953), pp. 181-182.

[21] Marks, *Search*, pp. 29-31.

> What in God's name are we proposing here? Does it not strike anyone but a few that these projects may be immoral and unethical, and that they may fly in the face of international laws? What really are we attempting to accomplish? Where does respect for life and human dignity come into play?[22]

Clearly there were inadequate mechanisms to allow such expressions of concern to reach higher levels of the bureaucracy. Moreover, a formal legal review of the proposed programs never took place, and the CIA's Office of General Counsel only learned of them in the 1970s.[23] Part of the reason for this cavalier attitude was that the goals of the LSD experiments were inherently illegal and unethical, and these qualities pervaded the effort from the outset. Of course, this observation begs the question of how such a questionable set of objectives could have been approved in the first place. One explanation is that because the goals of the MK programs were understood to be morally questionable if not outright illegal, they were considered highly sensitive and were therefore shrouded in secrecy.

The highly compartmented nature of the MK programs permitted very little oversight. Evidence suggests that the participants strictly limited the number of people read into the program. As a result, few people, even senior CIA officials, knew anything about the drug experiments, severely limiting the opportunities for dissent or alternative perspectives. Among those excluded from ongoing knowledge of the programs was the CIA's Medical Staff. Historical evidence also suggests that no members of Congress or officials in the Pentagon or the White House knew about the CIA's illegal use of drugs until the Senate hearings of the mid-1970s. Although CIA Director Dulles had approved MKULTRA, it is not clear whether or not his successor was ever briefed on the existence of the program.[24] Compounding the secrecy and compartmentalization of MKULTRA was the fact that CIA programs involving the use of chemical and biological agents were granted a waiver from standard accounting practices, such as written contracts and periodic audits. This exemption seriously limited the documentary record on which oversight depends. Ironically, the waivers from standard practices meant that

[22] Albarelli, *Terrible Mistake*, p. 231.
[23] Church Committee, *Final Report*, p. 408.
[24] Ibid., pp. 406-407.

the LSD programs, among the most sensitive that the agency engaged in, received significantly less oversight than more routine and less controversial programs.[25]

Although the reforms of the 1970s curtailed the ability of the intelligence agencies to act independently of Congress, the oversight process remains problematic because of the delicate balance between secrecy and transparency. Under the current U.S. system, the House and Senate leadership and the chairmen and ranking minority members of the House and Senate intelligence committees are briefed on significant covert programs. This approach is a great improvement over the total lack of institutionalized oversight that characterized the pre-1975 era, but it is still inadequate. There is an inherent tension between minimizing the risk of security breaches that could undermine the effectiveness of highly classified programs, and engaging a diverse set of individuals and institutions in the oversight process to prevent covert programs from straying beyond the bounds of the acceptable. Unfortunately, during times of perceived crisis or existential hazard—precisely when transgressions are most likely—national security concerns tend to weigh more heavily than accountability and oversight.[26]

The lack of routine independent legal review of all major projects also played a critical role in allowing the CIA's LSD programs to avoid challenge. Such a legal review should be part of every agency's approval process. Furthermore, the granting of waivers from formal accounting and audit standards should not be allowed; no institution is well served by blinding itself to its own mistakes. Agency ombudsmen and institutional protections for whistleblowers are also important because they give concerned individuals a place to go with their concerns and shield them from retaliation. Another element of governance involves the physicians who participated in the covert CIA programs and who, in principle, were governed not only by U.S. law but by the ethics of their profession. Unfortunately, the medical and psychiatric communities have been reluctant to investigate and discipline physicians who have participated in illegal or unethical military or intelligence programs involving psychoactive drugs. Today there is a need for greater discussion of the legal and ethical issues that confront government physicians

[25] Ibid., pp. 386, 403-406.
[26] John M. Oseth, *Regulating U.S. Intelligence Operations: A Study in Definition of the National Interest* (Lexington, Kentucky: University Press of Kentucky, 1985).

involved in activities such as interrogation.[27] Secure reporting mechanisms should also be established so that physicians who have misgivings about activities that they observe or participate in can report them without risk of retribution.

Conclusions

This case study has considered two different efforts to turn LSD into a weapon: by the U.S. Army to develop the drug as an incapacitating CW agent for battlefield use, and by the CIA to use it as a vehicle for mind control, neutralizing individuals, and enhancing interrogation. The CIA program was overtly illegal and immoral, both in its fundamental goals and in many of its methods. In contrast, the Army program was legal at the time, and most of the work adhered to established rules for the conduct of human experiments. Nevertheless, ever since the entry into force of the Chemical Weapons Convention (CWC) in 1997, any such program would be clearly illegal under international law. Given the near-universality of the CWC, its elaborate verification measures, and the difficulty of concealing a large-scale chemical weapons program, it seems unlikely that any country will ever launch such a development program again.

Nevertheless, the CWC contains a loophole that allows the use of psychoactive chemicals under certain circumstances. Article II.9 (d) permits the use of toxic chemicals for "domestic law enforcement including riot control." This exemption enables countries to conduct judicial executions by lethal injection and allows police to use tear gas and pepper spray to suppress riots. Although the scope of the permitted use of toxic chemicals under this clause is a matter of scholarly debate, the most widely held opinion—and the one under which most CWC member states are operating—is that the exemption allows the development of psychoactive chemical weapons for law enforcement purposes.[28] The Russian Federation, for example, has developed, produced, stockpiled, and used as a weapon on at least two occasions a potent anesthetic drug (a

[27] Steven H. Miles, *Oath Betrayed: America's Torture Doctors*, 2nd edition (Berkeley: University of California Press, 2009); Luis Justo, "Doctors, Interrogation, and Torture," *British Medical Journal*, vol. 332 (2006), pp. 1462-1463; Joby Warrick and Peter Finn, "Psychologists Helped Guide Interrogations: Extent of Health Professionals' Role at CIA Prisons Draws Fresh Outrage from Ethicists," *Washington Post*, April 18, 2009.

[28] David P. Fidler, "Incapacitating Chemical and Biochemical Weapons and Law Enforcement under the Chemical Weapons Convention," pp. 171-194, and Adolf von Wagner, "Toxic Chemicals for Law Enforcement Including Domestic Riot Control Purposes under the Chemical Weapons Convention," pp. 195-207, in Alan M. Pearson, Marie Isabelle Chevrier, and Mark Wheelis, eds., *Incapacitating Biochemical Weapons: Promise or Peril?* (New York: Rowman and Littlefield, 2007).

derivative of the synthetic opioid fentanyl) with no objection from other members of the CWC. During the best-known incident, in October 2002, Chechen rebels seized more than 800 hostages at the Dubrovka Theater in central Moscow. Russian security forces pumped an aerosol of the anesthetic drug into the theater, incapacitating the hostage-takers, who were then all killed. But 129 of the hostages also died from exposure to the agent and many others suffered permanent disability.[29]

It is unlikely that the Russian Federation is the only country developing pharmaceuticals for police use, including various delivery devices. Once such weapons have been developed for law enforcement and have been produced and stockpiled, it will be very difficult to prevent at least some countries from putting them to illegal military use or to prevent their adoption by despots, torturers, criminals, and terrorists. Accordingly, the wisdom of going down that path should be carefully considered before it becomes a *fait accompli*. Unfortunately, there is no consensus among CWC states parties that the law enforcement exemption should be narrowed, which would be the most obvious way to address the problem.[30]

The CIA's LSD program violated a variety of criminal laws and international agreements, and any such program today would be subject to the same prohibitions. In addition, the CWC bans such programs. The combination of the treaty, existing criminal law, and government regulation of prescription drugs and narcotics provides a fairly robust barrier to the future development of mind-control drugs, pharmaceutical aids to interrogation, or drugs that cause psychosis—but only if secret programs receive adequate oversight and governance. Since many countries have poor transparency and oversight mechanisms, it is possible that several of them are, or soon will be, developing psychoactive chemicals for covert use. Even in the United States, one of the most transparent and lawful countries in the world, there have been recurrent

[29] John B. Dunlop, *The 2002 Dubrovka and 2004 Beslan Hostage Crises: A Critique of Russian Counter-Terrorism* (Stuttgart: Ibidem, 2006).

[30] Mark Wheelis, "Nonconsensual Manipulation of Human Physiology Using Biochemicals," in Pearson, Chevrier, and Wheelis, eds., *Incapacitating Biochemical Weapons*; Board of Science and Education, British Medical Association, *Biotechnology, Weapons and Humanity II* (London: British Medical Association, 2004); Mark Wheelis and Malcolm Dando, "Neurobiology: A Case Study of the Imminent Militarization of Biology," *International Review of the Red Cross*, vol. 87 (2005), pp. 553-568.

claims that drugs have been used during the interrogation of detainees at Guantánamo and elsewhere.[31]

Although international legal opinion generally considers the use of drugs for police interrogation to constitute torture, the issue appears to be unsettled. At least one country (India) uses sodium pentothal occasionally during police interrogations, and does so openly.[32] These developments create a disturbing precedent for the development of other chemical agents that affect the human mind. Given the rapid increase in understanding of the chemical functioning of the brain and the development of drug-delivery systems that are more precise and specific, the potential for misuse is great.

Perhaps the most important lesson from the CIA's experiments with LSD is to remind us that some dual-use technology threats go beyond arms control and counterterrorism and into the realm of fundamental human rights. Our thoughts, beliefs, emotions, memories, and sanity may be subject to manipulation by the emerging technologies of the mind, without our permission or even our awareness. Such a potential is not as remote as it might seem. Accordingly, there is a need for much greater discussion of the ethical issues involved in non-consensual manipulation of the human mind, and perhaps explicit recognition of a basic right to protection from such assault.[33]

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[31] J. Meeks, "People the Law Forgot," *Guardian*, December 3, 2003; P. Sleven and J. Stephens, "Detainees' Medical Files Shared: Guantanamo Interrogators' Access Criticized," *Washington Post*, July 10, 2004, p. A1; Neil A. Lewis, "Man Mistakenly Abducted by C.I.A. Seeks Reinstatement of Suit," *New York Times*, November 29, 2006, p. A15; Deborah Sontag, "Videotape Offers a Window Into a Terror Suspect's Isolation," *New York Times*, December 4, 2006, p. A1; Raymond Bonner, "Detainee Says He Was Abused While in US Custody," *New York Times*, March 20, 2007; Alissa J. Rubin, "Bombers Final Messages Exhort Fighters Against US," *New York Times*, May 9, 2008; William Glaberson, "Arraigned, 9/11 Defendants Talk of Martyrdom," *New York Times*, June 6, 2008, p. A1.

[32] Jason R. Odeshoo, "Truth or Dare? Terrorism and 'Truth Serum' in the Post-9/11 World," *Stanford Law Review*, vol. 57 (2004), pp. 209-255; Jeremy Page, "'Truth Serum' Row in India After Interrogators Fail to Find Killer," *Times* (London), July 16, 2008; Rhys Blakely, "Mumbai Police to Use Truth Serum on 'Baby-Faced' Terrorist Azam Amir Kasab," *Times* (London), December 3, 2008.

[33] Mark Wheelis, "'Non-Lethal' Chemical Weapons: A Faustian Bargain," *Issues in Science and Technology* (Spring 2003), pp. 74-78; Françoise J. Hampson, "International Law and the Regulation of Weapons," pp. 231-260, and William J. Aceves, "Human Rights Law and the Use of Incapacitating Biochemical Weapons," pp. 261-284, in in Pearson, Chevrier, and Wheelis, eds., *Incapacitating Biochemical Weapons*.

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