INCAPACITATING BIOCHEMICAL WEAPONS
Science, Technology, and Policy for the 21st Century

Alan Pearson

Military interest in incapacitating biochemical weapons has grown in recent years as advances in science and technology have appeared to offer the promise of new "non-lethal" weapons useful for a variety of politically and militarily challenging situations. There is, in fact, a long and unfulfilled history of attempts to develop such weapons. It is clear that advances are opening up a range of possibilities for future biological and chemical weapons more generally. The treaties prohibiting biological and chemical weapons make no distinction between lethal and "non-lethal" weapons—all are equally prohibited. Indeed, a sharp and technically meaningful distinction between lethal and "non-lethal" biological and chemical weapons is beyond the capability of science to make. Thus, interest in incapacitating biochemical weapons, and efforts on the part of various states to develop them, pose a significant challenge to the treaty regimes, to the norms against biological and chemical warfare that they embody, and, ultimately, to the essential protections that they provide. Preventing a new generation of biological and chemical weapons from emerging will take concerted efforts and action at the local, national, and international levels.

KEYWORDS: Biological weapons; Chemical weapons; Biochemical weapons; Chemical incapacitating agents; Non-lethal weapons; Arms control; Fentanyl

In January 2006, the Institute of Medicine and the National Research Council of the U.S. National Academies of Science issued a report titled *Globalization, Biosecurity and the Future of the Life Sciences*. The report called attention to the ways in which rapid advances in the life sciences and biotechnology are generating new knowledge and capabilities that could enable the creation of a wide range of novel biological threats. "The accelerating pace of discovery in the life sciences has fundamentally altered the threat spectrum," said the report. It noted that "[t]he immune, neurological, and endocrine systems are particularly vulnerable to disruption by manipulation of bioregulators."[1]

Bioregulators are "naturally occurring organic compounds that regulate diverse cellular processes in multiple organ systems and are essential for normal homeostatic function."[2] They are a subset of the large number of biochemical compounds produced by living organisms, and numerous physiologically active natural and synthetic biochemical analogues of the bioregulators are known to exist. When introduced into the body in

Nonproliferation Review, Vol. 13, No 2, July 2006
ISSN 1073-6700 print/ISSN 1746-1766 online/06/020151-38

DOI: 10.1080/10736700601012029

quantities significantly greater than those that normally occur, these biochemicals can cause severe adverse effects or death.[3]

Concern about the use of bioregulators as weapons is not new—both the United States and Sweden, for example, discussed this potential as far back as the Second Review Conference of the Biological and Toxin Weapons Convention (BTWC) in 1986.[4] However, in recent years this concern is being heard with greater frequency, and the focus has tended to be on bioterrorism. Thus, the news release accompanying the Institute of Medicine report stated that ''the entire scientific community should broaden its awareness that bioterrorism threats now include, for example, new approaches for *manipulating* or killing host organisms.''[5] (Emphasis added.)

This statement was duly picked up by others.[6] In the United States, the most important expression of concern came from the White House in the form of a 2004 Presidential Directive, which stated that ''[a]dvances in biotechnology and life sciences—including the spread of expertise to create modified or novel organisms—present the prospect of new toxins, live agents, and *bioregulators* that would require new detection methods, preventive measures, and treatments.''[7] (Emphasis added.)

What these recent expressions of concern have missed is that the threat posed by the hostile use of bioregulators and other biochemical weapons primarily comes not from terrorists, but from the military organizations of states. The biological weapons program of the former Soviet Union reportedly included a special program for developing bioregulator-based weapons.[8] Moreover, several countries now appear to be pursuing incapacitating biochemical weapons based on analogues of bioregulators. Indeed, three years before its report on globalization and biosecurity, the National Research Council released a report from a different committee which strongly recommended that the U.S. military pursue a ''non-lethal'' biochemical weapons capability.[9]

It was an event in Moscow in 2002 that first brought the issue of incapacitating biochemical weapons to widespread public attention. On the evening October 23, 2002, a group of male and female Chechen terrorists raided the Dubrovka theater center during a performance of the play *Nord-Ost* and took approximately 800 people hostage. The 50-odd hostage takers were well armed and the women among them were wired with high explosives. They demanded the withdrawal of Russian troops from Chechnya and threatened to kill the hostages if their demand was not met. A little over two days later, on the morning of October 26, Russian Special Forces troops disseminated an unknown biochemical agent through the ventilation system, apparently putting both hostages and the Chechen women, who remained in the main theater, into a deep sleep. Approximately 30 minutes later, the troops stormed the theater, killing all of the Chechen hostage takers and ending the crisis. However, approximately 125 hostages died from the effects of the gas, and many more were severely injured. Several days later, the Russian Health Minister revealed that the gas contained a derivative of the potent narcotic fentanyl, a compound related to morphine, but did not reveal the specific nature of the agent used.[10]

The Moscow theater siege illustrated both the potential and the limitations of incapacitating biochemical weapons. The Russian government faced an extremely difficult and unenviable situation—it is impossible to know whether the use of the biochemical incapacitant saved more lives than it cost, or vice versa, once the decision to resolve the

crisis forcefully was taken. However, the military use of an apparently novel chemical agent did not generate any significant public comments from other governments. Instead, as one proponent has suggested, it may have generated more interest on the part of governments in exploring the potential of incapacitating biochemical weapons.[11] Indeed, as science and technology continue to advance, our rapidly increasing understanding of the human nervous system and of other physiological systems appears to suggest to some that the development of ''non-lethal'' incapacitating biochemical weapons is possible.

Should efforts to develop such weapons gather steam, the future of the Chemical Weapons Convention (CWC) and BTWC regimes will be in jeopardy, and the protections the conventions provide may begin to erode. Should such weapons come to be routinely used, the protections could ultimately be eliminated altogether. The path leading to incapacitating biochemical weapons is not one we should tread down lightly.

Defining Incapacitating Biochemicals

According to one widely used textbook, ''biochemistry is the chemistry of life.''[12] Biochemicals are biologically active chemicals; that is, they are chemicals that are produced by or act via specific chemical mechanisms in living organisms. Bioregulators are a subset of biochemicals, albeit a subset of particular concern and importance in relation to biological and chemical weapons. Toxins such as botulinum toxin and saxitoxin are also biochemicals. As will be discussed later, for purposes of arms control, biochemicals can be considered to be both chemical and biological agents.

Biochemicals may normally exist only transiently in a living organism, or they may be long-lasting products of biochemical reactions. Moreover, while most biochemicals are produced by living organisms, an increasing number can also be produced synthetically. A biochemical need not be essential for fundamental life processes, yet through its chemical activity it can have a profound effect on such processes. For instance, the statin family of drugs dramatically lowers cholesterol levels in humans by specifically inhibiting HMG-CoA reductase, an enzyme (a protein that catalyzes a specific biochemical reaction) responsible for the committed step in cholesterol biosynthesis. The statins, first discovered in certain strains of fungi, are biochemical analogs of the endogenous ligand HMG-CoA that compete with it for binding to the enzyme.[13] Several synthetic statins have also been developed based on fungal compounds, including atorvastatin (lipitor), which in 2004 was the largest-selling drug in the world.[14] Like synthetic versions of naturally occurring biomolecules, wholly synthetic organic compounds such as atorvastatin that are biologically active analogs of naturally occurring biomolecules are also biochemicals.

In the context of chemical and biological weapons, incapacitation is defined not in scientific terms based on the physiological action or effect of an agent, but in military terms based on the desired consequence of such action or effect. The meaning of the term *incapacitation* is thus context-dependent and can be somewhat elastic, but it must exclude death or permanent injury as an intended consequence. For example, according to U.S. Army Field Manual 3-11.9, ''in a military context, incapacitation is understood to

mean inability to perform one's military mission.''[15] Two U.S. military authorities note that ''when the word incapacitating is used, we should ask, 'incapacitating for what activity?' . . . Since missions vary, we could theoretically consider a particular agent to be incapacitating if it disrupts aspects of performance vital to a particular mission.''[16] In other words, a person who is ''incapacitated'' is unable to do whatever it is that the user wants to stop him or her from doing. Incapacitation could mean reducing vision and otherwise harassing fighters with tear gas to impede their effectiveness; it could mean blunting cognition so as to impede effective concentration or cooperation among members of operational units; it could mean ''knocking out'' a target with an agent that induces anesthesia, as occurred in the Moscow theater siege. These are all different endpoints pharmacologically. Regardless of the precise effect desired, incapacitation must be both predictable and significant from the user's point of view.

In turn, an ''incapacitating agent'' is a chemical agent that ''produces temporary physiological or mental effects, or both, which will render individuals incapable of concerted effort in the performance of their assigned duties,''[17] and ''the basic purpose of an incapacitating agent . . . [is] to reduce military effectiveness without endangering life.''[18] Incapacitating agents are often divided into two classes. Agents in the first class generally act locally and have effects which disappear rapidly (within minutes) after exposure ceases. These include tear gases and are typically referred to as irritants, harassing agents, or riot control agents (RCAs). Agents in the second class cause temporary incapacitation that lasts substantially longer (up to hours or days) than the time of exposure by acting on and thereby altering specific biochemical processes and physiological systems, particularly those of the central nervous system.[19] These are the incapacitating biochemical agents. They have also been called incapacitating agents, incapacitants, immobilizing agents, calmatives, pharmacological agents, and biotechnical agents. They include neurotransmitters, other neuro-regulators, and their synthetic analogs which are used for anesthesia, sedation, and other purposes. In the central nervous systems, these agents act as ligands for (that is, they bind to) specific receptor molecules located on the surface of nerve cells at the synapses (junctions) where one nerve cell transmits information to another. The distinction between these two classes is not firm; for instance, the effects of incapacitating biochemical agents are known to dissipate within minutes after exposure ceases.[20]

Factors Driving Efforts to Develop Incapacitating Biochemical Weapons

From the beginning, efforts to develop incapacitating biochemical weapons have been enabled by scientific and technological advances in the medical and life sciences. As one U.S. military scientist noted, '' . . . as credible military weapons, drugs did not receive serious consideration until the 1950s, when scientific psychopharmacology first came of age.''[21] The impact of scientific and technological advances will be discussed in greater detail below. The establishment of military-pharmaceutical industry relationships has also been important. For instance, at least two biochemical incapacitants pursued by the U.S. and U.K. militaries in the 1960s, 3-quinuclidinyl benzilate (BZ, a deleriant) and TL 2636 (a vomiting agent derived from thebaine, a biochemical found in opium) were obtained by

the military through industrial liaison programs.[22] Industrial partnerships were still being promoted in the year 2000 as a way of identifying potential new biochemical incapacitants.[23]

Efforts to develop incapacitating biochemical weapons have also been enabled by the ability of scientists and other advocates to argue effectively that such weapons could in fact be developed and would provide the military with useful new capabilities and greater operational flexibility, thereby enhancing the armed forces' ability to defeat adversaries while reducing political constraints on the use of force. Indeed, U.S. efforts to develop incapacitating biochemical weapons began in 1949 with the suggestion by a member of the Army Chemical Service that the use of psychoactive chemicals in a war with the Soviet Union might allow victory without horrific death and destruction.[24]

Later, proponents suggested that, depending on the scenario, incapacitating biochemical weapons could be nearly as effective as lethal chemical weapons for reducing the combat effectiveness of enemy troops, and less costly in both military and political terms. They could be useful in areas where civilians or opposing Warsaw Pact forces might be convinced to shift alliances. They could also provide a more ''flexible'' military posture adaptable to the conduct of limited warfare (including military interventions and counterinsurgencies) and hostage rescue operations. They could, for example, provide for greater freedom of action and more ambitious military operations in situations where enemy forces were present in heavily populated areas or even intermingled with friendly or noncombatant personnel.[25]

Today, incapacitating biochemical weapons are considered one of several types of potential ''non-lethal'' weapons ''designed and primarily employed so as to incapacitate personnel or material, while minimizing fatalities, permanent injury to personnel, and undesired damage to property and the environment.''[26] As before, such weapons are said to fill a capabilities gap and allow for ''*flexible and selective engagement*'' in ''circumstances [that] may limit the use of lethal means.''[27] (Emphasis in original.) They could thus ''enhance the utility and relevance of military force as a . . . policy option,'' especially in situations where combatants and noncombatants are often mixed, by ''bringing into balance the conflicting requirements of mission accomplishment, force protection, and safety of noncombatants.'' With the increase in peacekeeping operations since the end of the Cold War and the rise in terrorism, envisioned uses now focus on military operations other than war (crowd control, peacekeeping, humanitarian assistance, occupation and reconstruction, noncombatant evacuations, hostage rescue, counterterrorism, and management of violently belligerent prisoners), although they also include military operations in urban terrain (including counterinsurgency operations and major regional wars, and the capture of individuals ''behind enemy lines'').[28]

In short, today as 50 years ago, incapacitating biochemical weapons are being sought not to replace traditional military weapons, but to provide new weapons that expand the range of tactical and strategic options available to commanders and political leaders; not to reduce the use of force, but to enhance the ability to use force in situations where the use of more traditional means of force faces significant, and growing, political constraints. As the 1998 Joint Concept for Non-Lethal Weapons stated: ''The wider range

of options provided by non-lethal capabilities *augments* deadly force but *does not replace it*."[29] (Emphasis in original.)

Technical Requirements and Challenges: The Intersection of Politics and Science

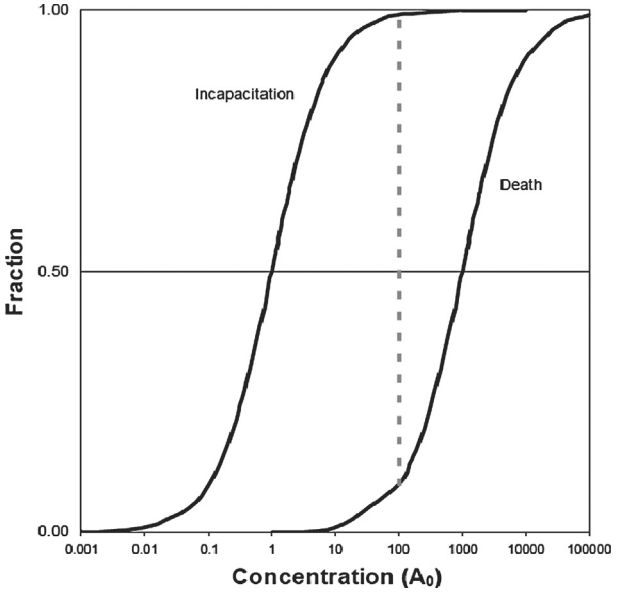
Based on publicly available information, there have thus far been no major successes in the development of incapacitating biochemical weapons. The U.S. experience with BZ provides a good example why. BZ is a member of the belladonoid/atropine class of plant toxins that causes torpor and sedation followed by delirium and often hallucinations, irritability, and paranoia. Its potency (i.e., the dose required to achieve the desired effect) compares favorably to that of the nerve agents.[30] Although BZ munitions were standardized in 1962 and produced until at least 1965, they apparently never entered the operational U.S. chemical weapons arsenal and were declared obsolete around 1976 with no replacement in sight.[31]

As an incapacitating biochemical weapon agent, BZ had a number of problems. At the ED50 (the dose at which 50 percent of exposed individuals exhibit the desired effect), BZ took eight hours to reach its full effect. That effect was itself unpredictable—at a given dose some individuals were completely incapacitated while others appeared relatively unaffected. Moreover, the range of behavioral responses elicited was quite variable and unpredictable, with some individuals exhibiting irrational rage and paranoia as the initial effects of the drug wore off, behaviors that could have very negative consequences for friend and foe alike. Finally, the method of disseminating BZ generated a visible cloud, virtually eliminating any chance for surprise or covert delivery.[32]

There was also a fourth complication, as the chair of the U.K. Chemical Defence Advisory Board pointed out: " . . . any chemical agent, a small dose of which is capable of profound disturbance of bodily or mental function, is certain to be able to cause death in large dose . . . and no attack with a chemical warfare agent is likely to be designed with the primary objective of avoiding overhitting."[33] This can be termed the "dose response problem," and it is at once a problem of science, application, morality, and politics. In considering the safety of a drug, doctors and scientists usually speak in terms of its safety margin or therapeutic index, which is generally defined as the ratio of the LD50 (the drug dose which causes lethality in 50 percent of a target population) to ED50 (see Figure 1). For BZ, which in addition to the effects mentioned above can also cause tachycardia (rapid heart rate), elevated body temperature, and even coma at high doses, this ratio was estimated on the basis of animal studies to be approximately 40.[34] For reasons to be explained next, and as will be illustrated by the subsequent review of later efforts to develop incapacitating biochemical weapons, this ratio would likely be considered inadequate by most if not all observers today.

Ultimately it is the ability of a prospective weapon to meet military and political requirements, within existing moral, political, and operational military constraints, that determines whether it is developed, fielded, and used.[35] Thus, the safety margin is a stand-in for the ratio that truly matters, which is the ratio of the dose that results in the "maximum acceptable" level of mortality and serious morbidity to the dose that achieves

FIGURE 1
Relationship between dose, incapacitation and lethality.[1]



1. From Lynn Klotz, Martin Furmanski, and Mark Wheelis, ''Beware the Siren's Song: Why 'Non-lethal' Incapacitating Chemical Agents are Lethal,'' Scientists Working Group on Biological and Chemical Weapons, March 2003. Reproduced with permission.

the minimum required operational impact. That ratio is determined by moral (societal), military, and political considerations. In the early days of the Cold War chemical weapons program in the United States, advocates within the U.S. Army Chemical Corps promoted the use of mustard gas as an incapacitating agent because it had exhibited ''only'' a 2 percent lethality rate among U.S. troops in World War I.[36] And for many applications in general warfare at the time, it might have been adequate to incapacitate only half of the enemy soldiers. Today, U.S. military requirements appear to be much tighter: at least 99 percent incapacitation, including no more than 0.5 percent mortality and no more than 1.0 percent combined mortality and serious long-term morbidity.[37] There is no reason to believe that these numbers will not change in the future. As the Joint Concept for Non-lethal Weapons states: ''Department of Defense policy does *not* require or expect non-lethal weapons 'to have a zero probability of producing fatalities or permanent injuries.' Rather, non-lethal weapons are intended to *significantly reduce* the probability of such fatalities or injuries as compared with traditional military weapons.'' (Emphasis in original.)

Klotz et al. have shown that an agent that could fulfill the fairly stringent requirements that exist in the United States today would need to have an exceptionally large safety margin, perhaps as high as 1,000 or more.[38] Even if a lethality rate of up to 5 percent were accepted, a very large safety margin would be required.[39] Some members of

the class of agents used in Moscow have been reported to have safety margins this high.[40] However, reported safety margins of potential incapacitating agents can be extremely misleading, for at least three reasons.

First, actual safety margins can only be determined in animal models. Yet, different animal models will often yield significantly different results, and extensive experience has shown that "animal data can not be extrapolated directly to human beings," most especially at the upper limits of exposure.[41] Indeed, fully one-fifth of all drugs entering clinical trials fail due to inadequate safety, even though most were previously tested in animals.[42] Although some information on upper exposure limits can often be gained from clinical data on surgical patients, this is possible only because doses can be tightly controlled, the patients are constantly monitored and often ventilated, rapid intervention can be administered in the case of adverse effects, and a host of other measures can be taken to ensure patient safety.[43] None of these characteristics of the hospital setting will be present on the battlefield, and this clinical experience only serves to illustrate that incapacitating agents have narrow safety margins in practice.[44]

Second, the characteristics (slope, location, and threshold effects) and predictive value of dose-response curves depend on the effect being measured and on the range of doses being tested. Yet, "no drug produces a single effect, and, depending on the effect being measured, the therapeutic index for a drug will vary."[45] An objective measure of militarily-relevant incapacitation can be quite difficult to define, and a safety margin based on analgesia (pain relief) is virtually meaningless if the desired effect is akin to surgical anesthesia (heavy sedation and/or sleep). Meanwhile, the range of doses tested in humans will often be quite narrow owing to safety concerns.[46]

Third, and perhaps most important, human effects determined under idealized and controlled settings do not reflect real operational contexts. In military studies, human-effects tests typically use healthy young adults who are exposed to defined doses for a defined length of time in noncombat settings where they can be carefully monitored for adverse effects. Such tests fail to account for two significant and uncontrollable sources of variability that would occur in the field. The first relates to differences in age, size, gender, health status, and individual susceptibility to the agent among those exposed.

> Therapists of every type have long recognized and acknowledged that individual patients show wide variability in response to the same drug or treatment method. . . . The concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population.[47]

For this reason, pharmaceutical agents must be delivered to individuals under controlled circumstances within a narrow range of doses.[48] The second relates to unavoidable differences in exposure time and agent distribution after an agent is disseminated. These differences make the uniform delivery of precisely controlled doses of incapacitating agents nearly impossible, a fact that will very likely encourage users to deliver more agent than needed to incapacitate most individuals in order to compensate for those individuals who inevitably would not receive a high enough dose.[49] This problem is complicated even more by the need for rapid incapacitation in most scenarios, as this

requires the delivery of higher doses than would normally be used for nonmilitary purposes. It is thus no surprise when one developer of incapacitating biochemical agents says that ''it's a very complex situation—it is hard enough to use them in the operating room without compounding the problem with larger groups.''[50]

It is now clear that efforts to develop effective incapacitating biochemical weapons face a complex set of interdependent technical challenges that are dictated by politico-military goals and requirements. A good incapacitating agent must generally:

1. Be highly potent (micrograms/kilogram [μ/kg] body weight, or less)
2. Have a rapid onset (minutes)
3. Have a defined, short (minutes-to-hours) duration
4. Have effects that are reversible
5. Be stable in storage and delivery
6. Have a significant and predictable effect(s) at a given dose or dose range
7. Be capable of rapid, often covert, dissemination in defined, controllable, and appropriate amounts
8. Have a high safety margin.[51]

Ironically, the ''siren's song'' of militarily significant yet non-lethal incapacitation has been both a driver of and an impediment to the development of incapacitating biochemical weapons.[52] Incapacitating biochemical weapons are not inherently ''non-lethal,'' even if used with non-lethal intent. For all practical purposes, any biochemical weapon that can significantly incapacitate the vast majority of those exposed will very likely cause a significant number of deaths at the same time.

Advances in Science and Technology

According to arms control researchers Mark Wheelis and Malcolm Dando, early efforts to develop incapacitating biochemical weapons failed primarily because scientific understanding of neurobiology and neuroreceptors was insufficient for enabling the development of agents with adequate specificity to elicit a narrow range of rapid and predictable responses.[53] For example, it is now known, but was not known in the 1960s, that there are five subtypes of muscarinic acetylcholine receptors (one of the two major groups of neuroreceptors that recognize the neurotransmitter acetylcholine), that BZ binds to all five subtypes, and that each of these subtypes has different functions in the brain.[54] It is thus not surprising that BZ had such pleiotropic and variable effects.

However, beginning with the introduction of biochemical techniques for the purification and study of receptors in the 1970s and their adoption by the pharmaceutical industry to speed up drug discovery, continuing with the cloning of neuroreceptor genes starting in the late 1980s and on through to the era of genomics, systems biology, and advanced neuroimaging techniques in the 1990s and the early part of this century, there have been enormous advances in our understanding of the structure, distribution, function, and integration of receptor subtypes within complex neurological circuits and systems.[55] In addition, as reviewed previously in this article and elsewhere, our ability to design, synthesize, test, and deliver novel chemicals that could affect these receptors has

also advanced rapidly in the past 15 years.[56] In many countries there is now a focus on applied science for drug development in order get "fundamentally better answers about how the safety and effectiveness of new products can be demonstrated in faster time frames, with more certainty, and at lower costs."[57]

These scientific and technological advances have continually revealed new possibilities for the development of incapacitating biochemical weapons. Wheelis and Dando thus ask whether our level of scientific understanding and technological development is now or will soon be sufficient to enable the development of new agents that have enough specificity to more safely elicit more predictable responses. The fentanyl family of synthetic opioid analgesics offers a good test case for studying this question, as both the U.S. and Soviet/Russian militaries have undertaken significant efforts to develop these agents into incapacitating biochemical weapons.[58]

The fentanyls, synthetic analogs of the naturally occurring biochemical morphine, are among the strongest analgesics known and among the fastest-acting neurochemical agents. Fentanyl itself is 100 times more potent than morphine, has a rapid (1–2 minutes) onset time when delivered intravenously, and a short (approximately 1 hour) duration of effect after exposure is terminated.[59] The fentanyls act by binding to and stimulating the activity of opioid receptors in the brain and spinal column (they are thus called receptor "agonists"). In addition to providing relief from pain, opioids can cause sedation and, at high doses, unconsciousness. These are unwanted side-effects when opioids are used as analgesics, but are beneficial when they are used during anesthesia.[60] Opioid compounds, including fentanyl, were investigated by U.S. and U.K. military researchers as potential biochemical incapacitants during the early Cold War programs but were discarded because their lethal doses were at most 10–20-fold greater than their incapacitating doses.[61] Indeed, in addition to causing sedation and unconsciousness, the opioids can cause vomiting, hypotension, bradychardia (reduced heart rate), muscle rigidity (including of the chest wall muscles), and severe, life-threatening respiratory depression.[62]

During the 1970s, a series of compounds related to fentanyl were discovered that were both more potent and said to have a much higher safety margin.[63] One such compound, sufentanil, is 5–10 times more potent than fentanyl and is the most potent opioid currently in routine clinical use. A second compound, carfentanil, is perhaps the most potent analgesic currently known with roughly 10,000 times the potency of morphine.[64] It is currently used as a veterinary drug to sedate large animals but is not approved for use in people. Like fentanyl, both of these opioids are fast acting and have a relatively short duration of effect.

These and other new fentanyls were the focus of extensive U.S. military research, including inhalation studies in nonhuman primates, to develop new incapacitating biochemical weapons during the 1980s and early 1990s.[65] According to a recently released 1994 Army research proposal, at least some of the new fentanyls had "shown promise in previous studies" and were "excellent candidates for situations where a quick knock-down agent is needed." However, they also had drawbacks. Specifically, "earlier materials showed high safety ratios in rodents, but much lower ratios in primates because of respiratory depression."[66]

These results clearly contradict the high safety margins of 10,000 or more that were reported for these agents after the Moscow theater siege.[67] That is not surprising, as the reported safety margins were based on studies of *analgesia* in rats (not anesthesia, which typically requires tenfold higher doses).[68] The therapeutic index, or safety margin, for sufentanil is reported to be 25 times lower for anesthesia in dogs, 800 times lower in ferrets, and not much more than 1 in humans for whom it is typically used during anesthesia at doses of 1–2 μ/kg.[69] Carfentanil can cause severe respiratory depression and death in nonhuman primates at doses ranging from 2–14 μ/kg, only 7–50 times the ED50 for analgesia in rats.[70]

Delivery of fentanyl as an aerosol is as effective as delivery intravenously.[71] If sufentanil and carfentanil act similarly, they may thus be as, or even more, toxic than the nerve agent VX, which has an LD50 of approximately 15 μ/kg, when delivered via inhalation.[72] As already noted, aerosol delivery of carfentanil was tested by U.S. researchers, although the results are not publicly known.[73]

To solve the dose-response problem, Army researchers tried mixing a fentanyl-type agonist with a receptor antagonist in an attempt to prevent or reduce respiratory depression.[74] This strategy may have been inspired by similar, though unsuccessful, efforts conducted before the new agonists and antagonists were known.[75] It was probably also inspired by the identification of mixed agonist-antagonist compounds in the 1970s, which provided evidence for the existence of more than one type of opioid receptor and suggested that the analgesic/anesthetic effects of opioids might be separable from their other, undesired effects.[76] According to the 1994 proposal, this strategy "led to materials with dramatically improved safety ratios." The Army was simultaneously working on the development of a grenade for delivery of the selected agent[s].[77] The authors of the 1994 proposal reported that "the most advanced technology exists for the fentanyls than for any other chemical immobilizer candidates."[78]

Nonetheless, the program was cancelled in 1992. Importantly, this was not because the problem of developing a highly potent, deliverable and "safe" biochemical incapacitant was seen as intractable, but "because of multilateral treaty [i.e., CWC] language restricting the use of riot control agents to law enforcement only."[79] Indeed, a low level of research into "utilizing anaesthetic compounds in combination with antidotes to enhance the dose safety of chemical incapacitants" for both civilian law enforcement and "special military operations, and low intensity conflict" was sponsored by the National Institute of Justice until at least 1997.[80] This work was not far removed from the military.[81]

Yet, more than a decade later there is still no publicly available evidence that the United States has developed and fielded biochemical incapacitating weapons for either military or police use, other than scattered reports that U.S. special forces are equipped with "knock-out" agents.[82] How then should the work described above be assessed? On the one hand, it is clear that any fentanyl known at the time could not be used on its own as a biochemical incapacitant. As for the agonist-antagonist combination, in 2003 the National Research Council's Naval Studies Board reviewed the data and concluded, "the principal effect was still unconsciousness, which is unacceptable under most interpretations of the CWC."[83] And the assessment of a former lead researcher for the

U.S. military in 2002 was that, to his knowledge, no one had yet ''solved the safety-effectiveness problem.''[84]

On the other hand, when it stated that unconsciousness was not acceptable, and that ''the goal is to ensure a wide margin of safety between quieting and unconsciousness,'' the Naval Studies Board effectively moved the goal post, noting that previous efforts had ''been aimed at understanding margins of safety between loss of consciousness and death.''[85] Moreover, the Russian military did go on to develop and use incapacitating biochemical weapons based on the fentanyls, and some have claimed that these weapons were in fact a success.[86] In the end, as the Naval Studies Board report illustrates, the answer to this question depends on what level of lethality and permanent harm individual governments and the international community decides is ''acceptable.''

Meanwhile, science and technology have continued to advance. As the Society of Neuroscience noted in 1999, ''the past decade has delivered more advances than all previous years of neuroscience research combined.''[87] In the case of the fentanyls, since 1992, advances have included the discovery of the new ultra-fast (30-second onset time) and ultra-short-acting (5–10 minutes duration after exposure terminated) opioid remifentanil, which was of particular interest to Army researchers in 1994; the cloning of all four human opioid receptor genes; the characterization of the anatomical locations at which each receptor is expressed; and the generation of strains of mice in which each opioid receptor has been eliminated.[88] As a result, it is now known that one opioid receptor, the mu opioid receptor (MOR), is responsible for mediating both the analgesia/anesthesia and the respiratory depression caused by morphine, such that ''any agent acting at the MOR will invariably cause [potent] analgesia in combination with [variable] respiratory depression.''[89]

These findings may explain the U.S. failure to develop an incapacitating biochemical weapon based on synthetic opioids in the 1980s and early 1990s. However, they also illustrate the recent dramatic increase in mechanistic knowledge of brain function at the molecular level. Results such as these have suggested to some that it is now becoming possible to develop new agents that have enough specificity to more safely elicit more predictable responses, and thus, that the outlook for incapacitating biochemical weapons has changed dramatically.[90] Indeed, even as it proclaimed earlier efforts unsuccessful, the Naval Studies Board concluded that the Army had identified ''a number of promising technologies,'' and it recommended ''calmatives'' as one of six highest-priority areas for research and development, strongly suggesting that it felt the area remained ripe for success.[91]

Certainly, a number of governments seem to believe that the pursuit of incapacitating biochemical weapons remains a worthwhile endeavor. For instance, in 1999 the U.S. Army solicited proposals on behalf of the Joint Non-Lethal Weapons Directorate (JNLWD) for projects that would ''demonstrate the feasibility of a safe, reliable chemical immobilizing agent(s) for non-lethal (NL) applications in appropriate military missions and law enforcement situations,'' noting that ''recent pharmaceutical developments suggest that new approaches to safer chemical immobilizers with improved performance characteristics may be available.'' Immobilizing agents were said to include

anesthetics/analgesics, tranquilizers, hypnotics and neuromuscular blockers.[92] A contract was subsequently awarded for a ''Front End Analysis'' that would review existing data on ''three new agent combinations with potential for meeting user objectives,'' define scenarios of use and operational parameters, and conduct toxicological animal tests and correlate their results with those from previous studies.''[93]

In fiscal year 2001, JNLWD launched its own two-year Front End Analysis of ''all potential riot control agents, calmatives, etc. with an emphasis on technology advances in the past 10 years'' in order to ''identify feasible non-lethal chemical materials for further testing which have minimal side effects for immobilizing adversaries.''[94] Calmatives were defined as ''biotechnical agents which are sedatives or sleep-inducing drugs, [including] alfentanil, fentanyls, ketamine, and BZ.''[95] They were one of 12 key technologies identified for further development at a JNLWD-sponsored Joint Mission Area Analysis Conference in October 2000.[96] JNLWD is also funding the development of delivery systems designed to carry a variety of potential chemical payloads, including ''markers, taggants, incapacitants, malodorants [and] OC/RCA,'' including long-range mortars and airbursting grenades.[97] And follow-on work to that project sponsored by the National Institute of Justice is also occurring.[98] Clearly, the Naval Science Board was correct when it concluded in late 2002 that biochemical incapacitants were once again ''under study . . . after [a] lull in R&D for 10 years.''[99]

What about other nations? Although very little specific information is known, there can be little doubt that Russia is continuing its efforts.[100] One knowledgeable observer has commented that ''it would not be surprising if a number of countries were conducting more detailed and renewed research'' as a result of the Moscow theater siege.[101] The Czech military is conducting such research, including studies in nonhuman primates and human volunteers to examine the effects of different mixtures of various drugs in order to determine which combinations and doses result in ''reversible immobilization.'' The drugs included ketamine (a dissociative anesthetic), dexmedetomidine (an alpha-2 adrenergic receptor agonist), midazolam (a benzodiazepine), and fentanyl.[102] The North Atlantic Treaty Organization has listed ''chemical technologies [that] could act on the central nervous system by calmatives, dissociative agents, [and] equilibrium agents,'' and ''by convulsives'' as two of its 17 anti-personnel non-lethal ''technologies of interest.''[103] And there are indications that China may be interested as well. An article written by two Chinese analysts that appeared in the U.S. Army journal *Military Review* in July 2005 argued that the ''times call for new kinds of weapons, and modern biotechnology can contribute such weapons.'' ''War through the command of biotechnology,'' they said, will ultimately ''lead to success through ultramicro, non-lethal, and reversible effects. . . . Modern biotechnology offers an enormous potential military advantage.''[104]

Very recently it has been shown that the neural circuits involved in MOR-mediated analgesia and respiratory depression are anatomically distinct, and that those neurons responsible for respiratory depression also express a particular serotonin receptor (called the 5-HT4a receptor) that is not expressed by those neurons responsible for analgesia. By treating mice with a 5-HT4 receptor-specific agonist, it was possible to overcome fentanyl-induced respiratory depression without affecting fentanyl's analgesic effects. In

other words, the analgesic (and presumably anesthetic) and respiratory depression effects of opioids have finally been separated chemically.[105]

In light of advances such as these and of the continuing efforts of various states, is ''success'' in the development of a truly effective and safe incapacitating biochemical weapon now possible? In this author's opinion, such a weapon, while theoretically possible, is still many years away. In the case of the opioids, for example, there is much about the roles of 5-HT4 receptors that remains unknown, the side-effects of 5-HT4 agonists (none of which are specific for the 5-HT4a receptor alone) have not been well characterized, and it seems at least as likely as not that once again promise will not translate to reality.[106] Further, aside from analgesia in general, and the opioids in particular, there is little drug discovery activity in the field of anesthesia today, largely because there appears to be little need for new anesthetic drugs and hence little market demand.[107]

But that may not matter. All that is really needed to keep military efforts active is for advances in science and technology to *appear* to be sufficient to enable the development of agents having enough specificity to more safely elicit more predictable responses. In turn, all that is really needed for a biochemical incapacitant to be used and to gain traction is for it to be viewed as being ''good enough''—and what is considered ''good enough'' can change from one time and place to another. Thus, when one proponent poses the question ''human immobilization: is the experience in Moscow just the beginning?'' the answer may well be ''Yes.'' [108]

The Chemical and Biological Weapons Conventions

With the ongoing revolution in the life sciences, the boundary between chemistry and biology, and thus the distinction between chemical and biological weapons, is becoming increasingly blurred.[109] Rather than thinking of chemical and biological weapons threats as distinct, it is more useful to conceptualize them as lying along a continuous threat spectrum running from the classical chemical weapons on one end, through mid-spectrum agents including pharmaceutical chemicals, bioregulators and toxins, and on to traditional and genetically modified biological agents.[110] Incapacitating biochemical weapons are captured by the prohibitions of both the CWC and the BTWC, because they use chemicals that are either components of biological organisms or are biologically active analogs of such components. This should constrain their development.[111] The comments of the Naval Studies Board about the effects of the CWC on U.S. military research and development of calmative agents indicate that the CWC has indeed impeded work in this area.

The CWC and the BTWC each capture incapacitating biochemical weapons through a ''general purpose criterion'' that establishes a prohibition based on intent rather than on specific agents. The general purpose criteria are at the heart of each treaty—if attended to by the states parties, they enable each treaty to stay abreast of scientific and technological advances, protecting the peaceful uses of new technology while safeguarding against the hostile ones. However, both treaties also contain certain ambiguities, and efforts to

develop incapacitating biochemical weapons attempt to exploit loopholes created by these ambiguities.

The general purpose criterion of the BTWC is contained in Article I, which prohibits each state party from developing, producing, stockpiling, or otherwise acquiring or retaining "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*."[112] (Emphasis added.) The criterion has two ambiguities. The first concerns whether the convention does in fact capture synthetic analogues of naturally occurring biochemicals. It has been argued that the convention does capture these synthetic analogues because (1) "toxins" means toxic chemicals produced by living organisms and any useful incapacitating biochemical would thus be a toxin, and (2) the Final Declaration of the Second Review Conference stated that "toxins . . . of a microbial, animal or vegetable nature and their synthetically produced analogues are covered."[113]

Whether all biochemicals are also toxins is arguable, but virtually all biochemicals, whether naturally or synthetically produced, certainly are components of biological systems and are thus covered by the BTWC according to the most recent Final Declaration, that of the Fourth Review Conference.[114] More importantly, the statement that analogs of either toxins or components of biological organisms are covered has not been reaffirmed in final declarations subsequent to that of the Second Review Conference, even though states parties have offered language that would do so.[115]

Even if the BTWC does capture all synthetic biochemicals, there is a larger potential ambiguity in the treaty—the term "other peaceful purposes" has never been explicitly defined. Given that the toxin oleoresin capsicum (pepper spray) is widely used by police forces in nations around the world, there would seem to be an inherent limitation in its meaning. In practice, for any agent captured by both treaties, the extent of this limitation is likely to be determined by the CWC. Although the CWC explicitly states that it in no way limits or detracts from the BTWC, states parties are likely to look to the CWC for guidance as it is more recent, detailed, and precise, and it has a working regime with policies, procedures, and mechanisms for verification and enforcement.

However, the status of incapacitating biochemical weapons under the CWC is even more ambiguous. The general purpose criterion of the CWC is given in Article II.1(a), which states that chemical weapons include all "*toxic chemicals* and their precursors, *except where intended for purposes not prohibited*, as long as the types and quantities are consistent with such purposes."[116] (Emphasis added.) A toxic chemical is defined in Article II.2: "any chemical which through its chemical action on life processes can cause death, *temporary incapacitation* or permanent harm to humans or animals." (Emphasis added.) Toxicity is the defining characteristic of a chemical weapon—there is no distinction between lethal effects and non-lethal effects, or between death and incapacitation, in this definition. The CWC thus very clearly captures all biochemical incapacitants.

The ambiguity in the CWC arises from the one of the "purposes not prohibited." Article II.9(d) lists "law enforcement including domestic riot control purposes," as such a purpose not prohibited, but the meaning of "law enforcement" is nowhere defined in the convention. Moreover, while the definition of an RCA (riot control agent) is given in Article

II.7, as ''any chemical not listed in a schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure,'' no definition of a ''law enforcement agent'' is provided. Indeed, while states parties must declare the agents they hold for riot control purposes under Article III.1(e), there is no such declaration requirement for agents held for other ''law enforcement purposes.'' Thus, not only is there ambiguity about the meaning of the term *law enforcement*, the difference between RCAs and law enforcement agents also remains ambiguous and subject to debate.[117]

The United States has additionally argued that Article I.5, which obligates states parties ''not to use riot control agents as a method of warfare,'' indicates that RCAs are in fact not toxic chemicals at all and are wholly exempt from the general purpose criterion of the CWC. Virtually all other nations and observers disagree with this position and more correctly argue that the definition of an RCA in Article II.7 as a chemical which causes ''disabling physical effects'' clearly means that RCAs are toxic chemicals subject to the general purpose criterion.[118]

In light of these ambiguities and debates, it is not surprising that a November 1997 preliminary opinion issued by the Office of the U.S. Navy Judge Advocate General (JAG) in response to a request from JNLWD suggested two ways in which incapacitating biochemical weapons might be consistent with the international legal obligations of the United States.[119] First, it noted that ''convulsives and calmative agents may . . . be RCAs.''[120] This conclusion is significant because the JAG also concluded that ''RCAs, while they may well contain toxic chemicals, are subject [only] to Article I(5)s limitation on the use of RCAs as a 'method of warfare,' and are not subject to Article II's proscriptions.'' Second, the JAG argued that if calmatives and gastrointestinal convulsives are found to ''rely on their toxic properties to have a physiological effect on humans . . . [and] are *not* considered RCAs, in order to avoid being classified as a prohibited chemical weapon, they would have to be used for the article II(9)(d) 'purpose not prohibited,' the law enforcement purpose . . . *the limits of this 'purposes not prohibited' are not clear and will be determined be the practice of states.*''[121] (Emphasis added.) In effect, according to a commentary published in the *Naval War College Review*, ''calmatives and gastrointestinal convulsives, if classified as riot control agents, can be acceptable.'' If not so classified, it could be argued, says the author, that the ''use of chemical-based antipersonnel NLWs [non-lethal weapons] . . . in operations other than war'' would still be allowable.[122]

In practice, it is difficult to see how efforts to develop incapacitating biochemical weapons could proceed very far under the purported RCA exemption alone. First, although most states do not accept the U.S. position that RCAs are not toxic chemicals, all nations including the United States do agree that all toxic chemicals fall squarely under the general purpose criterion of the CWC. To claim otherwise would be to attack the heart of the convention, and no state is likely to take such step lightly. If the disagreement over the status of RCAs has already severely constrained their use by military forces, as it apparently has, then it is difficult to see any agent more toxic than today's RCAs being used under the RCA ''exemption.''[123] This probably explains why the Committee of the Naval Studies Board concluded that unconsciousness ''is unacceptable under most interpretations of the CWC.''[124] Second, and probably even more relevant, any biochemical incapacitating agent

held as an RCA would have to be declared under Article III.1(e), most likely before it is ever used, thereby defeating the purpose of excluding agents held for ''law enforcement purposes'' from its declaration requirement.[125]

Thus, the central issue of debate will likely remain the scope of the law enforcement purpose not prohibited and the limits on the types and quantities of toxic chemicals whose use would be consistent with this purpose. As the *CBW Convention Bulletin* editors asked, ''what is 'law enforcement?' Nowhere in the Convention is it defined. Whose law? What law? Enforcement where? By whom?'' They add, ''if states parties come to act on differing interpretations of the ambiguity, even if they do so in good faith, the stability of the treaty regime will suffer, perhaps catastrophically.''[126]

At least four perspectives on the meaning of ''law enforcement'' and its implications for the types and quantities of agents that may be used are apparent. The first, represented by the JAG opinion, holds that the meaning of law enforcement will be determined solely by state practice. This would seem to be the very approach that the *CBW Convention Bulletin* editors have cautioned against. It is also incorrect, as it ignores some basic principles of treaty interpretation—namely, that a treaty must be interpreted ''in good faith in accordance with the ordinary meaning to be given to the terms of the treaty in their context and in the light of its object and purpose'' and taking into account any relevant rules of international law.[127]

The second perspective is offered by Ambassador Adolf von Wagner, chair for the final negotiations of the CWC, who argues based on the negotiating history of the CWC that ''law enforcement'' is essentially limited to riot control and capital punishment. Thus, only agents that meet the definition of an RCA in Article II.7 are of a type and quantity consistent with the law enforcement exemption.[128]

Such a limited interpretation of ''law enforcement'' seems difficult to sustain given the wording of Article II.9(d), and indeed, the third perspective, offered by Abram Chayes and Matthew Meselson, allows for law enforcement purposes beyond riot control and capital punishment. These would include ''actions taken within the scope of a nation's 'jurisdiction to enforce' its national law,'' and law enforcement actions taken under the authority of the United Nations (such as peacekeeping; these actions are not the same as the enforcement of international law), as long as such actions do not constitute a ''method of warfare.'' [129] Chayes and Meselson propose that only agents meeting the definition of RCAs in Article II.7 should be permitted for these law enforcement purposes, because only toxic chemicals with effects that do not endure beyond a short time would be of a type consistent with law enforcement purposes and the purposes of the CWC.

A fourth perspective is offered by David Fidler, who shares a similar, though not identical, view of the meaning of ''law enforcement'' with Chayes and Meselson. Where he differs is in his assessment that the ordinary meaning of the terms in Article II.1(a) do not limit the types of agents that can be used for domestic law enforcement purposes to RCAs. However, applying international humanitarian law and human rights law as relevant rules of international law applicable to CWC states parties, Fidler argues that the more difficult it is to control the dosage or exposure conditions, the more restrictive the ''types and quantities'' limitation does become. Thus, incapacitating biochemicals could be legally used only in ''extreme law enforcement situations,'' which he defines as those in which

"government authorities confront the need to resort to potentially lethal force to resolve urgent, life-threatening situations because less violent and dangerous means of resolving the problems have failed."[130] For law enforcement-type activities undertaken by military forces extraterritorially and permitted by international law (e.g., controlling rioting prisoners of war or civilian crowd control in occupied territory), only riot control agents could be used.

Fidler's conclusions are unlikely to satisfy either proponents or opponents of incapacitating biochemical weapons. On the one hand, his interpretation makes it more difficult to pass through the loophole created by Article II.9(d) without fundamentally undermining the CWC. On the other hand, his interpretation does not close the loophole off altogether, for it may allow states to continue to take advantage of ambiguity in the meaning of "extreme law enforcement situations" and the lack of definition of "law enforcement chemicals" in order to develop a potentially wide range of new toxic chemicals without having to declare the identities of these chemicals.[131]

Absent an amendment to the convention, the best that can be done to resolve this debate is for states parties to arrive at a common understanding of the meaning of the term "law enforcement," and of the types and quantities of agents that would be permitted for this purpose. Four alternative legal interpretations have been advanced. None unambiguously resolves the question of where the line between permitted and prohibited agents can be drawn. Among the interpretations of opponents, von Wagner's provides the least leeway to those who would develop and use such agents while Fidler's, because it takes the broadest view of the types and quantities of agents that would be consistent with permitted purposes, provides the most. However, all leave the CWC, and indeed international humanitarian law and human rights law more generally, more or less susceptible to technological change.[132] Thus, it is reasonable to ask whether the disincentives the opponents' interpretations create for the pursuit of incapacitating biochemical weapons will nonetheless be more than outweighed by the apparent attractions of scientific and technological advancement.

Implications

Incapacitating biochemical weapons, *if* they could rapidly and completely incapacitate individuals without causing death or permanent disability, might potentially be useful in a certain limited range of situations such as hostage rescue. But as the Moscow event illustrates, the "promise" of incapacitating biochemical weapons remains illusory. It is likely to remain so for the foreseeable future. The dose-response problem is extremely complex, and there are certainly no agents in existence today that can be said to have solved it. Even if a pharmacologically safe agent could ultimately be found, its utility could be dramatically reduced by the use of simple countermeasures, such as masking, that would protect adversaries while leaving noncombatants exposed.[133] Meanwhile, a certain number of those who are unprotected may collapse in ways that obstruct their airway, or be so disabled that they are more susceptible to being trampled or crushed during rioting, or be otherwise prevented from escaping dangerous situations, or not be recognized during the "fog of war" as "incapacitated" by an opposing war fighter who

thus resorts to the use of lethal force.[134] All in all, even if they could be developed, the benefits of incapacitating agents would likely be very limited.[135]

Moreover, incapacitating biochemical weapons should not be pursued simply because one can imagine scenarios in which their use might be beneficial and because the state of science and technology suggests that it might be possible to develop them at some point in the future. A more careful weighing of the potential advantages and disadvantages of continuing to pursue such weapons is required.

In 2002, JNLWD awarded two contracts for work to develop "smart" bullets and a "rocket assisted safe projectile" that would deliver both blunt trauma and "secondary payloads . . . includ[ing] chemical agents that can further incapacitate or maintain the incapacitation of the targeted individual." The developer noted that once "this new technology is widely presented, demonstrated and accepted by police forces, security personnel and security forces, a vast ammunition market will open up. This provides for great commercial opportunity, which can later extend to the entire ammunition world market."[136] Regardless of whether this particular technology succeeds or fails, whether it is bullets, mortars, aerosol generators, or other delivery and dissemination devices, if biochemical incapacitants become weapons in police or military arsenals, a global market would emerge.

Many damaging consequences of such a global market in incapacitating biochemical weapons can be envisioned. For instance, institutions and communities dependent on the development and use of incapacitating biochemical weapons would grow in size and influence and would likely work against efforts to control their development, trade, and use. In addition, as already noted, what is considered "good enough" in a biochemical incapacitant would vary from one country to the next, and we can be sure that the countries with the most demanding requirements for low lethality rates would not be the only ones participating in an incapacitating biochemical weapons market, either as buyers or as sellers. Moreover, a market in incapacitating biochemical weapons would likely be driven at least as much by the effectiveness of the weapons in causing incapacitation as by considerations of their safety. Although national export controls, the Australia Group, and other mechanisms might provide a means for controlling the proliferation of incapacitating biochemical weapons, as with controlling the trade in small arms in general, global regulation would likely be extremely difficult and meet with only limited success, and black markets would very likely emerge. Information controls would be even more difficult to institute.

Meanwhile, militaries and police forces would very likely not be the only users.[137] It is likely that criminals, terrorists, despotic regimes, paramilitary organizations, and armed factions in failing and failed states could all find utility in incapacitating biochemical weapons and that many would not feel as constrained by international law and concerns about lethality as nominally more legitimate users will.[138] As Mark Wheelis has pointed out, the ideal targets for attacks with biochemical incapacitants are people who cannot protect themselves—that is, ordinary civilians.[139] Criminals could thus find them useful for aiding in burglary, kidnapping, incapacitation of security guards, and other activities. Terrorists could find them useful for such things as facilitating hostage taking and attacks on critical infrastructures, such as chemical manufacturing facilities, for preventing flight

and thereby increase death tolls resulting from attacks with explosives, or for serving as force multipliers in surprise attacks on military and police forces.[140] While most despotic regimes and failing states probably would not have the resources to develop incapacitating biochemical weapons themselves, all probably would find them useful for enhancing their capabilities for domestic repression. Such weapons could, for example, facilitate more robust crowd control and easier capture of opposition leadership.[141] Paramilitary organizations and armed factions in civil wars could likewise find incapacitating biochemical weapons to be effective as force enhancers and force multipliers in attacks on each other, on government forces, and as happens all too often, on innocent civilians. Thus, against the limited benefits outlined earlier, numerous potential harmful consequences can be envisioned should incapacitating biochemical weapons become available.

There are also dangers inherent in the development and use of incapacitating biochemical weapons by regular military armed forces. One such danger arises from the temptation that would arise, once incapacitating biochemical weapons are introduced into a theater of conflict, to find new uses for them that go beyond those originally envisioned. Just such an event occurred with the use of tear gas by the U.S. military in Vietnam. Ostensibly introduced for crowd control and for use in special circumstances to save civilian lives, tear gas soon came to be used for a range of military purposes, including the enhancement of lethal force. Indeed, a postwar analysis could find no case in which tear gas had been used as originally stated, concluding that ''the reduction in casualties has not been in enemy or noncombatant personnel but, rather, friendly troops, as a result of using CS [tear gas] to make other fires more effective.''[142]

Biochemical incapacitants were used to enhance lethal force in the Moscow theater crisis as well: The Chechen women knocked out by the Russian gas were not disarmed while incapacitated and taken into custody; they were shot dead.[143] Another danger arises from the risk that a ''non-lethal'' incapacitating biochemical weapon used by one party to a conflict will be perceived by another party as being a lethal chemical weapon, thus triggering a retaliation/escalation cycle. Whether pursued under the law enforcement exemption or in the guise of RCAs, the development and stockpiling of incapacitating biochemical weapons would run the risk of defeating one of the fundamental purposes of the BTWC and the CWC—preventing states from entering conflicts of any kind with a stockpile of weapons whose use is proscribed but could nevertheless expand rapidly under the doctrine of military necessity.

Another danger arises from what is perhaps the most serious problem of all: the likelihood that the momentum associated with the growth of incapacitating biochemical weapons programs and the institutional interests that surround them will, over time, lead to an ever-broader and more powerful array of biological and chemical weapons. It is reasonable to predict, for instance, that the inevitable development of countermeasures will generate incentives for the corresponding development of ''new and improved'' biochemical agents. Because ''non-lethal'' biochemical weapons will not be entirely non-lethal, there will also be arguments and uncertainty over where to draw the fuzzy line between permitted and prohibited weapons—half a percent lethality, one percent, five? As already noted, the answer would likely differ from one place and time to another, regulation will be nearly impossible, and institutional pressures to

develop and use such weapons will tend to promote ''good enough''-type thinking. Moreover, as a Council on Foreign Relations Task Force recently noted, ''to press for an amendment to the CWC or even to assert a right to use RCAs as a method of warfare . . . would also free others to openly and legitimately conduct focused governmental R&D that could more readily yield advanced lethal agents than improved non-lethal capabilities.''[144] Indeed, it could reignite more general desires for chemical weapons in some countries.[145]

It also seems likely that, if an exemption is carved out of the CWC for biochemical incapacitants, there might soon be pressure to carve a similar exemption out of the BTWC, perhaps via the ''peaceful purposes'' clause of Article I (since the BTWC does not contain an exception for law enforcement purposes) so that biological ''non-lethal'' weapons may be developed. After all, non-lethal is non-lethal, whether it is a pharmaceutical drug or the bacterium that causes Q fever, and it is not hard to imagine scenarios in which a bacteria or virus might provide more effective and versatile delivery of some bioregulators than a chemical munition.[146] Indeed, if significant efforts to develop weapons based on neuroregulatory compounds get under way, it probably would not be long before they expanded to include ''non-lethal'' weapons based on other types of bioregulatory molecules. Such efforts have already been seen in the past.[147] At the most extreme, we confront the possibility that efforts to develop incapacitating biochemical weapons will turn out to be but the leading edge of what Dando and Wheelis call the wholesale ''militarization of biology.''

By breaching the norm against biological and chemical weapons, the pursuit of incapacitating biochemical weapons may thus be the most likely first step in the larger exploitation of pharmacology and biotechnology for hostile purposes.[148] In this age of terrorism, it would be a step most likely driven by states, for only states are likely to have the combination of motivation and resources needed to drive the development of truly novel weapons in any major way, and only states can legitimize their use. What is the likelihood of meaningful control once some biological and chemical weapons are deemed ''acceptable'' based on arbitrary and elusive criteria for lethality?

Solutions

Three years ago, the editors of the *CBW Convention Bulletin* offered their opinion that ''it is hard to think of any issue having as much potential for jeopardizing the long-term future of the Chemical and Biological Weapons Conventions as does the interest in creating special exemptions for so-called 'non-lethal' chemical weapons.''[149] Indeed, a partial ban that would allow some biochemicals but not others to be used for hostile military purposes would be fraught with ambiguity and would strike at the heart of the CWC, and by extension, the BTWC. The point is not that international treaties are somehow sacrosanct. Rather, as I have tried to illustrate above, the point is that if efforts to develop incapacitating biochemical weapons continue to gather steam, the *protections that the treaties provide* may begin to erode. Should such weapons come to be used, especially by a major state and without much objection, the protections could ultimately be eliminated altogether.

Unfortunately, efforts to develop incapacitating biochemical weapons may well gather steam as more nations become intrigued by them and, observing the efforts of Russia and the United States, become convinced not only that effective and acceptably "non-lethal" incapacitating agents can be found, but that their use will be legitimized. While the full ramifications will be long in coming and are impossible to predict with complete accuracy, we face an erosion of the norms and goals embodied in the treaty regimes. What then should we do?

First, we can recognize the wisdom of upholding the clear and simple dictum "no poisons in war." The importance of averting the hostile exploitation of biotechnology, with all of the negative consequences that could follow, outweighs whatever marginal benefits might be gained from the use, or even the continued pursuit of research and development, of incapacitating biochemical weapons. To quote again the Council on Foreign Relations Task Force,

> [t]here is much merit to . . . "no gas" (and no poison either), as expressed in the CWC and the BWC. Any other position opens a Pandora's box of national research and development of new agents, which can be far more toxic and more effective against . . . [friendly] forces than the existing agents. It may also lead to the legitimization of such weapons. . . . Expanding and strengthening the . . . commitment to the prohibitions on the use of chemicals and biological and toxic agents in warfare is essential if we are not to see such weapons developed by states and used by them or others to devastating effect.[150]

Second, we should act before incapacitating biochemical weapons make a heavy mark on the world. We can already anticipate that advances in science and technology may ultimately lead to the development and use of incapacitating or other biochemical weapons, even if they do not work as well as expected. Indeed, we have already had a demonstration of this in Russia, and there is clear evidence of growing state interest in exploring such weapons. By anticipating where technology is leading, we can act to channel it toward peaceful uses and divert it away from hostile ones before it is too late to put it back in the box.

The BTWC, and especially the CWC, provide frameworks and mechanisms for action, if the states parties decide to use them. Together with the 1925 Geneva Protocol, these treaties effectively outlaw the development, production, stockpiling, or use of the full spectrum of biological and chemical weapons, whether lethal or incapacitating. Steps can be taken to strengthen the treaties so that they do not fall behind current advances in science and technology.

The Sixth Review Conference of the BTWC in November 2006 offers an opportunity to begin discussions of this matter. As a first step toward reigning in the development of incapacitating biochemical weapons, states parties should use the final declaration of the review conference to clarify that the convention covers all biological agents or toxins, whether naturally or artificially created or altered, as well as their components *and synthetically produced analogs* of these agents, toxins or components.[151] Such a statement would have the effect of unambiguously bringing all incapacitating biochemical weapons, and indeed, all biochemical weapons, under the purview of the BTWC.

Such a statement would also help lay the groundwork for important action that states parties should take at the 2008 CWC Review Conference. It has already been noted that it is important for states parties to come to a common understanding of the meaning of the term ''law enforcement'' in Article II.9(d) and of the limits on the types and quantities of toxic chemicals whose use would be consistent with this purpose. The states parties should do so at the 2008 Review Conference, bringing in considerations of international humanitarian law and human rights law in order to narrow the ambiguities as much as possible before state practice establishes new norms that run counter to those embodied in the convention. One possibility would be to declare that law enforcement refers only to domestic law enforcement and to law enforcement actions taken under the authority of the United Nations. As part of any such action, states parties should also make it clear that any use of incapacitating biochemical weapons or RCAs in situations where combatants and noncombatants are mixed is prohibited by the CWC.

The problem associated with Article III.1(e), that it does not require states parties to declare the agents they hold for ''law enforcement purposes,'' cannot be fixed without amending the CWC. Combined with a clarification of the meaning of ''law enforcement,'' that is probably the best long-term solution to the problem. But it would be a daunting endeavor, and attempts made too soon could result in weakening rather than strengthening the convention. Thus, efforts should be placed on building momentum and consensus toward such an amendment in the future. The steps already outlined would help in these efforts. Meanwhile, as an interim measure, states parties could agree and affirm that the only agents that may be used for law enforcement purposes under the convention are those that meet the Article II.7 definition of a ''riot control agent.''

Collectively, these efforts to strengthen the treaty regime would not only help demonstrate that states parties are committed to foregoing the pursuit of incapacitating biochemical weapons, with all the consequences such pursuit portends, they would also help prepare the treaty regime for scientific and technical advances yet to come. However, they may not eliminate all military research on and development of incapacitating biochemical weapons. Since it would be difficult to distinguish legal development of new RCAs from prohibited development of incapacitating biochemical weapons, there may be value in states further coming to a consensus that the term ''riot control agent'' encompass only those RCAs already in common police use around the world.[152] However, it seems unlikely that states would readily forego the chance to develop new ''riot control agents'' for domestic law enforcement purposes, and there is a long history of military and law enforcement efforts reinforcing each other.[153] Moreover, restricting research and development efforts to the law enforcement sector would not solve the problem that stockpiles of biochemical incapacitants developed for law enforcement purposes could be easily diverted to military purposes should a need be perceived.[154]

Nonetheless, if the actions recommended above with regard to the BTWC and the CWC are taken, the issue of law enforcement development and use of incapacitating biochemical weapons and potential spillover to the military sector may not be as big a problem as it might seem. The bar for ''acceptable non-lethality'' will be much higher for domestic law enforcement than for military applications, and the above actions would still significantly constrain military research and development activities. This issue is worth

more exploration, and as science and technology advance, there may be value in an international convention prohibiting and criminalizing the nonconsensual manipulation of human physiology.[155]

Actions taken to strengthen the treaties will not be effective unless they are complemented by other actions taken outside of, but in concert with, the formal treaty regime. States should take steps to greatly increase the transparency and strengthen the oversight of relevant areas of research and development, most particularly of military and law enforcement activities in the life sciences and the area of non-lethal weapons. The goal would be for states to demonstrate to each other that they are not pursuing the development of incapacitating biochemical agents and other weapons based on bioregulatory molecules. Of course, improved transparency measures should also be brought into the treaty regime itself.

Here scientists themselves can play a critical role in helping to design and advocate for a realistic, appropriate, and effective system of national and international regulation of life sciences research and military development.[156] More generally, it is essential that there be increased dialogue about incapacitating biochemical weapons between the scientific, medical, legal, and policy communities, and those concerned with questions of human rights and humanitarian law, so that potential problems and effective solutions can be identified, developed, and implemented. The science and technology required for the development of incapacitating biochemical weapons, and of other weapons that target specific human (and animal and plant) physiological mechanisms and systems, will come from academia, medicine, and industry. Academia is responsible for developing most of the basic knowledge that underlies drug discovery and development. The biotechnology and pharmaceutical industries are most responsible for identifying and developing new therapeutic compounds, and industry has historically been the major source of compounds for military researchers attempting to develop incapacitating biochemical weapons. Medical researchers are most responsible for gathering clinical data critical for the successful development of such weapons. If a useful biochemical incapacitant is discovered, it will most likely come from one or more of these sectors rather than being discovered first in a military lab.[157] Each of these sectors thus has a particular responsibility for the future. Biologists, chemists, toxicologists, pharmacologists, and doctors can and should bring their special expertise to bear on efforts to strengthen both the treaty regimes and, even more, the norms enshrined within them.

The world may be witnessing a ''renaissance'' of military research into biochemical incapacitants.[158] Until the states parties to the CWC and BTWC clarify the ambiguities in these conventions, most particularly those surrounding the ''law enforcement exemption'' in Article II.9(d) of the CWC, and until practices and procedures designed to prevent application of the life sciences for hostile purposes are put into place, the development of incapacitating biochemical weapons is likely to continue, albeit under a cloud of military, legal, political, and scientific uncertainty. It will take a concerted effort, from the local to the national to the international levels, to ensure that biotechnology does not become the next military technology, with incapacitating biochemical weapons leading the way.

NOTES

1. Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, Board on Global Medicine, Institute of Medicine and National Research Council, *Globalization, Biosecurity and the Future of the Life Sciences* (Washington, DC: National Academies Press, 2006), p. 5. See also pp. 178–181 and references at notes 141, 144, and 150 on p. 208 of this report.
2. Elliot Kagan, "Bioregulators as Instruments of Terror," *Clinics in Laboratory Medicine* 21 (Sept. 2001), pp. 607–618.
3. [3] U.S. Army, *Potential Military Chemical/Biological Agents and Compounds*, Field Manual 3-11.9, Jan. 10, 2005, p. I–7, <www.fas.org/irp/doddir/army/fm3-11-9.pdf>.
4. Sweden stated that by the year 2000, the "scientific and technological achievements . . . may make it possible to produce products of human origin as B-weapons. Such products could be hormones or transmitter substances which to take effect are needed in extremely small quantities." Background Document on New Scientific and Technological Development 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.II/4, Geneva, Sept.r 8–26, 1986, p. 3, <www.opbw.org>. The United States discussing peptides, stated that "[t]heir range of activity covers the entire living system, from mental processes . . . to many aspects of health such as control of mood, consciousness, temperature control, sleep or emotions, exerting regulatory effects on the body. Even a small imbalance in these natural substances could have serious consequences, inducing fear, fatigue, depression or even causing death." BWC/CONF.II/4, Add.2, p. 3, <www.opbw.org>.
5. National Academies of Science, Press Release, Jan. 31, 2006, "Global Effort Needed to Anticipate and Prevent Potential Misuse of Advances in Life Science," <www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11567>.
6. Kurt Kleiner, "US 'unaware' of emerging bioterror threats," New Scientist.com News Service, Jan. 31, 2006, <www.newscientist.com/article.ns?id=dn8656>; Emily Singer, "Could Terrorists Hijack Your Brain?" *Technology Review* (Feb. 1, 2006), <www.technologyreview.com/read_article.aspx?id=16221&ch=biotech>.
7. Executive Office of the President, *Biodefense for the 21st Century*, Homeland Security Presidential Directive 10/National Security Presidential Directive 33, Washington, DC, April 28, 2004, <www.fas.org/irp/offdocs/nspd/hspd-10.html>.
8. Christopher J. Davis, "Nuclear Blindness: An Overview of the Biological Weapons Programs of the Former Soviet Union and Iraq," *Emerging Infectious Diseases* 5 (July–Aug. 1999), pp. 509–512.
9. Committee for an Assessment of Non-Lethal Weapons Science and Technology, Naval Studies Board, National Research Council, *An Assessment of Non-Lethal Weapons Science and Technology* (Washington, DC: National Academies Press, 2003), p. 4.
10. Paul M. Wax, Charles E. Becker, and Steven C. Curry, "Unexpected 'Gas' Casualties in Moscow: A Medical Toxicology Perspective," *Annals of Emergency Medicine* 41 (Aug. 2003) pp. 700–705.

11. See Neil Davison and Nick Lewer, *Bradford Non-Lethal Weapons Research Project Research Report No. 5,* (Bradford, UK: Centre for Conflict Resolution, University of Bradford, May 2004), p. 39, <www.bradford.ac.uk/acad/nlw/research_reports/docs/BNLWRPResearchReportNo5_May04.pdf>.
12. Donald Voet, *Biochemistry,* 3rd ed. (New York: Wiley, 2004), p. 13.
13. Eva S. Istvan and Johann Deisenhofer, ''Structural Mechanism for Statin Inhibition of HMG-CoA Reductase,'' *Science* 292 (May 11, 2001), pp. 1160–1164.
14. Bruce D. Roth, ''The Discovery and Development of Atorvastatin, a Potent Novel Hypolipidemic Agent,'' *Progress in Medicinal Chemistry* 40 (2002), pp. 1–22. For sales data see IMS Health, ''Leading Products by Global Sales, 2005,'' at <www.imshealth.com/ims/portal/front/articleC/0,2777,6599_77478579_77479663,00.html>.
15. Field Manual 3-11.9, p. I–6.
16. James S. Ketchum and Frederick R. Sidell, ''Incapacitating Agents,'' in Frederick R. Sidell, Ernest T. Takafugi, and David R. Franz, eds., *Medical Aspects of Chemical and Biological Warfare*, TMM series, Part I (Washington, DC: TMM Publications, 1997), p. 288.
17. Field Manual 3-11.9, p. I–6.
18. U.S. Army Field Manual 8-285, *Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries*, (Dec. 22, 1995), P. 3–1, available at <www.globalsecurity.org/wmd/library/policy/army/fm/8-285/index.html>.
19. Ibid.
20. See information for Remifentanil at ''Opioids'' at <www.anaesthetist.com/anaes/drugs/opioids.htm>.
21. Ketchum and Sidell, ''Incapacitating Agents,'' p. 291.
22. Ibid. For TL 2636 see Caitriona McLeish, ''The Governance of Dual-Use Technologies in Chemical Warfare,'' M.Sc. dissertation, University of Sussex, 1997, pp. 55–65.
23. Joan M. Lakoski, W. Bosseau Murray, and John M. Kenny, *The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique* (University Park, PA: Applied Research Laboratory, Pennsylvania State University, 2000), p. 48.
24. Martin Furmanski, ''Military Interest in Low-lethality Biochemical Agents: The Historical Interaction of Advocates, Experts, Pragmatists and Politicians,'' (June 2005), p. 19, <www.armscontrolcenter.org/cbw/symposium/papers/pdf/20050601_symposium_military_interest.pdf>.
25. Furmanski, ''Military Interest;'' See also: Malcolm Dando, ''The UK's Search for an Incapacitating ('Non-Lethal') Chemical Agent in the 1960s,'' *Bradford Science and Technology Report No. 6* (Bradford, UK: Dept. of Peace Studies, University of Bradford, Jan. 2006); <www.brad.ac.uk/acad/nlw/research_reports/docs/BDRC_ST_Report_No_6.pdf>; Stockholm International Peace Research Institute, *The Problem of Chemical and Biological Warfare* (New York: Humanities Press, 1971), Vol. 2, pp. 124, 154, 265, 273, and Vol. 5, pp. 47–49, 127–128; J. P Perry Robinson, ''Disabling chemical weapons: some technical and historical aspects,'' paper delivered to the Second Workshop of the Pugwash Study Group on Implementation of the CBW Conventions, Den Haag/Noordwijk, Netherlands, May 27–29, 1994.
26. U.S. Dept. of Defense, *Directive 3000.3 Policy for Non-Lethal Weapons* (July 9, 1996), p. 2.

27. Lt. Col. Randy Copeland, ''Joint Non-Lethal Weapons Program,'' (June 2002), slide 2, <www.dtic.mil/ndia/2002mines/copeland.pdf>. U.S. Marine Corps, ''Joint Concept for Non-Lethal Weapons'' (Jan. 5, 1988), available at <www.fas.org/man/dod-101/sys/land/docs/NONLETH.HTM>.
28. Naval Studies Board, *An Assessment of Non-Lethal Weapons*, pp. 12–15, 20, 26, and 27. See also US/UK Non-Lethal Weapons (NLW)/Urban Operations Executive Seminar Assessment Report (Nov. 30, 2000), p. 28, at <www.sunshine-project.org/incapacitants/jnlwdpdf/usukassess.pdf>; U.S. Marine Corps, ''Joint Concept''; Nick Lewer, ''Introduction'' in Nick Lewer, ed., *The Future of Non-Lethal Weapons: Technologies, Operations, Ethics and Law* (London/Portland, OR: Frank Cass, 2002), p. 1; Brian Rappert, *Non-Lethal Weapons as Legitimizing Forces?* (London/Portland, OR: Frank Cass, 2003), pp. 63–65, 228–234.
29. U.S. Marine Corps, ''Joint Concept.'' For in depth information about, and arguments for and against, ''non-lethal'' weapons more generally, see John B. Alexander, *Future War: Non-Lethal Weapons in 21st Century Warfare* (New York: St. Martin's Press, 1999); Graham T. Allison, Paul X. Kelley, and Richard L. Garwin, *Non-lethal Weapons and Capabilities*, Report of an Independent Task Force sponsored by the Council on Foreign Relations (New York: Council on Foreign Relations Press, 2004); Malcolm Dando, *A New Form of Warfare: The Rise of Non-Lethal Weapons* (London: Brassey's, 1996); Lewer, *The Future of Non-Lethal Weapons*; Douglas C. Lovelace and Steven Metz, *Nonlethality and American Land Power* (Carlisle, PA: Strategic Studies Institute, U.S. Army War College, 1998); Rappert, *Non-Lethal Weapons*.
30. Ketchum and Sidell, ''Incapacitating Agents,'' p. 295. Compare to value for VX in Table 30-2 in David R. Franz, ''Defense Against Toxin Weapons,'' in Sidell,. Takafugi, and Franz, *Medical Aspects of Chemical and Biological Warfare*, p. 607.
31. Malcolm Dando and Martin Furmanski, ''Midspectrum Incapacitant Programs,'' in Mark Wheelis, Lajos Rozsa, and Malcolm Dando, eds., *Deadly Cultures: Biological Weapons Since 1945* (Cambridge, MA: Harvard University Press, 2006), pp. 246–249.
32. Ibid.
33. Ibid, p. 243.
34. Ketchum and Sidell, ''Incapacitating Agents,'' p. 295.
35. Jean Pascal Zanders, ''Assessing the Risk of Chemical and Biological Weapons Proliferation to Terrorists,'' *Nonproliferation Review* 6 (Fall 1999), pp. 23–25.
36. Furmanski, ''Military Interest,'' p. 19.
37. John M. Kenny, ''Human Effects Advisory Panel Program,'' presentation at the Non-Lethal Defense IV Conference, sponsored by the National Defense Industrial Association, March 20–22, 2000, slide 23, <www.dtic.mil/ndia/nld4/kenny.pdf>.
38. Lynn Klotz, Martin Furmanski, and Mark Wheelis, ''Beware the Siren's Song: Why 'Non-Lethal' *Incapacitating Chemical Agents are Lethal*,'' Scientists Working Group on Biological and Chemical Weapons, March 2003, <www.armscontrolcenter.org/cbw/wg/wg/wg_2003_sirensong_non-lethal_chemical_agents.pdf>.
39. V.L. Klochikhin, A.A. Lushnikov, V.A. Zagaynov, A.V. Putilov, V.V. Selivanov, and M.A. Zatevakhin, ''Principles of Modeling of the Scenario of Calmative Application in a Building

With Deterred Hostages,'' paper presented to the 3rd European Symposium on Non-Lethal Weapons, Stadthalle, Germany, May 10–12, 2005.

40. L.E. Mather, ''Clinical pharmacokinetics of fentanyl and its newer derivatives,'' *Clinical Pharmacokinetics* 8 (Sept.–Oct. 1983), pp. 422–46; Center for Nonproliferation Studies, Chemical and Biological Weapons Nonproliferation Program, ''The Moscow Theater Hostage Crisis: Incapacitants and Chemical Warfare,'' (Nov. 4, 2002) <http://cns.miis.edu/pubs/week/02110b.htm>.
41. Wax et al., ''Unexpected 'Gas' Casualties.''
42. Tufts Center for the Study of Drug Development, ''Outlook 2005,'' p. 1, <http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2005.pdf>.
43. On the use of anesthesia in clinical settings, see, for example, David A.E. Shephard, ''The changing pattern of anesthesia, 1954–004: A review based on the content of the *Canadian Journal of Anesthesia* in its first half-century,'' *Canadian Journal of Anesthesia* 52 (March 2005), pp. 238–248.
44. See, for example, Roche Pharmaceuticals, ''Versed (midazolam HCl) Injection,'' package insert, <www.fda.gov/ohrms/dockets/dailys/01/Mar01/032101/cp00001_exhibit_02.pdf>; Bedford Laboratories, ''Propofol Injectable Emulsion 1%,'' package insert, <http://66.70.89.95/information/propofol.pdf>.
45. Alan S. Nies, ''Principles of Therapeutics,'' in Joel G. Hardman and Lee E. Limbird, eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed. (New York: McGraw-Hill Professional, 2001), p. 51.
46. See, for example, Ketchum and Sidell, ''Incapacitating Agents,'' p. 296.
47. Nies, ''Principles of Therapeutics,'' p. 48.
48. The principle of individualized treatment is the result of extensive clinical experience with the use of powerful pharmaceutical agents such as anesthetics.
49. Klochikhin et al., ''Principles of Modeling,'' arrive at the following important conclusion on the basis of their study: ''If the level of 95% efficiency is absolutely required to neutralize terrorists and to prevent mass destruction, there is no chance to eliminate hard consequences and fatalities. Calculations show that the majority of hostages can get serious poisoning and part of them—fatality. This is the cost of releasing if no other solutions left,'' p. 3. See also, Furmanski, and Wheelis, ''Siren's Song,'' p. 4.
50. Guy Gugliotta, ''U.S. Finds Hurdles in Search for Nonlethal Gas,'' *Washington Post*, Nov. 1, 2002, p. A30, quoting C. Parker Ferguson. In 1994, U.S. Army researchers had this to say about the problem: ''For many scenarios the desired characteristics of chemical immobilizers are similar to these depicted in James Bond films. In fiction, a chemical agent knocks out people instantaneously. In reality the onset time for immobilization or unconsciousness takes longer, even when deploying the most potent anesthetic materials known. For other scenarios, a delayed onset or a less severe degree of immobilization may be desired. The other myth usually associated with stereotypical immobilizers is rapid recovery and lack of side effects.'' See Edgewood Research, Development & Engineering Center (hereafter ERDEC), ''Demonstration of Chemical Immobilizers,'' Research Proposal , April 27, 1994, <www.sunshine-project.org/incapacitants/jnlwdpdf/edgedemon.pdf>.

51. This list of requirements summarizes information synthesized from a wide variety of sources. For some particular requirements, see the following: Lakoski, Murray, and Kenny, *Advantages and Disadvantages*, p. 5; Naval Studies Board, *Assessment of Non-Lethal Weapons*, pp. 22, 27, and 107; Ketchum and Sidell, ''Incapacitating Agents,'' p. 288; U.S. Army Field Manual 8-825, p. 3–1. The last three requirements are of particular importance according to the committee of the Naval Studies Board: ''Major research and development . . . issues involving the use of calmatives are (1) the quantification of the effectiveness and margin of safety for these materials and (2) the development of the method of delivery that can rapidly provide the appropriate dose.'' The committee added: ''to elicit the desired level of mood alteration without causing a dangerous level of respiratory depression . . . requires a tight control on dose level,'' p. 27. See also their comment on p. 107: ''Few reliable, low-risk, and low-cost methods exist for delivering and dispensing chemical NLWs precisely and accurately. This capacity . . . becomes critical in the delivery of calmatives, where proper doses must be achieved.'' The committee recommended the development of microencapsulation to create more deliverable forms of incapacitants and sensor systems to achieve accurate delivery on target at the proper dose level. Weapons developer C. Parker Ferguson said that ''major challenges remained to developing an incapacitant both potent enough to be effective and safe enough to be used,'' stating ''[i]t's often a tradeoff.'' Quoted in David Ruppe, ''New Research Offers Safer Incapacitating Chemicals,'' Global Security Newswire, Nov. 6, 2002, <http://www.nti.org/d_newswire/issues/newswires/2002_11_6.html#7>.
52. Klotz et al., *Beware the Siren's Song*.
53. Mark Wheelis and Malcolm Dando, ''Neurobiology: A case study of the imminent militarization of biology,'' *International Review of the Red Cross* 87 (Sept. 2005), p. 561. See also Malcolm R. Dando, ''The Danger to the Chemical Weapons Convention from Incapacitating Chemicals,'' First CWC Review Conference Paper Number 4 (Bradford, UK: Dept. of Peace Studies, University of Bradford, March 2003), pp. 5, 11.
54. See entry for ''Acetylcholine receptors, muscarinic'' at the IUPHAR Receptor Database, <www.iuphar-db.org/GPCR/index.html>.
55. For reviews of some of these important developments, see Robert J. Lefkowitz, ''Historical review: a brief history and personal retrospective of seven-transmembrane receptors,'' *Trends in Pharmacological Sciences* 25 (Aug. 2004), pp. 413–422; Soloman H. Snyder and Gavril W. Pasternak, ''Historical overview: Opioid receptors,'' *Trends in Pharmacological Sciences* 24 (April 2003), pp. 198–205; Mark S. Boguski and Allan R. Jones, ''Neurogenomics: at the intersection of neurobiology and genome sciences,'' *Nature Neuroscience* 7 (May 2004), pp. 429–433; Seth G. N. Grant, ''Systems biology in neuroscience: Bridging genes to cognition,'' *Current Opinion in Neurobiology* 13 (Oct. 2003), pp. 577–582.
56. Mark Wheelis, ''Biotechnology and Biochemical Weapons,'' *Nonproliferation Review* 9 (Spring 2002), pp. 48–53. For example, Committee on Advances, *Globalization, Biosecurity*''; Richard Kramer and Dalia Cohen, ''Functional Genomics to New Drug Targets,'' *Nature Reviews Drug Discovery* 3 (Nov. 2004), pp. 965–972.
57. U.S. Food and Drug Administration, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (Washington DC, March 2004), <www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.

58. Robinson, ''Disabling Chemical Weapons''; J.P. Perry Robinson, ''Disabling Chemical Weapons: A Documentary Chronology of Events, 1945–2003,'' unpublished working paper, Harvard Sussex Program, University of Sussex, Nov. 1, 2003 (hereafter Robinson Chronology); David Brown and Peter Baker, ''Moscow gas likely a potent narcotic,'' *Washington Post*, Nov. 11, 2002, p. A12; Naval Studies Board, *Assessment of Non-Lethal Weapons*, pp. 63–64. The author is indebted to J.P. Perry Robinson for sharing his documentary chronology, which provides by far the most complete account of publicly available information on attempts to develop and use incapacitants between 1945 and 2003.
59. The WorldWide Anaesthetist Web Site, ''Opioids,'' <www.anaesthetist.com/anaes/drugs/opioids.htm>.
60. P.L. Bailey, J. Wilbrink, P. Zwanikken, N.L. Pace, and T.H. Stanley, ''Anesthetic induction with fentanyl,'' *Anesthesia and Analgesia* 64 (Jan. 1985), pp. 48–53.
61. Ketchum and Sidell, ''Incapacitating Agents,'' p. 293; Dando and Furmanski, ''Midspectrum Incapacitants''; McLeish, ''Governance''; Robinson Chronology.
62. Taylor Pharmaceuticals, ''Sufenta (Sufentanil Citrate) Injection,'' package insert, <www.akorn.com/documents/catalog/package_inserts/11098-050-01.pdf>. The package insert states, ''As with all potent opioids, profound analgesia is accompanied by respiratory depression . . . which may persist into or recur in the postoperative period.'' See also note 69.
63. Mather, ''Clinical pharmacokinetics.''
64. W.F. Van Bever, C.J. Niemegeers, K.H. Schellekens, and P.A. Janssen, ''N-4-Substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin,'' *Arzneimittel-forshung* 26 (1976), pp. 1548–1551.
65. Thomas Stanley, ''Human immobilization: Is the experience in Moscow just the beginning?'' *European Journal of Anaesthesiology* 20 (June 2003), pp. 427–428.
66. ERDEC, ''Synthetic Opioids''; see also Brian D. Anderson and Patrick M. Grant, ''Dose Safety Margin Enhancement for Chemical Incapacitation and Less-Than-Lethal Targeting,'' NIJ (National Institute of Justice) Final Report (Livermore, CA: Lawrence Livermore National Laboratory, Jan. 1997); Lois Pilant, ''Less-than-Lethal Weapons: New Solutions for Law Enforcement,'' *Science and Technology*, publication of the International Association of Chiefs of Police (Dec. 1993), p. 3, reporting a safety ratio of 4 for alfentanil in the operating room. The source for this figure is unknown.
67. For example, Center for Nonproliferation Studies, ''The Moscow Theater Hostage Crisis: Incapacitants and Chemical Warfare,'' <http://cns.miis.edu/pubs/week/02110b.htm>.
68. Van Bever et al., ''Novel series''; C.J. Niemegeers, K.H. Schellekens, W.F. Van Bever, and P.A. Janssen, ''Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs,'' *Arzneimittel-forschung* 26 (1976), pp. 1551–1556. The WorldWide Anaesthetist Web Site, ''Opioids''; Taylor Pharmaceuticals, ''Sufenta.''
69. J. de Castro, A. Van de Water, L. Wouters, R. Xhonneux, R. Reneman, and B. Kay, ''Comparative study of cardiovascular, neurological and metabolic side effects of 8 narcotics in dogs,'' *Act Anaesthesiologica Belgica* 30 (March 1979), pp. 55–69; see also Klotz et al., *Beware the Siren's Song*, p. 7; Secretary of the Army, ''Opiate analgesic

formulation with improved safety,'' U.S. Patent Number 5834477, Nov. 10, 1998, <www.patentstorm.us/patents/5834477-fulltext.html>; The WorldWide Anaesthetist Web Site, Opioids.'' Extensive clinical experience demonstrates that the fentanyls can have significant adverse effects in a substantial portion of patients when used at doses required for anesthesia, and even at doses required for analgesia. They are considered safe in hospital settings because dosages can be individualized and for the reasons discussed in the text. One authoritative source has this to say: ''SUFENTA (sufentanil citrate) SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND EPIDURAL ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.'' (Emphasis in original.) Taylor Pharmaceuticals, ''Sufenta.''

70. Karen S. Kearns, Brent Swenson, and Edward C. Ramsay, ''Dosage trials with transmucosal carfentanil citrate in non-human primates,'' *Zoo Biology* 18 (Jan. 24, 2000), pp. 397–402.
71. L.E. Mather, A. Woodhouse, M.E. Ward, S.J. Farr, R.A. Rubsamen, and L.G. Eltherington, ''Pulmonary administration of aerosolised fentanyl: Pharmacokinetic analysis of systemic delivery,'' *British Journal of Clinical Pharmacology* 46 (July 1998), pp. 37–43.
72. Franz, ''Defense Against Toxin Weapons,'' p. 607.
73. Stanley, ''Human immobilization.''
74. ERDEC, ''Opioids''; Naval Studies Board, *An Assessment of Non-Lethal Weapons,* p. 27.
75. U.S. Patent Number 5834477.
76. Snyder and Pasternak, ''Opioid receptors''; Robinson Chronology, entry for Nov. 13, 1990.
77. Robinson Chronology, entry for Jan. 1992.
78. ERDEC, ''Opioids.''
79. ERDEC, ''Chemical Immobilizers.''
80. Anderson and Grant, ''Dose Safety Margin Enhancement.''
81. John Lancaster, ''Pentagon, Justice Dept. Set Plans for Sharing Non-Lethal Technology,'' *Washington Post*, March 23, 1994, p. A3. See also U.S. Dept. of Justice, National Institute of Justice, *NIJ Research Plan 1995–1996* (Washington, DC: Dept. of Justice, 1995), p. 20, regarding Memorandum of Agreement signed with the Dept. of Defense. Cooperation is ongoing, including with the Dept. of Homeland Security. See Trent DePersia ''Homeland Security Advanced Research Projects Agency,'' presentation dated Jan. 25, 2004, <www.hsarpabaa.com/main/HBCU/9_DePersia.pdf>.
82. Mark Wheelis, '''Nonlethal' Chemical Weapons: A Faustian Bargain'', *Issues in Science and Technology* (Spring 2003), <www.issues.org/19.3/wheelis.htm>, citing statement by retired Rear Admiral Stephen Baker that U.S. special forces were equipped with ''knockout gases.''
83. Naval Studies Board, *An Assessment of Non-Lethal Weapons,* p. 27.
84. Ruppe, ''New Research.''
85. Naval Studies Board, *An Assessment of Non-Lethal Weapons,* p. 107.
86. See Neil Davison and Nick Lewer, *Bradford Non-Lethal Weapons Research Project Research Report No. 8,* (Bradford, UK: Centre for Conflict Resolution, University of Bradford, March 2006), p. 52, <www.brad.ac.uk/acad/nlw/research_reports/docs/BNLWRPResearchReportNo8_Mar06.pdf>.

87. Society for Neuroscience, quoted in Malcolm Dando, ''Scientific and technological change and the future of the CWC: The problem of non-lethal weapons,'' *Disarmament Forum* 4 (2002), p. 38, <www.unidir.org/pdf/articles/pdf-art1824.pdf>.
88. ERDEC, ''Synthetic Opioids''; The WorldWide Anaesthetist Web Site, ''Opioids''; also see Y. Chen, A. Mestek, J. Liu, J.A. Hurley and L. Yu, ''Molecular cloning and expression of a mu-opioid receptor from rat brain,'' *Molecular Pharmacology* 44 (July 1993), pp. 8–12; C. Mollereau, M. Parmentier, P. Mailleux, J.L. Butour, C. Moisand, P. Chalon, D. Caput, G. Vassart, and J.C. Meunier, ''ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization,'' *FEBS Letters* 341 (March 14, 1994), pp. 33–38; I. Kitchen, S.J. Slowe, H.W.D. Matthes, and B. Kieffer, ''Quantitative autoradiographic mapping of mu, delta and kappa-opioid receptors in knockout mice lacking the mu-opioid receptor gene,'' *Brain Research* 778 (Dec. 5, 1997), pp. 73–88; H.W. Matthes, R. Maldonado, F. Simonin, O. Valverde, S. Slowe, I. Kitchen, K. Befort, A. Dierich, M. Le Meur, P. Dolle, E. Tzavara, J. Hanoune, B.P. Roques, and B.L. Kieffer, ''Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene,'' *Nature* 383 (Oct. 31, 1996), pp. 819–823.
89. R. Romberg, E. Sarton, L. Teppema, H.W. Matthes, B.L. Kieffer, and A. Dahan, ''Comparison of morphine-6-glucuronid and morphine on respiratory depressant and antinociceptive responses in wild type and mu-opioid receptor deficient mice,'' *British Journal of Anaesthesia* 91 (Dec. 2003), pp. 862–870).
90. Wheelis and Dando ''Neurobiology''; Dando, ''Danger''; Slavko Bokan, John G. Breen, and Zvonko Orehovec, ''An Evaluation of Bioregulators as Terrorism and Warfare Agents,'' *ASA Newsletter*, 02-3, Issue 90 (June 28, 2002), p. 1, <http://www.asanltr.com/newsletter/02-3/articles/023c.htm>; Lakoski, et al., *Advantages and Limitations*, p. 5, stating that '' the premier status of the US pharmaceutical industry in the world markets, combined with the exponential developments in the fields of pharmacology, neuroscience, anesthesia, and biotechnology fields, among others, has brought forth a diverse array of compounds that produce sedation and/or a calm state as either a primary or secondary effect.''
91. Naval Studies Board, *An Assessment of Non-Lethal Weapons,* pp. 5, 79.
92. U.S. Army, ''Chemical Immobilizing Agents for Non-lethal Applications,'' Topic CBD 00-108, Small Business Innovation Research Solicitation CBD 00.1, <www.acq.osd.mil/osbp/sbir/solicitations/sbir001/cbd001.htm>.
93. Optimetrics, Inc., ''Chemical Immobilizing Agents for Non-Lethal Applications,'' SBIR phase I award from the CBD 00.1 Solicitation, <www.nttc.edu/resources/funding/awards/dod/2000sbir/001cbd.asp>.
94. Copeland, ''Joint Non-Lethal Weapons Program''; see also U.S. Joint Non-Lethal Weapons Directorate, *Joint Non-Lethal Weapons Directorate Newsletter*, 2nd Quarter, 2001, as cited in Tobias Feakin, *Bradford Non-Lethal Weapons Research Project, Research Report* 3 (Bradford, UK: Dept. of Peace Studies, University of Bradford, Aug. 2001), <www.brad.ac.uk/acad/nlw/research_reports/researchreport3.php>.
95. Robert Bunker, ed., *Nonlethal Weapons: Terms and References*, INSS Occasional Paper 15 (Colorado Springs: U.S. Air Force Academy, USAF Institute for National Security Affairs, Dec. 1996), p. 10, <http://www.usafa.af.mil/df/inss/OCP/ocp15.pdf>. Calmatives were

classified together with gastrointestinal convulsives, malodorants, biodegrading microbes, and biomaterials as "Biotechnical" in a "Non-Lethal Technology: Taxonomy" presented by the JNLWD Director in March 2000; Col. George Fenton, "The U.S. Dept. of Defense Joint Non-Lethal Weapons Program, March 2000 Overview," presentation at the Non-Lethal Defense IV Conference, sponsored by the National Defense Industrial Association, March 20–22, 2000, slide 10, <www.dtic.mil/ndia/nld4/fenton.pdf>.

96. Naval Studies Board, *An Assessment of Non-Lethal Weapons,* p. 24.

97. OC/RCA is oleoresin capsicum/riot control agent; OC is also known as pepper spray. See Robert J. Hegarty, "Joint Non-Lethal Weapons Program: Non-Lethal Mortar Cartridge (NLMC)," presentation at National Defense Industry Association 2003 Picatinny Chapter/PEO Mortars Conference, Oct. 2003, <www.sunshine-project.org/incapacitants/jnlwdpdf/usamort03.pdf>; Camilo A. Sanchez, "Non-Lethal Airburst Munition(s) for Objective Individual Combat Weapon," presentation at 2001 National Defense Industry Association Joint Services Small Arms Symposium, Aug. 15, 2001, <www.sunshine-project.org/incapacitants/jnlwdpdf/sanchez.pdf>. Although not analyzed in detail here, achieving rapid delivery of tightly controlled doses of biochemical incapacitants remains by far the greatest challenge facing those who would use existing agents or agents likely to be developed in the near future. As a 2002 technical review of the airburst non-lethal munition under development by JNLWD noted, achieving effective payload dissemination is critical for success yet remained "the highest technological risk area" in the program. "[T]he issue has not been resolved." See Applied Research Laboratory, Pennsylvania State University, *Independent Technology Assessment Report of Findings: The Objective Individual Combat Weapon Non-Lethal Munition* (Oct. 10, 2002), pp. 10, 15, <www.sunshine-project.org/incapacitants/jnlwdpdf/oicwairburst.pdf>. See also Klochikhin et al., "Principles of Modeling"; Naval Studies Board, *An Assessment of Non-Lethal Weapons*, note 52.

98. Ibid., p. 124.

99. Ibid, p. 125.

100. Klochikhin et al., "Principles of Modeling."

101. See Davison and Lewer, *Bradford Report No. 5,* p. 39, <www.bradford.ac.uk/acad/nlw/research_reports/docs/BNLWRPResearchReportNo5_May04.pdf>.

102. Ladislav Hess, Jitka Schreiberova, and Josef Fusek, "Pharmacological non-lethal weapons," paper presented to the 3rd European Symposium on Non-Lethal Weapons, Stadthalle, Germany, May 10–12, 2005.

103. NATO Research and Technology Organization, *Non-Lethal Weapons and Future Peace Enforcement Operations*, RTO-TR-SAS-040, Dec. 2004, pp. 3–10, <www.rta.nato.int/Main.asp?topic=sas.htm#>.

104. Guo Ji-wei and Xue-sen Yang, "Ultramicro, Nonlethal, and Reversible: Looking Ahead to Military Biotechnology," *Military Review* 85 (July–Aug. 2005), pp. 75–78, <http://usacac.army.mil/CAC/milreview/download/English/JulAug05/yang.pdf>. Like much of the work by non-lethal weapons enthusiasts and technology boosters, this article, which talks about a wide range of biotechnology-enabled weapons, is more science fiction than science fact. But it reveals a clear interest in the future of biotechnology for military purposes. It also includes such statements as "such devastating, non-lethal effects will

require us to pacify the enemy through postwar reconstruction efforts and hatred control,'' p. 76; and ''[w]e can control the degree of injuries and damage produced and even provide an antidote or a cure . . . Providing such an anodyne to our enemies would represent real 'mercy,'" p. 77.

105. Till Manzke, Ulf Guenther, Evgeni G. Ponimaskin, Miriam Haller, Mathias Dutschmann, Stephan Schwarzacher, and Diethelm W. Richter, ''5-$HT_{4(a)}$ Receptors Avert Opioid-Induced Breathing Depression Without Loss of Analgesia,'' *Science* 301 (July 11, 2003), pp. 226–229.

106. Helge Eilers and Mark A. Schumacher, ''Opioid-induced Respiratory Depression: Are 5-HT_{4a} Receptor Agonists the Cure?'' *Molecular Interventions* 4 (Aug. 2004), pp. 197–199.

107. Gavin J. Kilpatrick and Gary S. Tilbrook, ''Drug development in anaesthesia: industrial perspective,'' *Current Opinion in Anaesthesiology* 19 (Aug. 2006), pp. 385–389.

108. Stanley, ''Human immobilization.''

109. In June 2005, for example, *Nature* launched a new journal, *Nature Chemical Biology,* whose goal is to provide ''an international forum for the timely publication of significant new research at the interface between chemistry and biology.'' See <www.nature.com/nchembio/about/index.html>. The Committee on Advances has also written about this convergence: ''The present report has several times noted that technologies are bringing chemistry and biology closer together. That toxins and synthetic biological agents, including bioregulators, immunoregulators, and small interfering RNAs, fall within the scope of both treaties is one such linkable feature.'' Committee on Advances, *Globalization, Biosecurity*, p. 246.

110. Graham Pearson, *Relevant Scientific and Technological Developments for the First CWC Review Conference: The BTWC Review Conference Experience*, CWC Review Conference Paper No. 1 (Bradford, UK: Dept. of Peace Studies, University of Bradford, Aug. 2002), p. 5.

111. Wheelis, ''Biotechnology and Biochemical Weapons.'' The recent report of the Committee on Advances in Technology offers a definition of biological weapons which incorporates the incapacitating biochemical agents: ''The terms 'weapon' and 'bioweapon' are also used broadly, and include any biological agent or biologically active molecule or other entity that is used or developed and/or stockpiled for use in an effort to cause harm to humans, plants, or animals.'' Committee on Advances in Technology, *Globalization, Biosecurity*, p. 27.

112. United Nations, ''Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction,'' (hereafter BTWC) April 10, 1972, 1015 UNTS 164 280, <www.opbw.org/>.

113. Wheelis, ''Biotechnology''; World Health Organization, *Public health response to biological and chemical weapons: WHO guidance*, *Annex 2: Toxins* (Geneva: World Health Organization, 2004), <http://www.who.int/csr/delibepidemics/biochemguide/en/>. United Nations, ''Second Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapon and on their Destruction, Final Declaration,'' Geneva, Sept. 8–26, 1986, BWC/CONF.II/13, p. 3, <www.opbw.org>.

114. United Nations, ''Second Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biologi-

cal) and Toxin Weapon and on their Destruction, Final Document, Part II, Final Declaration,'' Geneva, Nov. 25–Dec. 6, 1996, BWC/CONF.IV/9 Part II, p. 15, <www.opbw.org>.

115. See the failed proposal of Chile to include the words ''as well as chemical components and products of living organisms and their analogs and modified derivatives'' in the reaffirmation of the coverage of Article I in the Final Declaration. United Nations, ''Fourth Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapon and on their Destruction, Draft Final Declaration,'' Geneva, Nov. 25–Dec. 6, 1996, BWC/CONF.IV/L.1 at <www.opbw.org>, p. 22.

116. United Nations, ''Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction,'' (hereafter CWC), Geneva, Sept. 3, 1992, I-33757, <www.opcw.org>.

117. David P. Fidler, ''The meaning of Moscow: 'Non-lethal' weapons and international law in the early 21st century.'' *International Review of the Red Cross* 87 (Sept. 2005), pp. 525–552.

118. David A. Koplow, ''Tangled Up in Khaki and Blue: Lethal and Non-Lethal Weapons in Recent Confrontations,'' *Georgetown Journal of International Law* 36 (Spring 2005), p. 737. During testimony before the Senate Committee on Foreign Relations on the CWC negotiations, Ambassador Stephen J. Ledogar stated: ''My current instructions propose that riot control agents simply be defined out of the convention, not included. That position has not gained a lot of support. The majority position would take the opposite side and would have riot control agents defined in and therefore covered by all of the provisions . . . .Now, at present the United States is reviewing my instructions on riot control agents, I am told, to see whether some compromise between the two extremes that are on the table now in Geneva might be reached.'' Committee on Foreign Relations, U.S. Senate, *Chemical Weapons Ban Negotiation Issues*, S. HRG. 102-719 (May 1, 1992), pp. 9–10.

119. Dept. of the Navy, Office of the Judge Advocate General, International & Operational Law Division, *Preliminary legal review of proposed chemical-based non-lethal weapons*, Nov. 30, 1997, <www.sunshine-project.org/incapacitants/jnlwdpdf/jagchemi.pdf>.

120. JAG, *Preliminary Review*, p. 21.

121. Ibid., p. 22.

122. Margaret-Anne Coppernoll, ''The Nonlethal Weapons Debate,'' *Naval War College Review* 52 (Spring 1999), <www.nwc.navy.mil/press/review/1999/spring/art5-sp9.htm>.

123. Koplow, ''Tangled Up,'' pp. 737–738.

124. This is also what probably drove the committee to change the goal posts for work on calmatives, as discussed in note 90**.** It also appears to have led the committee, in the draft version of the report, to draw a distinction between ''permissible psychological effects (e.g. calming)'' versus ''impermissible physiological (e.g. unconsciousness) effects.'' Such a distinction ignores the fact that chemical agents that act on the brain to cause psychological effects do so by their biochemical action on physiologic systems. Committee for an Assessment of Non-Lethal Weapons Science and Technology, Naval Studies Board, National Research Council, *An Assessment of Non-Lethal Weapons Science*

and Technology, DRAFT version (Washington, DC: National Academies Press, 2002), p. 2–39. This language was removed from the final version of the report because the State Dept. and the Defense Dept. held differing legal interpretations of the CWC. Naval Studies Board, *An Assessment of Non-Lethal Weapons*, p. xiii.

125. Ambassador Ledogar stated in his May 1, 1992, testimony before the Senate Foreign Relations Committee: ''The US is concerned that declarations of all chemicals intended to be used for law enforcement would reveal sensitive information, such as how to defeat the chemical's effects or how to create the same chemicals for illegal use. The Chairman's text addresses this problem by requiring only declaration of chemicals held for riot control purposes.'' Committee on Foreign Relations, *Chemical Weapons Ban*, p. 35.

126. CWC Bulletin Editors, ''New Technologies and the Loophole,'' *CBW Convention Bulletin* No. 23 (March 2004), <http://fas-www.harvard.edu/~hsp/bulletin/cwcb23.pdf>.

127. See Fidler, ''The meaning of Moscow,'' citing Articles 31.1 and 31.3(c) of the Vienna Convention on the Law of Treaties, May 23, 1969, UNTS Vol. 1155, p. 331.

128. Adolf von Wagner, ''Toxic Chemicals for Law Enforcement including Domestic Riot Control Purposes under the Chemical Weapons Convention,'' in Marie Chevrier, Alan Pearson, and Mark Wheelis, eds., *Incapacitating Biochemical Weapons*, (unpublished).

129. Abram Chayes and Matthew Meselson, ''Proposed Guidelines on the Status of Riot Control Agents and Other Toxic Chemicals Under the Chemical Weapons Convention,'' *Chemical Weapons Conventions Bulletin* 35 (Harvard Sussex Program on CBW Armament and Arms Limitation, March 1997), pp. 13–17.

130. Fidler, ''The meaning of Moscow,'' p. 538.

131. The interpretations of Chayes and Meselson and von Wagner might be open to the same objection, albeit to a lesser degree, insofar as advances in science and technology are identifying powerful but short-acting analgesics/anesthetics such as remifentanil, whose specific action on central nervous system functions qualitatively differs from the non-specific action of traditional riot control agents such as tear gas.

132. Robin M. Coupland '''Calmatives' and 'Incapacitants' – Questions for humanitarian law brought by new means and methods of warfare with new effect,'' paper presented to the Open Forum on the Chemical Weapons Convention—Challenges to the Chemical Weapons Ban, The Hague, Netherlands, May 1, 2003, p. 23, <www.central.susx.ac.uk/Units/spru/hsp/OpenForumCWC.pdf>. See also David P. Fidler, '''Non-lethal' weapons and international law: Three perspectives on the future,'' *Medicine, Conflict and Survival* 17 (2001), pp. 199–201.

133. Of course, this would create an incentive to develop the next, ''new and improved'' incapacitating biochemical weapon.

134. Coupland, ''Calmatives''; Wheelis, ''Faustian Bargain''; Naval Studies Board, *An Assessment of Non-Lethal Weapons*, p. 27.

135. Such agents could have some utility in domestic law enforcement for the apprehension of individual criminals or the resolution of hostage crises arising spontaneously. But in many countries, the requirement for non-lethality in domestic law enforcement applications will be extremely high, much more so than for military uses. Such agents might also have some military use in the apprehension of terrorists and other adversaries.

This is likely one reason for current military interest in these agents and may also explain in part why special forces may be equipped with ''knock-out'' agents.

136. Agentai, Inc., ''Smart Non-Lethal Bullets,'' Topic # Navy 02-122; and Agentai, Inc., ''Rocket Assisted Safe Projectile,'' Topic # Navy 02-119, Navy Small Business Innovation Research Awards, 2002, <www.sunshine-project.org/publications/pr/pr080903support.html>.

137. Not considered here are private military contractors (or PMCs), who are increasingly prominent, but largely unregulated, purveyors of security services and armed force at the local, national, and global levels. It seems likely that PMCs could find great utility in any incapacitating biochemical weapons that might come on the market. For more information on PMCs, see for example Peter W. Singer, *Corporate Warriors: The Rise of the Privatized Military Industry* (Ithaca, NY: Cornell University Press, 2003).

138. Wheelis, ''Faustian Bargain.''

139. Ibid.

140. Others have also expressed these concerns. See for example references 2, 4, 7 and Committee on Advances, *Globalization, Biosecurity,* pp.178–183; also see J. Patocka and J. Fusek, ''Chemical Agents and Chemical Terrorism,'' *Central European Journal of Public Health* 12, Suppl. (2004), pp. S75–S77, stating that ''calmatives'' are among the chemical weapons that terrorists could use and that ''prohibition of chemical weapons is not respected by terrorists and by non-conventional [sic] countries.'' Noting that Dr. Fusek is among the Czech researchers involved in developing these same weapons for the Czech military, Davison and Lewer comment that ''with the ongoing development of these pharmaceutical weapons many observers fear that 'conventional' countries such as the Czech Republic, Russia, and the United States have also lost this respect.'' Davison and Lewer, *Bradford Report* 8, p. 52.

141. Biochemical incapacitants could also provide new tools for interrogation and torture. This capability will probably emerge even in the absence of incapacitating biochemical *weapons* programs, but it would certainly be facilitated by such programs.

142. Paul L. Howard, *Operational Aspects of Agent CS*, USATECOM Deseret Test Center technical report DTC-FR-S700M, April 1973 (unclassified Dec. 1979), as quoted in Mathew S. Meselson and Julian P. Perry Robinson, '''Non Lethal' Weapons and Implementation of the Chemical and Biological Weapons Conventions,'' paper delivered to the 20th Pugwash Workshop Study Group on the Implementation of the CBW Conventions, Geneva, Switzerland, Nov. 8–9, 2003, p. 3. See also Furmanski, ''Military Interest,'' p. 16.

143. John Hart, Frida Kuhlau, and Jacqueline Simon, ''Chemical and biological weapons developments and arms control,'' in *SIPRI Yearbook 2003: Armaments, Disarmament and International Security* (Oxford: Oxford University Press, 2003), pp. 645–682.

144. Allison et al., *Non-lethal Weapons and Capabilities*, p. 32.

145. *CBW Conventions Bulletin*, News Chronology entry for Dec. 5, 2000, 51, Harvard Sussex Program on CBW Armament and Arms Limitation, March 2001, p. 35. The Council on Foreign Relations Task Force adds: ''While a world free of BW and CW is not within our grasp, it is highly probably that if the United States espouses BNLW or CNLW several nations (and not only the renegades) will adopt serious military programs for the development of lethal agents in the guise of advancing the capabilities of non-lethal ones.'' Allison et al., *Non-Lethal Weapons,* p. 61.

146. James B. Petro, Theodore R. Plasse, and Jack A. McNulty, ''Biotechnology: Impact on Biological Warfare and Biodefense,'' *Biosecurity and Bioterrorism* 1 (Sept. 2000), pp. 161–168.
147. Davis, ''Nuclear Blindness.''
148. Wheelis, ''Faustian Bargain,'' p. 78.
149. CBW Conventions Bulletin Editors, '''Non-lethal' weapons, the CWC and the BWC,'' *CBW Conventions Bulletin* 61 (Harvard Sussex Program on CBW Armament and Arms Limitation, Sept. 2003), p. 1.
150. Allison et al., *Non-lethal weapons*, pp. 62–63.
151. Graham S. Pearson, *New Scientific and Technological Developments of Relevance to the Fifth Review Conference*, Bradford Review Conference Paper No. 3 (Bradford, UK: University of Bradford, Dept. of Peace Studies, 2001), p. 26, <www.brad.ac.uk/acad/sbtwc/briefing/rcp3.pdf>.
152. Wheelis, ''Biotechnology and Biochemical Weapons.''
153. Furmanski, ''Military Interest.'' See also notes 83 and 84. The report of the US/UK Executive Seminar on ''non-lethal'' weapons included a recommendation from the U.S. Dept. of Defense that ''[i]f there are promising technologies that DOD is prohibited from pursing, set up MOA [memoranda of understanding] with DOJ [Dept. of Justice] or DOE [Dept. of Energy].'' US/UK Non-Lethal Weapons (NLW) Seminar Report, p. 8.
154. Wheelis, ''Faustian Bargain.''
155. Ibid.
156. See, for example, John D. Steinbrunner, Elisa D. Harris, Nancy Gallagher, and Stacey Okutani, *Controlling Dangerous Pathogens: A Prototype Protective Oversight System* (University of Maryland, Center of International and Security Studies, Dec. 2005), <www.cissm.umd.edu/papers/files/pathogens_project_monograph.pdf> and <www.biosecurityboard.gov>.
157. ''Both preclinical and clinical research provides important information vital toward identification of calmatives that may be best suited for use as non-lethal techniques.'' Lakoski et al., *Advantages and Limitations*, p. 8.
158. Feakin, *Bradford Non-Lethal Weapons Report No. 3*.