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EDITOR'S NOTE

The revolution in the life sciences is driving new discoveries and applications in medicine, psychology and health. Our developing understanding of how the body and its components work at the most basic levels allows us to envision treatments and cures hitherto unimaginable. However, the possibilities for malign use of these breakthroughs are both terrifying and vast. The ability to influence life processes at the molecular level means the ability to turn the body into a weapon against itself. This is particularly disturbing as international discussion and the relevant legal prohibitions appear to lag far behind the pace of scientific progress.

This issue of *Disarmament Forum* focuses on advances in science and technology and their implications for the chemical and biological weapons regimes. After an overview of scientific and technological developments and their relation to the regimes, authors explore a few worrying applications made possible by developments in neuroscience and immunology, current research on "non-lethal" weapons, and the possible utility of a code of conduct for those working in the life sciences.

The next issue of *Disarmament Forum* will examine the dynamic and complex region of North-East Asia, which is at the heart of several security and defence concerns. Proliferation concerns, unresolved conflicts and grievances, and the future of the Korean Peninsula affect the stability of the region as a whole—and have global repercussions. Articles in this issue will focus on efforts to stabilize the Korean Peninsula, initiatives to reduce tensions and build confidence region-wide, the issue of missile proliferation and defences, the role of external actors, and regional security policies.

Two new projects have recently started at the Institute. The first, the *European Action on Small Arms, Light Weapons and Explosive Remnants of War*, will examine the European Commission's responses to these weapons, with the objective of formulating recommendations to enhance coordination, harmonize policies and address gaps (see UNIDIR Focus, page 69, for details).

The second project is entitled *Disarmament as Humanitarian Action: Making Multilateral Negotiations Work.* This project adopts a problem-solving approach involving practitioners in the multilateral negotiating field and emphasizes practical means grounded in the humanitarian dimensions of disarmament. On 3 November 2004, UNIDIR convened an initial half-day gathering of practitioners in the disarmament, arms control and humanitarian fields to introduce the project, outline some of the basic concepts behind it and present examples of alternative perspectives and approaches to disarmament and arms control negotiations.

UNIDIR, United Nations Development Programme and United Nations Department for Disarmament Affairs (with the Small Arms Survey as a technical consultant) have completed their analysis of the national reports submitted to the 2003 Biennial Meeting of States. This evaluation has been published as *Implementing the United Nations Programme of Action on Small Arms and Light Weapons: Analysis of the Reports Submitted by States in 2003* by E. Kytömäki and V. Yankey-Wayne

(see UNIDIR Focus, page 69, for details). An executive summary will be published in all official UN languages in advance of the 2005 Biennial Meeting. The project partners are exploring the possibility of continuing and further expanding the assistance project.

On 24 November, the Director-General of the United Nations Office at Geneva, Mr. Sergei Ordzhonikidze, and UNIDIR Director Dr Patricia Lewis hosted a high-level discussion with Mrs. Suzanne Mubarak, First Lady of the Arab Republic of Egypt and President of the NGO Women's International Peace Movement. This meeting followed a three-day conference hosted by the Women's International Peace Movement entitled "Women Defending Peace". Mrs. Mubarak presented an overview of that conference, and invited discussion on the contributions that UN agencies and research institutes could make towards supporting the role of women in peace-making and security building.

Kerstin Vignard

SPECIAL COMMENT

Science has long served to advance humanity. In recent years, major discoveries in the life sciences and fantastic advances in biotechnology have become the stuff of daily news. New cures, a safer environment and better food sources are promised. There can be no doubt that the ever-increasing pace of such discoveries and advances—which go hand-in-hand with advances in information technology—will revolutionize our lives.

These same advances sit behind the articles of this *Disarmament Forum* by reminding us of an uncomfortable fact and a corresponding but as yet unanswered question. The fact is that all major advances and discoveries in science have, at some point, been turned to hostile use on a massive scale. The First World War demonstrated this in relation to chemistry and, obviously, the Second World War could not have culminated in the use of nuclear weapons without the prerequisite advances in nuclear physics. The question is: what are the implications for humanity if the advances in life sciences and biotechnology also are turned to hostile use? An additional consideration is that, as compared with the use of chemical or nuclear weapons, the effects of any future hostile use of the advances in life sciences could result in a contagious disease. Nobody can predict the outcome.

Use of chemical weapons has been rare; the use of biological weapons even rarer. But advances in life sciences and biotechnology may bring in an era that sees the use of new biological or chemical weapons; and some would fulfil the definitions of both biological and chemical agents given in the 1972 Biological and Toxin Weapons Convention (BTWC) and the 1993 Chemical Weapons Convention (CWC) respectively. New agents could be more easily designed, more specific in their effects or more difficult to detect. New ways to deliver "traditional" and new agents might be found in parallel with the means to overcome the targets' natural or acquired defences. The user could carry out an attack in greater safety. In brief, many of the recognized disadvantages of chemical or biological weapons could be eliminated; new biological or chemical weapons would then become a much more attractive option for anyone contemplating their use.

Considerable confusion has been introduced (in my opinion, intentionally) by using the term "non-lethal" in relation to certain new weapons. There is talk of "non-lethal" biological and chemical weapons and their proponents have even gone so far as to advocate revision of the BTWC and CWC to accommodate these "non-lethal" alternatives. There is no evidence that any biological or chemical weapon is necessarily "lethal"; likewise, there is no evidence that any new agent would be "non-lethal". One cannot talk about lethality without considering the dose received by the victim and the victim's vulnerability. In other words, the proportion of people affected by a weapon who ultimately die (lethality) is the outcome of a context; it is not an inherent property of a weapon. Scientific research that results in "non-lethal" biological or chemical weapons will not serve to advance humanity. This is why such research is prohibited.

We have buried our collective head in the sand with regard to these issues; one reason is that they are very complex. They are so complex, I believe, that the means to address them will only be found by reverting to basics and considering two fundamental and obvious points. The first is that this whole subject is about preventing advances in life sciences and biotechnology from being used for poisoning or deliberate spread of infectious disease; by extrapolation, this lends itself to a preventive public health approach. Second, humanity is both the motivation for and beneficiary of such prevention. The links between these two facts are intuitive; however, to find practical and effective prevention and a meaningful dialogue at an international level that supports such prevention we need to look beyond our intuition.

When considering any complex issue related to weapons, the International Committee of the Red Cross (ICRC) refers to a scientifically valid model of armed violence and its effects. The model provides a standardized approach, uses public-health methodology, and applies to any use of any weapon in any context with any effect on the victims. The model stipulates that the design and development of weapons, their production, and their transfer are prerequisites for their use and so, in turn, for victims suffering the effects. The model then links the effects of any act of armed violence on the victim to certain necessary determinants of those effects—including factors relating to design, production, transfer and use of weapons. As applied to use of chemical or biological weapons, the determinants of whether victims suffer poisoning and deliberate spread of infectious disease are:

- the *vulnerability* of the victim (the potential to suffer poisoning or deliberate spread of infectious disease);
- the way the chemical or biological weapons are used (*use*);
- the potential number of weapons in use (corresponding to *production* and *transfer* of chemical or biological weapons); and
- the potential of the weapon to cause the effect (corresponding to *design* and *development* of the chemical or biological weapon).

Each determinant is necessary but not in itself sufficient to cause the effects. (In relation to "non-lethal" biological or chemical weapons, each determinant is necessary but not sufficient for the death—or survival—of affected people. This emphasizes the fact that lethality—or lack of it—is not an inherent property of a weapon.)

Any single measure that might prevent poisoning and deliberate spread of infectious disease is referable to one or more of the determinants. Examples are how public-health preparedness reduces *vulnerability*; the total prohibition and, at a national level, criminalization of poisoning and deliberate spread of disease aim to eliminate *use*; inspections, intelligence and customs regulations impact on *production* and *transfer* to would-be perpetrators; promoting notions of responsibility among scientists would address *design* and *development*. These measures overlap and integrate with states' obligations under the BTWC and the CWC. It becomes obvious how each preventive measure is necessary but not in itself sufficient to minimize the risk of poisoning and the deliberate spread of infectious disease.

This approach provides the basis of what the ICRC is promoting as the "web of prevention". Practical aspects of this are communicated in a series of imperatives: Recognize the risks! Maximize what you can do in your domain to reduce the risks! Listen to what others are doing! Coordinate your thinking and action! Individual scientists who fear this approach might bring greater regulation of their work are the most resistant to these messages. Many say "But we are not the problem. We do not make chemical or biological weapons!" The correct response is: "We know you are not the problem, but you are part of the solution because you have legal and professional responsibilities to prevent poisoning and deliberate spread of disease." We must all learn to think and act within a web of prevention.

Apart from providing a framework for action, the web of prevention helps us to talk common sense about something that we seem to have difficulty approaching in common-sense terms. It serves to emphasize that minimizing the risks of the advances in life sciences and biotechnology being used for poisoning and deliberate spread of infectious disease is, by necessity, a multidisciplinary and collaborative endeavour. It is difficult to see how else to maximize the benefits to humanity of these advances and minimize the risk of their hostile use with potentially catastrophic results for humanity.

But what do we mean by humanity? For our purposes, the word humanity has two meanings. One meaning refers to the collective existence of all humans; the other implies an attitude, morality or sentiment of goodwill towards fellow humans. Some may think looking beyond this too academic. However, a closer consideration of both meanings of humanity and how they interact is important.

Humanity in the first sense implies more than just the species *Homo sapiens.* It implies collective living of humans and the security that this brings. However, to achieve this security, laws are enforced and nations are defended; this necessitates a capacity for armed violence in the hands of designated sections of our society and this capacity is, or should be, carefully regulated. In other words, a capacity for armed violence and regulation of this capacity are prerequisites for our successful collaborative existence. In this way, we see how international law, by avoiding costly armed confrontation between states, promotes humanity in the collective sense. If we accept our successful collective existence depends on a carefully regulated capacity for armed violence, we must ask why use of chemical or biological weapons is not part of this picture. The obvious answer is that poisoning and the deliberate spread of infectious disease have never been compatible with the notion of reasonable use of force within a society and in warfare have always been deemed abhorrent. That such weapons are totally prohibited by the BTWC and the CWC is both consequence and confirmation of this abhorrence. In other words, there is no acceptable use of chemical or biological weapons. (I accept a possible exception is the controlled and open-air use of lachrymatory agents in specific contexts, i.e. for riot control.) Finally, to emphasize the link between notions of humanity in the collective sense, both the BTWC and the CWC contain preambular paragraphs which read "Determined, for the sake of all mankind, to exclude completely the possibility of [use of chemical and biological weapons.]"

Humanity in the second sense—the spirit, sentiment or morality—is a cited source of international law. The one-page 1868 St Petersburg Declaration, which prohibited the use of exploding bullets, is the single parent of modern arms control (and also of many principles of international humanitarian law). The declaration, which was the outcome of a *military* commission, refers once to the "requirements of humanity" and twice to the "laws of humanity". It is abundantly clear that those drawing up this declaration believed that technical developments in weaponry should be accountable to humanity. The famous Martens clause originating in the 1899 Hague Peace Convention and articulated in the 1907 Hague Convention (IV) invokes "the laws of humanity, and the dictates of public conscience". Humanity, as the first principle of the International Red Cross and Red Crescent Movement, clearly refers to the spirit in which certain actions are undertaken; nevertheless, it remains an ambiguous concept. This second notion of humanity becomes more concrete if considered as the converse of inhumanity and there are few, if any, acts of inhumanity that do not ultimately involve use of, threat of or coercion by armed violence. (The definition of "crimes against humanity" in the 1998 Rome Statute of the International Criminal Court serves as evidence, although there is no indication of which humanity is being referred to in this category of crime. Perhaps it is both?) Whatever the case, would not most people working to ensure the total prohibition of biological or chemical weapons consider armed violence involving poisoning and deliberate spread of disease an act of inhumanity?

Enough of playing with words! These two notions of humanity are co-dependent. By this I mean an inherent morality or sentiment of goodwill towards fellow humans (including an abhorrence of inhumanity) is necessary for the positive collective existence that all humans aspire to. The co-dependence

of the two humanities makes it clear that humanity in a general sense is both a prerequisite for and is protected by international law. International law that regulates armed violence and so prevents some effects of armed violence is where the two senses of humanity ultimately fuse; this is epitomized in relation to the two principal conventions that prohibit poisoning and the deliberate spread of infectious disease. An inescapable conclusion is that the BTWC and the CWC are rooted deeply in humanity in both senses and are necessary for the future of humanity in the collective sense.

Preventing the use of advances in life sciences and biotechnology to facilitate poisoning and deliberate spread of infectious disease should be considered for what it is: a critically important issue for humanity and one that cannot be ignored for much longer. The web of prevention permits a common-sense dialogue and maximizes the potential of any single measure to reduce the risks to a minimum. However, the web of prevention will lack a vital strand if the politicians, diplomats, lawyers and scientists working on the BTWC and CWC do not feel accountable to humanity and adapt their beliefs and behaviour accordingly.

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The opinions expressed are the author's own and do not represent the views or policy of the ICRC.

Science, technology and the CBW control regimes

Alexander KELLE

Advances in science and technology (S&T) can have both positive and negative effects on societies and the relations among them. In chemistry, biology and the life sciences more generally the intention of scientists doing cutting-edge research will generally be to better the human condition, such as through the development of new medicines. However, a considerable number of chemical compounds and micro-organisms have potential for harmful, as well as beneficial, effects.

Many toxic chemicals, their precursors, as well as pathogens and processes involved in their production have perfectly legitimate civilian applications. At the same time the history of chemistry and biology provides ample examples of new discoveries in these areas being used for weapons' purposes. Thus, the dual-use character of toxic chemicals and pathogenic micro-organisms is not just an abstract quality they possess. Rather, the different purposes to which these substances and organisms can be put have had profound implications on military thinking and—in the case of chemical weapons (CW)—the history of warfare. Any effort to control the use of toxic chemicals or pathogenic micro-organisms for offensive military purposes has to take into account the dual-use nature of many of these chemicals, organisms and related equipment and processes.

To give but a few examples, chlorine and phosgene—two of the major chemical warfare agents used in the First World War—are used on a large scale as industrial chemicals in a variety of applications. Among other uses, phosgene is used in pesticides, pharmaceuticals and dyes. Current industrial operations utilizing cyanide-based compounds include fumigation, processing of metal ore and fabrication of metal polishes. This dual-use character is equally pronounced in the biological weapon (BW) area, which has implications for the verification of the peaceful applications of both potential chemical and biological warfare agents.

The next section will provide a brief overview of past S&T advances and their use in offensive chemical and biological warfare programmes. This will be followed by a discussion of present control mechanisms for chemical and biological weapons (CBW) and how they relate to the state of development of the life sciences. The final section will analyse how the biotechnology revolution might impact the future of CBW controls. Given the availability of detailed analyses of some aspects of the biotechnology revolution and its impact on BW controls, in general this paper will focus more on the impact on CW controls.

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Past S&T advances and their use in CBW programmes

Scientific and technological advances in the second half of the nineteenth century were instrumental in enabling offensive CBW programmes. In the case of chemistry, it was a particular aspect of the industrial revolution that made chemical warfare during the First World War a possibility[1]—the "large-scale liquefaction of chlorine gas and its packaging into pressure cylinders."[2] This was accomplished in 1888 by the German company BASF. [3]

Therefore it does not come as a surprise that when large-scale use of CW first occurred, it was chlorine that was used: almost 150 tons of which were released by the German army on 22 April 1915 near Ypres on the Western front. As defences in the form of gas masks were developed against chlorine and phosgene, the first offensive-defensive chemical arms race ensued with CW agents like mustard gas being developed to overcome the respiratory protection that the masks afforded.[4]

Despite several peace treaties and the 1925 Geneva Protocol, chemical rearmament was taking place in the 1920s and 1930s. In the case of Germany, for example, this chemical rearmament stood in stark contrast to the obligations undertaken in the Versailles peace treaty signed after the First World War. Yet it was in Germany where civilian research into a new group of organophosphorous compounds led to the development and production of the first nerve agent, Tabun, in December 1936. This discovery was followed by the synthesis of Sarin in 1939 and Soman in 1944. After the Second World War civilian work to exploit the new group of toxic organophosphates continued, leading to the development of even more toxic compounds, some of which were introduced as pesticides but then had to be withdrawn due to their toxicity to man. One of these super-toxic compounds was adopted by the US military during the 1950s and became known as the VX chemical warfare agent.[5]

The use of biological agents in warfare goes back at least several hundred years.[6] However, only with the advances in the scientific understanding of life and its underlying processes has a systematic utilization of pathogens or naturally produced toxic substances for warfare purposes been possible. The nature and scope of biological warfare has changed dramatically due to the revolution in the life sciences that began in the late nineteenth century. As Dando has shown for the "three generations of offensive biological warfare programs" of the twentieth century, all the military programmes were "developing on the back of growth in scientific knowledge."[7] According to his account, military BW programmes followed scientific discoveries in the areas of: *bacteriology*, providing the ground for the BW-based sabotage activities during the First and Second World Wars; *aerobiology*, providing for the knowledge to spread biological warfare agents over large geographic areas, and thereby giving non-contagious agents their potential to be used as mass casualty weapons; and *genetic engineering*, which played an important role in the offensive BW programme of the former Soviet Union.[8]

Present CBW control mechanisms and their relationship to developments in the life sciences

The CBW control regimes go back to the 1925 "Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or Other Gases, and of Bacteriological Methods of Warfare". The Protocol was originally conceived as a response to the widespread use of CW during the First World War, and only upon a Polish initiative were "bacteriological methods of warfare" included into the Protocol text. It entered into force in 1928 and has currently 133 member states. Today, the CBW regimes revolve around two international treaties: the Biological and Toxin Weapons Convention (BWC)[9] and the Chemical Weapons Convention (CWC).[10]

The CWC was opened for signature in January 1993 and entered into force on 29 April 1997. It bans the development, production, use and retention of CW and requires states possessing CW to destroy them over a ten-year period. The dual-use problem led to the inclusion in the CWC of the so-called general purpose criterion. According to this provision, toxic chemicals that could be misused as CW are not prohibited altogether. Negotiators of the CWC also realized that the area the convention regulates would be subject to advances in S&T. They have therefore provided for a procedure to review these developments at CWC review conferences and created the Scientific Advisory Board (SAB) to advise the Organisation for the Prohibition of Chemical Weapons (OPCW) on S&T matters.

Chemical warfare agents and means for their production are based on long-established, well-known and proven technologies. Thus, a potential proliferator determined to operate a clandestine CW programme does not necessarily have to look for the latest developments in chemistry or related disciplines to obtain a militarily significant CW capability. Nevertheless, at least three developments are taking place in both the civilian and military applications of chemistry that might well change the way we (need to) think about chemical warfare agents and the ways and means to prevent the misuse of toxic chemicals for offensive military purposes. Two of these developments—the evolution of chemical industry, and the renewed interest in "non-lethal" weapons—are directly linked to the CW control regime and its effectiveness. The third one, the impact of the biotechnology revolution on the long-term viability or robustness of the CW control regime, will be discussed in the final section.

Evolution of the chemical industry

Two developments in the chemical industry pose particular challenges to the verification of the peaceful applications of toxic chemicals. First, there is a clear trend away from the continuous production of large quantities of a chemical in a facility specifically designed for the purpose. Rather, many companies increasingly rely on the use of smaller, more versatile production facilities, which can be adapted from the production of a batch of one chemical to another one in a short period of time. Such facilities could easily fall through the cracks of the declaration and inspection system of the CWC. Utilization of such batch-production facilities would theoretically enable a potential proliferator to distribute the production of CW precursor chemicals or even chemical warfare agents themselves among a number of such facilities to avoid detection.

Many companies increasingly rely on the use of smaller, more versatile production facilities, which can be adapted from the production of a batch of one chemical to another one in a short period of time. Such facilities could easily fall through the cracks of the declaration and inspection system of the CWC.

Secondly, over the last decade a considerable number of traditional chemical firms were broken up and replaced by so-called "industrial parks". This poses a potential problem for verification under the CWC as the convention's definitions that form the basis for the verification measures assume the existence of plant sites—which were prevalent in the late 1980s when the CWC was negotiated. A good example of this trend is the transformation of the former Hoechst AG near Frankfurt, Germany into an industrial park with more than seventy-five international life-science and chemical companies, employing more than 22,000 people.[11] In order to maintain an effective and efficient industry verification system under the CWC, developments like these have to be monitored closely, and the verification procedures have to be adapted to the changed environment. As debates during the First CWC Review Conference, held in 2003, have shown, however, many CWC states parties are not inclined to support such an adaptation. Instead they argue that the OPCW's industry verification activities should remain unchanged, thereby risking that the regime will become irrelevant due to developments in the chemical industry at some point in the future.[12]

Interest in "non-lethal" weapons

Equally important, renewed interest in so-called "non-lethal" CW threatens to undermine the current control regime and calls into question its future robustness. If there was the need for a wake-up call to raise awareness of this problem, this was most certainly provided by the use of a "fentanyl-derivative"—as it was called by Russian authorities—to end the Moscow theatre hostage crisis in 2002.[13] However, this incident represents just the tip of the iceberg, as Russia is not the only state interested in utilizing "non-lethal" CW in a number of police and military scenarios other than war. Certainly the US military shows a strong interest in developing this kind of capability.[14]

From a scientific and technical point of view the major problem with "non-lethal" weapons lies in the fact that they are not non-lethal, as the Moscow theatre situation has clearly demonstrated: about 130 of the 830 hostages died from the effects of the gas used.

From a scientific and technical point of view the major problem with "non-lethal" weapons lies in the fact that they are not non-lethal, as the Moscow theatre situation has clearly demonstrated: about 130 of the 830 hostages died from the effects of the gas used. This represents a mortality rate of approximately 16%. In comparison, the chemical warfare agents of the First World War like chlorine, phosgene and mustard gas, which are prohibited under the CWC and listed on its schedules of chemicals, have a lethality of around 7%.[15]

Even if truly non-lethal CW were technically feasible, is it questionable whether their use would have the effect to merely incapacitate temporarily and not lead to the death of those exposed to the agents. Again, the Moscow theatre scenario offers some insights: Russian security forces obviously had orders to shoot the hostage-takers, which were incapacitated by the gas used in the theatre. Although this might have been the best way to ensure that none of the hostage-takers would be able to detonate their explosives, it reveals a central weakness of the argument of proponents of "non-lethal" CW. These incapacitants are often used in conjunction with lethal military force and in this context act mainly as a force multiplier and not as a life-saving tool. Exactly the same pattern of "non-lethal" CW usage occurred during the Viet Nam War, in which the US military employed 10 million pounds of the irritant CS.

A post-war analysis of the operational use of CS declassified in 1979 could find no report of its use against non-combatants or to save civilians and concluded that "the reduction in casualties has not been in enemy or non-combatant personnel but, rather, friendly troops, as a result of using CS to make other fires more effective."[16]

Before the First CWC Review Conference a number of contributions on S&T developments of relevance to the CWC were made by NGOs, including the International Union of Pure and Applied Chemistry, which were then taken up by organs of the OPCW, most notably the SAB, and states parties individually.

In its report to the Review Conference, the SAB noted that *inter alia* it:

> was aware of concerns about the development of new riot control agents (RCAs), and other so-called "non-lethal" weapons utilising certain toxic chemicals (such as incapacitants, calmatives, vomiting agents, and the like). … [B]ased on past experience and the fact that many of these compounds act on the central nervous system, it appears unlikely from a scientific point of view that compounds with a sufficient safety ratio would be found. …
>
> The SAB stressed the importance that all new toxic chemicals, no matter what their origin or method of synthesis, are covered by the Convention's definition of CW … .[17]

S&T issues did not have a prominent position on the agenda of the Review Conference. However, S&T issues—more specifically the Report of the SAB as submitted to the conference by the Director-General—resurfaced in the Review Document, both in the sections on general verification provisions and on activities not prohibited under the CWC.

Although the topics of "non-lethal" weapons and chemical incapacitants received considerable attention in the run-up to the meeting, discussion on them was almost completely suppressed during the Conference. Two states parties—New Zealand and Switzerland—made explicit reference during the General Debate to the dangers emanating from "non-lethal" weapons to the regime, however the only opportunity to discuss these matters publicly arose at the "Open Forum on the Chemical Weapons Convention", hosted by the OPCW and supported by a number of NGOs. The Open Forum included a panel discussion entitled "The Chemical Weapons Ban and the Use of Incapacitants in Warfare and Law Enforcement". Not surprisingly, then, the text of the Review Document did not contain any language explicitly referring to incapacitants or "non-lethal" weapons. However, the document did contain language in relation to the definitions in Article II of the Convention, pointing out that these were found by the conference to adequately cover developments in science and technology.

Turning now to biological weapons, the BWC stipulates in its Article I that:

> Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:
>
> (1) 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*. [emphasis added]

Like in the case of the CWC, the general purpose criterion not only makes it clear that peaceful uses of the biosciences are legitimate undertakings for states parties to the BWC, but also allows the use of pathogenic organisms or toxins in quantities and for purposes other than use as weapons. However, unlike the CW control regime, there are neither verification provisions foreseen in the BWC nor has an international organization been set up to oversee the implementation of the regime provisions. Due to the collapse in 2001 of the Ad Hoc Group's efforts to negotiate a legally binding verification protocol to the BWC, which would have provided for these structures and mechanisms, states parties are left to address S&T advances at the BWC review conferences and include their assessment as to relevant S&T developments and their impact on the BW control regime in the final documents issued by these conferences.

At the First BWC Review Conference in 1980 the reaffirmation of the comprehensive scope of Article I merely stated that "The Conference believes that Article I has proved sufficiently comprehensive to have covered recent scientific and technological developments relevant to the Convention."[18] The brevity of this statement is not surprising as the biotechnology revolution was still in its infancy.

With advances in biotechnology and genetic engineering steadily progressing, the Second Review Conference in 1986 saw the need to be more specific in its Final Declaration by mentioning the fields that states parties were most concerned about being misused. Therefore, the 1986 Final Declaration singled out "the fields of microbiology, genetic engineering and biotechnology, and the possibilities of their use for purposes inconsistent with the objectives and the provisions of the Convention". It continued that "Article I applies to all such developments" and "that the Convention unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production."[19]

The Final Declaration of the Third Review Conference in 1991 basically repeated that of 1986. States parties at the Fourth Review Conference in 1996, however, felt the need to add to the

previous statement by pointing out that "any application from genome studies" was covered by the BWC's prohibitions as well.[20] Thus, the states parties proved to be very perceptive of future applications of scientific breakthroughs and included genome studies applications well before the human genome was decoded.

The continuous and accelerating progress in various areas of the life sciences between the Fourth and the Fifth Review Conferences was reflected in a number of submissions by states parties to the Fifth Review Conference, held in 2001. As the US statement explained:

> Since the 4th Review Conference in 1996, there have been significant advances in the field of biotechnology. … Of special interest to the BWC are applications in directed molecular evolution (i.e., genetic modification), proteomics, bioinformatics, and vaccinology. The number of countries which are developing and enhancing their biotechnology capabilities continues to grow as the applications continue to expand into commercial sectors ... .[21]

South Africa focused in its contribution "exclusively on developments in terms of biocontrol agents and plant inoculants",[22] thereby reminding states parties that the prohibitions of the BWC apply to biological warfare against plants—and animals, for that matter—as well. Unfortunately, due to the failure to negotiate a Final Document during the Fifth Review Conference, these interpretations by BWC states parties concerning scientific advances of relevance to the BWC have not been recorded in a consensual document.

In sum, the CW control regime in terms of organizational structures and processes is much better equipped to deal with S&T advances that might endanger the effectiveness and robustness of the regime than the BW control regime is. However, as the examples of the changes in the chemical industry and the resurgent interest in chemical incapacitants show, when it comes to tackling S&T challenges head on, the willingness of CWC states parties to engage in these issues leaves much to be desired.

When it comes to tackling S&T challenges head on, the willingness of CWC states parties to engage in these issues leaves much to be desired.

The biotechnology revolution and the future of CBW controls

It is commonly assumed that the biotechnology revolution and the increased utilization of genetic engineering will only impact the BW control regime, and not (or only marginally) the CW control regime. Yet what is often overlooked is the fact that many of the products flowing from the biotechnology revolution that can impact life processes at various levels are basically chemical compounds. All chemical compounds that have toxic properties fall under the prohibitions of the CWC. More specifically, the dangers stemming from uncontrolled twenty-first century chemistry are twofold: first, new toxic biochemical compounds, which are highly effective at low dosage levels, could be developed and used as CW. This would undermine the prohibitory norm against CW. The second danger lies in the possible circumvention strategies for the production of known—or novel—CW agents that these new technologies might offer to a determined proliferator. Developments with respect to both of these areas are likely to challenge our current understanding of what is a chemical weapon.

The chemistry of the twenty-first century is a far cry from the one of the 1980s, which guided negotiations for the CWC verification regime. Chemistry now utilizes other scientific disciplines and technologies in its quest for new chemical compounds. Especially in the area of drug development and delivery, scientific and technological advances in biotechnology and genomics, robotics,[23] information technology[24] and nanotechnology[25] act as enablers of combinatorial chemistry and high throughput screening, which in turn have become the driving forces in pharmaceutical research and development.[26]

The genomics revolution, in particular progress in functional genomics (the ability to attribute specific functions to a particular gene), furthers our understanding of fundamental life processes at a molecular level. To mention but a few examples, such research is concerned with allergies and immunology, breathing, sleep and depression. Clearly, all of this work is geared towards a better understanding of disease origins at the genetic level in order to treat or cure these diseases. However, the use of a "knock-out gas" in the Moscow theatre crisis serves as a powerful reminder that drugs with perfectly legitimate medical applications might be turned to a different use. Although in the Russian case this use was by state authorities, the spread of technologies and knowledge brings such misuse potential well within the reach of sub-state groups like terrorist organizations.

The biotechnology revolution is producing vast amounts of new data, both in relation to genomes that are sequenced and new chemical compounds that are produced by combinatorial means and have to be screened for their properties and potential as new drugs. According to a conservative estimate,[27] more than 1 million such compounds are screened each year in the US alone, 50,000 of which are subsequently eliminated from further consideration because of their toxic properties. Yet developments in this area are progressing rapidly as well: in order to reduce drug development times a new information system called DrugMatrix was developed by three US companies.[28] This system contains a 2,000 drug reference set and "models the new entity's probable effects (biological, toxicological, and clinical)". The misuse potential of a system that allows for the identification of new chemical compounds according to their toxicity is obvious. As data mining algorithms become more elaborated,[29] the potential to identify specific toxic effects of chemical compounds and exploit them for malign purposes will increase.

The technology revolution across the life sciences will not only affect drug development but also drug delivery. As one recent review of the field has outlined, "currently, the most potential is offered by pulmonary delivery, i.e. inhalation of drugs to the deep lung."[30] In order for this to be effective it is necessary to create "drug particles or droplets … in the range [of] 1–5 microns."[31] This is exactly the particle size that was sought in the weaponization of known CW and BW agents, making the dual-use aspects of new discoveries in this realm all too clear. The potential of misuse is compounded by the application of nanoparticles, which could either be used to increase the susceptibility of lung tissue to a CW agent or be directed at specific target tissue in the human body, such as in order to block defence mechanisms.[32]

The potential of misuse is compounded by the application of nanoparticles, which could either be used to increase the susceptibility of lung tissue to a CW agent or be directed at specific target tissue in the human body, such as in order to block defence mechanisms.

Similarly, with respect to the BW control regime, S&T developments—such as in the fields of neurology and immunology—are racing ahead.[33] As no control mechanisms exist, the gap between the technologies that should be monitored and controlled and the actual controls being agreed upon and implemented is widening constantly. If this situation persists for much longer it is questionable whether the political will can be mustered to set up a multilateral system of controls that would actually provide warning of a misuse of cutting-edge life-sciences research.

Around the time of the Fifth BWC Review Conference, several developments in the life sciences occurred that many observers saw as opening wide the door for potential misuse. The "contentious research" in question involved:[34]

- unintentionally potentiating the virulence of the mousepox virus through inserting an IL-4 gene into the mousepox genome;
- synthesis of the poliovirus genome from "chemically synthesized oligonucleotides that were linked together and then transfected into cells", thereby creating an infectious virus from scratch;[35] and

- transfer of the virulence factor of *variola major* (which causes smallpox) into the *vaccinia* virus, which is of much lower virulence and usually used for vaccinations against smallpox.

Concerns expressed over these experiments in the media and policy communities (mostly in the United States) led the US National Academies of Science to establish a committee to investigate ways to prevent S&T advances from being misused for hostile purposes.[36] The so-called Fink Committee issued a set of recommendations to address the new environment in which the life sciences are operating and to prevent scientific advances from being misused by states or terrorist groups in BW programmes, while at the same time "enabling legitimate research to be conducted."[37] The Fink Committee's recommendations included *inter alia* "self-governance by scientists and scientific journals to review publications for their potential national security risks" and the establishment of a National Science Advisory Board for Biodefense (NSABB) "to provide advice, guidance, and leadership for the system of review and oversight …".[38]

With a view to the recommendation concerning restrictions on the publication of problematic research a number of journal editors had already imposed restrictions on themselves before the publication of the Fink Committee's report: in January 2003 a group of thirty-two journal editors agreed on guidelines related to "Scientific Publication and Security". After first being published in *Science*, the statement also appeared in February in the *Proceedings of the National Academy of Sciences* and in *Nature*. The authors of the statement:

> recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published research, but also recognize that research in the very same fields will be critical to society in meeting the challenges of defense. … We recognize that on occasion an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published.[39]

The NSABB has been established in the office of the director of the National Institutes of Health.[40] The NSABB advises on and recommends "specific strategies for the efficient and effective oversight of federally conducted or supported dual-use biological research, taking into consideration both national security concerns and the needs of the research community."[41] The Board is composed of a maximum of twenty-five voting members whose areas of expertise cover *inter alia* genomics, bacteriology, virology, laboratory biosafety and biosecurity, public health, pharmaceutical production, bioethics, national security, intelligence and law enforcement. In addition, more than a dozen government departments and agencies are ex officio members of the board.[42]

Although these parallel controls of S&T that are increasingly taking shape in the United States point in the right direction, they face the same shortcomings as do the deliberations by BWC states parties in the so-called new process created by the last BWC Review Conference: both of these attempts do not lead to coordinated action at the international level and are thus decoupled from developing the regime as a whole. At the very least these shortcomings would have to be remedied to make a substantial contribution to BW control efforts. Moreover, in the area of CW controls some of these measures would have to be taken on board as well. In order to prevent the misuse of twenty-first century chemistry, CWC implementation cannot continue as if the regime existed in a time warp. Otherwise, S&T advances in chemistry, biology and the life sciences in general can be expected to again leave their mark on military thinking and the history of warfare.

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Notes

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5. See SIPRI, *op. cit.,* pp. 71–75.
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9. Also known as the BTWC. See <www.opbw.org> for the convention's text and most review conference documents issued over the thirty-year history of the BWC.
10. See <www.opcw.org> for the CWC's text and other useful related information.
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14. See the website of the Sunshine Project for documentation of the US non-lethal weapons programmes, at <www.sunshine-project.org>.
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18. *Final Declaration of the First Review Conference*, document BWC/CONF.I/10, p. 2, at <www.opbw.org/rev_cons/1rc/docs/final_dec/1RC Final Doc.pdf>, last accessed 12 July 2004.
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35. Ibid., p. 27.
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37. Ibid., p. 32.
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The malign misuse of neuroscience

Malcolm DANDO

In discussing the possible hostile misuse of the ongoing revolution in the life sciences, George Poste famously suggested that we need to think "beyond bugs" and to consider what he called "the brain bomb". He explained, "as we begin to understand the exquisite molecular mechanisms that regulate this remarkable structure called the human body ... the ability to understand those circuits means that simultaneously we gain the capacity to scramble them".[1]

Certainly there is a strong opinion in the commercial world that there will be rapid developments in applicable neuroscience in coming decades,[2] and it is also well known that there is keen military interest in the development of new "non-lethal" weapons based on such discoveries.[3]

Many scientists and other observers of the revolution in the life sciences may, however, think that little has changed since the days of the middle of the twentieth century when the first crude incapacitants (such as the fentanyl derivative[4] used to break the Moscow theatre hostage siege) were developed on the back of the initial detailed discoveries of chemical means to help people with mental illnesses. Poste clearly does not agree. He believes an understanding of brain circuits, which allows us to scramble them, means that "you can engineer ... a complete spectrum of activity from transient immobilization ... to catastrophic effects which can be acute or chronic".[5]

This article aims to demonstrate that point by reference to two specific examples of our increasing knowledge of the brain. There are many such examples that could be described so it must be understood that these are merely illustrative of the general problem of the increasing extent of our dual-use science and technology. We must begin, however, with a brief review of the basis of our knowledge of the nervous system.

Structure and function in the nervous system

Only in the last few centuries has the link between the brain and behaviour become clear, and only at the end of the nineteenth century was it demonstrated that the nervous system was made up of billions of separate nerve cells or neurons. We now know that during evolution complex networks of such neurons have developed in order to effect certain behaviours. Whilst the neurons of the central, peripheral and autonomic nervous systems vary enormously in form and function, they can be classed into three broad groups: *sensory neurons*, which convey information into the central nervous system; *effector neurons*, which carry information out of the central nervous system to muscles

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and other effector organs; and *interneurons* within the central nervous system, which link the sensory and effector neurons and also have links with one another.

Information is conveyed *within* individual neurons by electrical means—generating nerve impulses that can be recorded and displayed on an oscilloscope. In the twentieth century it was shown that information is conveyed *between* neurons predominantly by chemical means. When a nerve impulse (an action potential) travelling along the long extension (axon) of a neuron arrives at a junction (synapse) with another neuron, it causes the release of a neurotransmitter chemical from the pre-synaptic cell. This chemical affects the electrical properties of the post-synaptic neuron through its interaction with specialized receptor proteins embedded in the surface membrane of the post-synaptic cell. It has been shown that there are numerous kinds of neurotransmitter chemicals that, depending on the specific receptors involved, can either cause an electrical change that enhances the possibility of an action potential occurring in the post-synaptic cell or, alternatively, decreases that possibility. Various chemical mechanisms ensure that the neurotransmitter is cleared from the synaptic area, so that its effect does not persist and so that another action potential in the pre-synaptic neuron can exert its effect in turn.

This then is the basis for modern insights into how the brain—and therefore behaviour—can be manipulated by chemical means. Clearly, as our understanding of the neuronal circuits underlying specific behaviour increases, and we understand more about the neurotransmitters and receptors functioning in such circuits, we have more chance of helping people who are suffering from various malfunctions of the nervous system (mental illnesses). It has to be accepted, however, that such information may be misused by those with malign intent.

Post-Traumatic Stress Disorder

According to the standard *Diagnostic and Statistical Manual of Mental Disorders* you have Post-Traumatic Stress Disorder (PTSD) if:

> You have been exposed to a horribly traumatic event that made you feel extremely fearful, helpless, or terrified.
>
> You keep reexperiencing the event in different ways, such as upsetting memories or nightmares; flashbacks that it is happening again; or having a severe reaction whenever you are exposed to anything that reminds you of it.
>
> You avoid things that are associated with the traumatic event; cannot remember the details of what happened; feel detached from everyday life; or feel like you will never have a normal life again.
>
> You are jumpy and hypervigilant, have trouble sleeping, have angry outbursts, or have trouble concentrating.
>
> These symptoms persist for at least a month and cause either severe distress or problems with school, work, or other people.[6]

The human species has evolved mechanisms to ensure that dangerous events are well remembered for the obvious good reason of avoiding such events, or taking great care about them, in the future. If this response gets out of hand we call it PTSD, and it clearly causes great distress to those who suffer from it. There is every reason to try to understand how it comes about and to find better ways of dealing with it.

It is not too difficult to discern that PTSD involves at least two components: learning and memory. These concepts may be defined in this way: the acquisition of reproducible alterations in behaviour as

a result of particular experiences is *learning* whereas *memory* is the storage of the altered behaviour over time. We are clearly dealing here with learning about aversive events and strengthening (consolidation) the memory of such events. The basic elements of the system for dealing with fearful events is built into all mammals so if we hear a loud explosion we will exhibit a startled response and freeze momentarily before the "fight or flight" response kicks in.[7] As one of the main investigators of the fear response, Joseph LeDoux, explained:

> In a situation of danger, a variety of physiological responses occur. Blood is redistributed to the body parts that are more in need (the muscles). This results in changes in blood pressure and heart rate. In addition, the hypothalamic-pituitary-adrenal, or HPA, axis is activated, releasing stress hormones. In general, the body is readied to move quickly. In addition, the brain activates the release of natural opiate peptides, morphine like substances that block the sensation of pain ... .[8]

It is possible to gain much insight into the human fear system from investigations of those in other mammals, like the rat.

It is relatively easy to study the impact of fear on the rat through what is called classical fear conditioning. The rat is repeatedly subjected to a sound (which it does not fear) followed by a mild electric shock (to which it does react with fear). Soon it learns to react to the sound alone in anticipation of the shock. Investigators like LeDoux knew that sound picked up in the ear is processed in the auditory mid-brain, then the auditory thalamus and finally in the auditory cortex (the highest relevant level of the brain).

Surprisingly, when lesions were made in the auditory cortex it was found that rats could still associate the shock and sound and were therefore reacting with fear to the sound alone. The auditory cortex is clearly not required to support such behaviour. Further investigation showed that lesions in either of the sub-cortical levels (auditory mid-brain and auditory thalamus) eliminated the fear conditioning. The information was obviously being processed somewhere beyond the thalamus, but not in the auditory cortex, in order that the fear reaction occurred. This location was found to be the amygdala region of the brain—which was not too surprising since the amygdala has been known for years to be important in emotional responses. LeDoux continued his explanation as follows:

> The low road, or the thalamo-amygdala pathway, is a quick and dirty system. Because it doesn't involve the cortex at all, it allows us to act first and think later. ... We freeze first, and that gives us a few seconds to decide what to do: Run away? Hold still? Try to fight?

If we are in a forest and see a stick that might possibly be a snake we are better reacting immediately as if it were indeed a snake. However, "The cortex—the high road, so to speak—also processes the stimulus, but it takes a little longer". While the amygdala pathway prepares for action, the cortex pathway is simultaneously processing the information, and if it decides that what is seen is actually a stick and not a snake little effort is wasted as it can switch off the emergency response. So the amygdala is involved in the learning process. However:

> In addition, there is a strong consensus that the amygdala is involved in mediating the effects of emotional arousal on memory. Findings of many studies indicate that the amygdala mediates the consolidation of long-term explicit memories of emotionally arousing experiences by influencing other brain regions involved in memory consolidation.[9]

It is this second process of memory consolidation that is surely of more interest in relation to PTSD.

A variety of evidence shows that the amygdala is not the site of long-term memory. For example, "[l]esions of the amygdala ... induced between one week and one month after aversive training do not block inhibitory avoidance performance".[10] So something more complex is happening than the amygdala operating in isolation. In fact, the system is very complex and is far from completely understood. Enough is known, however, to suggest that biologists will decipher it rather quickly.

It is well known that under stress the hypothalamus (the central link between the nervous system and the hormonal system of the body) through a complex process causes the secretion of glucocorticoids (steroids). At the same time the sympathetic (alerting) part of the autonomic nervous system activates the secretion of adrenaline. These two agents, glucocorticoids and adrenaline, have significant effects on the body, but they also affect the functions of the amygdala. There is considerable evidence that adrenaline, despite not being able to pass the protective blood-brain barrier, still has an indirect impact, which leads to enhanced output of a closely related neurotransmitter known as noradrenaline in the amygdala.[11]

However, the noradrenaline does not act alone in this respect. The glucocorticoids released also have an effect in the consolidation of memory of stressful events. Glucocorticoids are able to pass the blood-brain barrier and there they have multiple effects. In particular, glucocorticoid effects on memory consolidation require them to act on the amygdala. Infusion of glucocorticoid agonists (substances that have the same effect) into the amygdala after training enhances retention whereas infusion of antagonists (substances having a blocking effect) impairs retention. Again it can be concluded that the amygdala is the location for the impact of glucocorticoid enhancement on memory consolidation.[12]

A full account of the circuits involved in the total stress response will be very complex,[13] but it is clear that the amygdala is on one of the pathways leading to the initial readiness of the body to respond to danger signals. Subsequently, input from the body leads to noradrenaline and glucocorticoid activation of cells in the amygdala, and output from the activated cells has a considerable impact on the enhancement of memory consolidation by other brain structures. Furthermore, consolidation enhancement via the amygdala can be interrupted by the use of chemical antagonists that interfere with these processes in the amygdala.

What then does this have to do with treatment of people suffering from PTSD? It has been found, first, that less technically detailed studies on humans produce similar results to those on animals.[14] Neuroimaging also shows that the amygdala is selectively activated when negative emotional stimuli are being processed and in fear conditioning. This and much other evidence support the view that the amygdala plays a similar role in humans to that in animals in dealing with frightening situations.

Whilst the events are much more complex than in animals, it can be considered that noradrenaline neurotransmission is crucial in humans too because very traumatic events would lead to overproduction of the transmitter and thus overconsolidation of the memory of these events. As the traumatic memory causes the events to be relived in flashbacks and nightmares a feedback system could therefore lead to the further consolidation of the memory as the body responded again and again to the stress.

This idea of a direct relationship between noradrenaline and memory for emotional events has been tested in humans. Healthy subjects were either given a placebo or propranolol (which passes the blood-brain barrier and opposes the action of noradrenaline) one hour before viewing a series of either neutral or emotionally stressful scenes. One week later people who had received the placebo had significantly better memories of the emotional slides but those who had received the propanolol did not remember them any better than the neutral ones.[15]

Such results have obviously led to efforts to prevent people from developing PTSD, in one example giving victims of car crashes propranolol quickly after the event. Some observers, however, are concerned that such treatment might be used to enable people to carry out dreadful actions and retain no

memory of them. Dr Leon Kass, chairman of the President's Council on Bioethics in the United States, has been quoted as saying "It's the morning-after pill for just about anything that produces regret, pain, or guilt."[16]

Imagine how debilitating it would be for any organization—civil or military—if a large percentage of its members were made very susceptible to PTSD even in relation to relatively minor stressors?

A national co-ordinator for Vietnam Veterans Against the War agreed and argued that such treatment could "make men and women do anything and think they can get away with it". A different possibility, of course, is that those with malign intent might find means—through a chemical agent—to enhance PTSD, not prevent it. Imagine how debilitating it would be for any organization—civil or military—if a large percentage of its members were made very susceptible to PTSD even in relation to relatively minor stressors?

Narcolepsy

We have discussed something of the neurobiology of fear and cognition—but such higher functions rest on a whole set of more automatic homeostatic functions that maintain the body in its normal state. No animal could operate without effective regulation of, for example, its temperature or blood pressure. These kinds of functions are normally regulated from centres in lower parts of the brain near the junction with the spinal cord. Here we will consider an aspect of one regulatory system—sleep—and, in particular, one of its malfunctions, *narcolepsy*. Before discussing narcolepsy and how its investigation will likely lead to means of helping sufferers but also open up new roads to misuse, a brief review of modern knowledge of biological clocks will be necessary.

Many of our basic physiological functions exhibit a circadian (daily) rhythm. Most noticeably, we tend to sleep each night for about eight hours, but other functions—core temperature and production of pituitary hormones, for example—also exhibit such a rhythm. If sensory cues, most importantly light, are eliminated then our sleeping/waking cycle will elongate from twenty-four to about thirty hours. It is therefore clear that sensory inputs affect the basic circadian cycle, but what has been dramatically demonstrated recently is that the basic rhythm is driven by an internal clock located in a group of nerve cells (the superchiasmatic nucleus, SCN) of the front part of the hypothalamus. The output from this intrinsic clock then flows to complex circuits in other parts of the brain to regulate the various circadian cycles. Light input direct from the retina synchronizes the output of the SCN with the twenty-four-hour cycle.[17] What is particularly important is not only that the genetic basis for the cyclic form of output from the SCN (with neuronal firing peaking during the day) has been elucidated, but how this output is integrated from the single cell through the SCN, the brain and then the behaving animal is also increasingly being understood.[18] From the neurobiologists' viewpoint, it is also crucial to note that the role of the different neurotransmitters in circuits governing the various physiological functions is being steadily clarified.[19]

Sleep, of course, is not just a quiescent state the opposite of wakefulness. During the second half of the last century a great deal was learned about what happens when we sleep from recordings of the electrical activity of the brain picked up from electrodes placed on the scalps of volunteers. When we are awake these electroencephalography (EEG) recordings are of low amplitude and high frequency. When we fall asleep we pass through four phases of what is called slow wave sleep in which the EEG recordings have high amplitude and low frequency. If awoken from such sleep, people are confused, find it difficult to think clearly and easily go back to sleep. However, at about ninety-minute intervals a quite different type of sleep appears. This type of sleep is called rapid eye movement sleep (REM) or paradoxical sleep (because the EEG resembles that of the awake state). In this kind of sleep people dream and muscle tone is absent apart from the extraocular eye muscles producing rapid eye

movements.[20] Again, the mechanisms underlying this behaviour are being elucidated—even if we still cannot explain *why* we sleep.

Despite much effort to find cures, there are many people who suffer from sleep disorders such as insomnia, obstructive sleep apnoea and narcolepsy so there is every good reason for further investigation of the underlying neuronal mechanisms.[21] Narcolepsy is characterized by four essential features:

> ... excessive daytime sleepiness (EDS), catalepsy (sudden loss of muscle tone in response to strong emotion such as laughter or anger), hypnagogic hallucinations (dream-like experiences occurring at sleep onset), and sleep paralysis (the inability to move while falling asleep or upon awakening) ... .[22]

The total amount of sleep and REM sleep is of the same order as in people without narcolepsy but, clearly, the control mechanism is severely disrupted with two main problems: "first, an inability to maintain wakefulness, and second, intrusion of REM sleep into wakefulness or at sleep onset resulting in hallucinations, sleep paralysis, and possibly catalepsy".

Whilst this condition is quite widespread and debilitating, until recently very little was known about its causation. It was known that some dog families exhibited very similar symptoms to those of human narcolepsy, and this suggested a genetic basis for the disease. However, as there was also a strong link with aspects of the immune system, an autoimmune disorder was also strongly suspected and this, of course, might have an environmental trigger.

This whole field of research was revolutionized over a few years at the turn of the century through the discovery of two new transmitters produced by cells of the hypothalamus. These new transmitters are called hypocretins (Hcrt-1 and Hcrt-2), and are clearly the key to understanding narcolepsy and a good deal of the normal sleep mechanism. The dog narcolepsy cases are associated with genetic mutations of this system, mice with targeted deletions of the gene for these transmitters display symptoms of narcolepsy, and the majority of humans with narcolepsy and the associated immune system characteristics lack hypocretins in their brain.

The hypocretins and their associated receptors were discovered in 1998.[23] Progress in elucidating the nature of narcolepsy has been phenomenal since these discoveries. Human Hcrt-1 and Hcrt-2 are very similar to those found in other mammals. These transmitters have been strongly conserved during evolution, suggesting important functions. In all experiments carried out so far, hypocretins have had excitatory effects on post-synaptic cells. For example, the brain noradrenergic neurons, which are important components of the arousal and vigilance systems, are densely packed with receptors for hypocretins.

Narcolepsy affects twenty to sixty people per 100,000 of the population in western countries. This is about the same level of incidence as Parkinson's disease or multiple sclerosis, but unlike those diseases it usually begins in the teens or twenties when it is very debilitating at a crucial formative period and continues to be so for many years. At present most patients require drug treatment, such as stimulants or modafinil, to combat their excessive daytime sleepiness.[24] Other symptoms have to be treated with other drugs and none are free of side effects. The need to find better treatments is obvious and research will clearly continue to achieve this end.

Work on dogs with narcolepsy has supported the view that a noradrenaline neurotransmitter mechanism is involved. High activity of cells producing this neurotransmitter occurs in wakefulness. In normal sleep, as the characteristic synchronization of the EEG occurs, noradrenaline and other associated transmitter activity decreases. During REM sleep there is little noradrenaline activity. Clearly, drugs that affect REM sleep can have profound effects, as can natural agents such as the hypocretins, which

strongly affect the noradrenergic (arousal) neurons and have excitatory effects. In particular, human beings with narcolepsy have low or non-existent levels of hypocretins in their brains and thus would lack this excitatory input to the noradrenergic neurons. These would therefore be much less active, which probably explains many of the symptoms such as excessive daytime sleepiness. Certainly, direct application of Hcrt-1 onto cells of the noradrenergic neurons leads to an increase in wakefulness and a decrease in sleep in rats.[25]

In some dog families narcolepsy is caused by a gene mutation. In humans there may be a genetic susceptibility in some people, but an autoimmune causation—presumably with an environmental trigger involved—is the most likely explanation for most human cases. If this is indeed found to be the correct explanation, given the ongoing elucidation of the mechanisms of normal sleep patterns and the abnormal sleep patterns of narcolepsy, it is not impossible that means will be found to trigger narcolepsy. Such a disruption of normal functioning would, of course, be profoundly debilitating for an individual or groups of people affected.

To those who find that idea far-fetched, it has to be pointed out that the drug Provigil (modafinil), which is used to help people with narcolepsy keep awake during the day, is now being used by some armed forces as a means of prolonging the hours that troops can stay awake while on active duty.[26] Thus intentional modification of behaviour related to knowledge of narcolepsy is already being carried out.

Conclusion

It has to be stressed again that these are but two examples of our growing understanding of the molecular basis of human behaviour and that there are many other such examples. The rapidity of the recent elucidation of the causes of narcolepsy is quite startling and should remind us that new knowledge can be discovered very quickly. Fundamentally, however, what the work on PTSD and narcolepsy illustrates is that much of that growing knowledge is dual-use and could be subject to hostile misuse if the prohibitionary norm embodied in the 1925 Geneva Protocol, the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC) is not upheld in coming decades. One urgent requirement, if that objective is to be achieved, is for neuroscientists—along with everyone else involved in the life sciences—to regard it as central to their work to uphold the norm against the hostile use of their science and technology. For that reason the BTWC meetings in 2005 related to codes of conduct for scientists are of immediate and critical importance.

The work on PTSD and narcolepsy illustrates that much of that growing knowledge is dual-use and could be subject to hostile misuse if the prohibitionary norm embodied in the 1925 Geneva Protocol, the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC) is not upheld in coming decades.

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Assault on the immune system

Kathryn NIXDORFF

The immune system plays a crucial role in protecting against infectious diseases, and the ability of a micro-organism to cause disease can only rightly be defined within the scope of its interaction with the immune system. To be a successful pathogen, a micro-organism must possess strategies that enable it to evade immune defence mechanisms. Immune responses are regulated to a great extent through the production of *cytokines*, bioregulators that can exert both positive and negative effects depending upon the amounts produced. The immune system is thus very vulnerable to malign use of both immune evasion strategies and immune bioregulators.

In this age of rapid biomedical and biotechnological advances, far-reaching manipulations of micro-organisms are now possible that can change their properties drastically. Experiments to manipulate micro-organisms are being carried out daily, with mostly peaceful aims in mind, such as the elucidation of the pathogenic mechanisms of an infectious agent, which could in turn point the way to the development of better prophylactic and therapeutic measures to counter infections more successfully.

However, it has become evident that these experiments can lead to the creation of particularly dangerous micro-organisms that can evade the immune responses in devastating ways. A prime example is the inadvertent creation of a killer mousepox virus by researchers trying to develop a virus-based contraceptive vaccine to control the rodent population in Australia.[1]

In addition to micro-organisms attacking the immune system, certain *biochemical agents* (substances produced by living organisms that act on biological systems but are chemical in nature) are also of particular concern. This represents a change of focus away from the possibility of using micro-organisms malignly *to cause infectious diseases* to the possibility of using biochemical agents *to disrupt the operation of biological systems*. It is also evident that with the rapid expansion of research activities in the areas of molecular biology and biotechnology, advances occur at an exponential rate—along with increasing capabilities for misuse.

In order to appreciate the dilemma of dual use and the possibilities of misuse in this area, a brief description of scientific and technological aspects underlying research activities in this field, including the elements of the innate and the adaptive immune systems, will be given. Because a successful pathogen has to be able to evade immune defence mechanisms, a few evasion mechanisms will be

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described before turning to an overview of the vulnerability of the immune system to modulation with bioregulators and targeted delivery systems, to modulation after immunization, and the potential for an assault on the immune system in interaction with the neuroendocrine system.

Structure and function of the immune system

The hallmark of the immune system is its ability to respond to an invasion of the body by micro-organisms or toxic components in ways that afford protection against detrimental effects that could occur. The responses of the immune system include both non-specific (innate immune system) and specific (adaptive immune system) components (see Table 1). These react in different ways to *antigens* (chemical components—mainly proteins and polysaccharides—of the micro-organisms), which are substances that can elicit an immune response if they are foreign to the host. Many antigens are not harmful by themselves, the exception being, of course, toxins. Micro-organisms are composed of a mosaic of many different antigens.

Antigens let the immune system detect what micro-organism is present, because there will be antigens that are very specific for a particular micro-organism. The immune system reacts to these antigens, mounting defence mechanisms that are designed to get rid of the micro-organisms. The non-pathogenic micro-organisms are removed readily, but the immune system must fight with pathogens and, as a result, initiate a response directed against those micro-organisms.

INNATE IMMUNE SYSTEM

The innate immune system represents the all-important first line of defence against pathogens and is absolutely essential for keeping an infection in check before adaptive immunity can be induced. If innate immunity is malignly attacked, the battle against infections is lost from the start.

The innate immune system includes components that are present and ready for action even before an antigen challenge is encountered. These cellular and molecular components are less specific than those of the adaptive system. That is, they are not specific for a particular antigen but react to classes of antigenic substances from micro-organisms called pathogen-associated molecular patterns (PAMPs). A simple analogy using car models and a specific manufacturer can be used to illustrate. All models of Volkswagen cars carry an identical VW emblem. A PAMP is like the emblem, which is present on all different models of Volkswagen vehicles. Any vehicle carrying this emblem would be recognized as manufactured by Volkswagen. However, this emblem provides no information as to the particular model of vehicle. This is very similar to the way in which the innate immune system recognizes many different micro-organisms carrying a particular PAMP as a class of micro-organism, but it is not able to identify the particular micro-organism. The adaptive immune system, on the other hand, is able to distinguish one particular micro-organism from another by recognizing other, more specific or distinctive, features of the model.

PAMPs are recognized by receptors on the cell's surface. Changing analogies, a PAMP could be considered as a key, and the receptor a lock. When a PAMP key fits a receptor lock, an immune response is "unlocked" within the cell.

Although several components of the innate immune system must be activated by activator substances (agonists) such as PAMPs in order to initiate an effective immune response, this activation can occur relatively rapidly, within minutes or hours.

The importance of innate immunity relative to the control over infectious diseases can be seen by the fact that the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health has expanded its programme significantly in order to attract immunologists to the area of biodefence research.[2] In this regard, NIAID reported that it "awarded a multi-component grant to create an 'encyclopedia' of innate immunity: a comprehensive and detailed picture of this ancient, essential first line of defense against bacterial and fungal diseases". The stated goal of this undertaking is to gain knowledge that could lead to the development of treatments for infectious diseases. At the same time, however, this information could provide a blueprint for malign attack of the innate immune system.

Adaptive immune responses

The cellular components of adaptive immunity (white bloods cells called *lymphocytes*) must be driven by antigens to go through different phases of activation, expansion (multiplication of cells) and differentiation in order to carry out their functions. Therefore, adaptive immune responses take days to activate, rather than the minutes or hours of an innate immune response. Additionally, adaptive immunity has a "memory" that allows a quicker and stronger response the next time that specific pathogen is encountered. Thus, adaptive immunity affords a high degree of specific protection, but it takes time to be induced.

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When receptors on the surface of a lymphocyte bind to specific antigens, this initiates a signal that is carried to the inner part of the cell, leading to its activation—which will enable it to carry out its function. The function of B lymphocytes is to produce antibodies while the function of T lymphocytes is to help regulate immune responses (in the case of T helper cells) or to initiate the death of infected cells (in the case of cytotoxic T cells).

The lymphocytes of adaptive immunity (B and T cells) are able to react to an antigen challenge with a high degree of specificity. As a result, immunity is afforded against one specific infectious agent carrying those antigens. However, B and T lymphocytes recognize antigens in different ways. B lymphocytes recognize the antigen itself, while T lymphocytes can only recognize an antigen when it

Table 1. Features of innate (non-specific) and adaptive (specific) immunity

Feature	Innate Immunity	Adaptive Immunity
Characteristics		
Specificity for micro-organisms	Relatively low (PAMPs)[a]	High (specific antigens)
Diversity	Limited	Large
Memory	No	Yes
Components		
Physical and chemical barriers	Skin, mucosal epithelia; anti-microbial chemicals, e.g. defensins	Cutaneous and mucosal immune systems; secreted antibodies
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes (B cells that produce antibodies; T cells that carry out cell-mediated reactions)

Source: modified from A.K. Abbas, A.H. Lichtman and J.S. Pober, 1997, *Cellular and Molecular Immunology* (third ed.), Philadelphia, W.B. Saunders Company.
[a]PAMPs: pathogen-associated molecular patterns

is on the surface of another cell, bound to a specific molecule (known as a major histocompatibility complex, or MHC, molecule). MHC molecules serve an important function in the body as they allow the body to identify the difference between self and non-self. This self/non-self distinction that is dictated by MHC molecules determines to a great extent uniqueness at the cellular level. This is encountered when an organ from one individual is transplanted to another. The immune system identifies the MHC molecules of the transplanted organ as foreign and mounts a defensive response. If this natural response is not successfully suppressed though medication, it can lead to rejection of the transplanted organ. Only when the MHC molecules between donor and recipient are identical (i.e. self, as in the case of identical twins) will the immune system not respond.

However, when self MHC molecules present foreign antigens (such as antigens from a virus that has infected a cell of the body) to cytotoxic T lymphocytes, these respond with a reaction leading to the death of that virus-infected cell. In this way, the cell that was infected with the virus can no longer serve as a factory for producing more virus particles. Thus, T lymphocytes recognize that the MHC molecules are self, but what is attached to them (in this case, a foreign antigen) isn't.

Macrophages

Macrophages are a type of white blood cell that devours foreign antigens and invading microbes and then assists T lymphocytes in recognizing and reacting against cells that have been invaded by pathogens. They occupy a central position in the immune system, being active both in innate and adaptive immune responses.

In innate immunity, macrophages are activated through engagement of receptors on the cell surface by substances called agonists. Most prominent among receptors on the macrophage surface are the Toll-like receptors (TLRs), which bind PAMPs. The binding of a PAMP (agonist) to a TLR activates the cell to produce *cytokines*.[3] Cytokines serve as messengers in the immune system; they facilitate communication among immune system cells and between immune system cells and the rest of the body. One type of cytokine is known as an *interferon*; interferons are essential for a successful defence against many viral infections. Macrophages are also potent producers of *proinflammatory cytokines,* which mediate reactions designed to fight infections.

When cytokines are produced in moderate amounts, they contribute greatly to defence mechanisms directed against pathogens and to the healing process in general. If they are produced in particularly large amounts or continually during chronic illnesses, this can lead to various disorders such as autoimmunity, coronary insufficiency, thrombus formation, hypoglycemia, and in some cases even to shock and death.[4] On the other hand, if their production is suppressed, protection against infections may be compromised. Therefore, the activities of cytokines are particularly vulnerable to malign modulation to induce hyper- or inhibiting responses that could have detrimental effects.

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Macrophages bridge innate and adaptive immunity. After they have devoured foreign antigens or microbes as part of their role in innate immunity, they assist B cells and T cells in adaptive responses by producing cytokines that regulate lymphocyte function or by presenting antigens bound on MHC molecules so that these antigens can be recognized by T cells. Furthermore, they increase other substances (called co-stimulatory molecules) on their cell surface that can generally enhance their interaction with T cells.

Immune evasion by micro-organisms

In order for a micro-organism to be pathogenic, it must have a mechanism that permits it to evade immune defences. There is a great deal of interest in studying these processes with the aim of developing means of countering evasion strategies, which would permit, for example, the development of vaccines that defeat the evasion tactics of antigenic variation used by micro-organisms. At the same time, exploitation of evasion strategies with malign intent should be of particular concern. Some evasion strategies are described below.

Antigenic variation or mutation

Some micro-organisms frequently mutate or vary their antigenic composition so that they can no longer be recognized by the antigen receptors of immune system cells. With regard to particular antigens, some micro-organisms exhibit a much higher mutation rate than is normal. This is encountered, for example, in connection with the flu virus and HIV. This is one reason these infectious diseases are resistant to vaccination. In addition, some micro-organisms are subject to mutation due to pressures exerted by the immune system itself. Ironically, when the immune system reacts to a micro-organism, it is, in effect, encouraging the micro-organism to mutate.[5] In this regard, those antigens that elicit the strongest immune response will be subject to the greatest immune selection pressures.

Regulation of complement activity

One of the most important components of immunity is the *complement system*. This is some thirty or so substances in blood serum that become activated in a series of reactions during an immune response (known as a "complement cascade"). This process can be activated by microbial substances during innate immune responses, but also by antibodies in adaptive responses.

This is a further example of the importance of system balance. Insufficiencies in key components of complement would result in a devastating outcome with regard to certain infectious diseases, despite the use of antibiotics or other chemotherapeutic agents. On the other hand, unrestrained complement activation would cause severe damage to bystander cells. In a healthy body, complement activity is held in check by a variety of regulatory factors, known as regulators of complement activation (RCA).[6]

Members of the poxvirus, herpesvirus and retrovirus families produce homologues that mimic RCA proteins and are thus able to escape complement action.[7] The smallpox virus *Variola major* causes a serious, virulent infection in humans, while the virus that is used for vaccination against smallpox, vaccinia virus, usually causes only a very mild or even unapparent infection, at least in individuals with an intact immune system.

A component of the smallpox virus that may contribute to its pathogenicity (ability to cause disease) is the smallpox inhibitor of complement enzymes (SPICE). SPICE has the ability to inactivate one of the key complement components (human C3b) that serves to induce the innate immune process by which cells engulf material which is eventually digested, destroyed or killed. By inactivating the complement activity, a vital area of innate immunity would be disabled. Vaccinia virus also has a complement regulatory protein (called vaccinia virus complement control protein, VCP), which is, however, much less effective (100-fold less) than SPICE. In a recent report,[8] researchers mutated the

VCP gene of vaccinia virus to have the same nucleotide sequence as SPICE. The recombinant mutant VCP proved to be much more efficient than normal VCP in inactivating complement in a test tube reaction. Although the researchers did not actually outfit vaccinia virus with this mutated gene, the work was only one step away from this manipulation. Presumably, vaccinia virus with the mutated gene would be much more pathogenic.

Regulation of cytokine activity

As previously mentioned, interferons are cytokines produced by cells to protect them from viral infection, and anti-interferon strategies are a part of the immune evasion repertoire of most viruses. These mechanisms include the production of soluble versions of interferon receptors, which act as decoys. These decoys bind and inactivate interferons before they reach their "destination"—normal, membrane-bound receptors.[9]

Other cytokines, such as proinflammatory cytokines, are essential in directing the activities of different arms of the immune system. One of the most interesting evasion mechanisms identified in recent years is the mimicry of cytokines and cytokine receptors by large DNA viruses (herpesviruses and poxviruses). Cytokine homologues might redirect the immune response for the benefit of the virus, for example by suppressing the anti-viral activity of cytotoxic T cells. Alternatively, viruses that infect immune cells might use these homologues to induce signalling pathways in the infected cell that promote virus replication.[10] Furthermore, soluble cytokine receptors made by the virus might neutralize cytokine activity before the cytokines could react with their normal, membrane-bound receptors.

Inhibiting programmed cell death

A further immune evasion strategy includes the production of a variety of viral inhibitors of cell death (apoptosis), the so-called programmed cell death. In this regard, apoptosis can be viewed as a response to limit the intracellular propagation of viruses. The immune system recognizes a cell that has been infected by a virus through the presentation by that cell of fragments of viral proteins bound to MHC molecules on the surface of the cell. As stated above, unlike a B lymphocyte, a T lymphocyte will only recognize a virus that is attached to a MHC molecule. This recognition leads to the activation of cytotoxic T lymphocytes, which attack and kill the cell through the induction of apoptosis.

Some viruses can cause the suppression of the production of MHC molecules. This would mean that viral antigens would not be bound to MHC molecules and could not be recognized by T cells. The cell and therefore the virus production factory would be protected from cytotoxic T lymphocyte destruction.[11] Alternatively, viruses such as cytomegalovirus induce the expression of a certain type of MHC molecule that can bind a receptor on the surface of natural killer cells, inducing suppression of the activity of these cells that are normally an important component of innate immunity.[12]

Vulnerability of the immune system to modulation with bioregulators

In addition to immune evasion by pathogens, there has to be a great deal of concern about the possibility of modulating immune responses in a negative way with bioregulators that are not micro-organisms, but rather substances found normally in the body that regulate biological processes.

The inappropriate production of proinflammatory cytokines can be taken as an example of malign use of bioregulators. Enhancing the proinflammatory cytokine production by using PAMPs to engage Toll-like receptors on the surface of macrophages could at the very least lead to sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite (normally signs that the immune system is "kicking in").[13] However, if the proinflammatory cytokines are produced in particularly large amounts, this could lead to autoimmunity, or eventually even to shock and death.[14] On the other hand, inhibiting the production of these cytokines by using bioregulators that can negatively regulate their synthesis might result in a lack of innate immune protection.

If the proinflammatory cytokines are produced in particularly large amounts, this could lead to autoimmunity, or eventually even to shock and death. On the other hand, inhibiting the production of these cytokines by using bioregulators that can negatively regulate their synthesis might result in a lack of innate immune protection.

A second example of modulation of immune responses with bioregulators concerns "super-antigens". The immune system is particularly vulnerable to attack by certain super-antigens. Normally, less than 0.01% of B or T lymphocytes respond to a particular antigen. In contrast, a number of super-antigens has been described that can react with a significant proportion of T lymphocytes (between 5–25%).[15]

For example, the bacterial product *Staphylococcus* enterotoxin B (SEB) is a biological agent that also falls into the category of a potential chemical weapon. This toxin was on the US list of favoured anti-personnel agents as early as 1949[16] and was apparently weaponized by the US Army prior to the negotiation of the Biological and Toxins Weapons Convention (BTWC).[17] It has also been the subject of extensive research in the biomedical literature. SEB acts as a super-antigen in that it can activate a large proportion of T lymphocytes to produce excessive amounts of cytokines, which can cause systemic reactions including inflammation, fever, widespread blood clotting and shock.[18]

Recently, a B cell super-antigen has been described that can bind up to 50% of the B cell population, resulting in an increased rate of apoptosis (death) of the bound cells.[19] Researchers are engineering this B cell super-antigen to achieve higher binding affinities and different specificities in order to specifically target malignant B cell populations such as lymphoma and leukaemia; therefore it could be considered for therapeutic use.[20]

Targeted delivery systems

Targeted delivery systems are components that allow an activity to be targeted to a particular site in the body where that activity is desired. Targeted delivery systems have to be characterized as being strongly dual purpose. While they may be potentially very useful in vaccine and gene therapy, they can also serve as delivery vehicles for dangerous toxins or bioregulators.

One example of a targeted delivery system is a *virus that is used as a vector to transfect a foreign gene* into a cell for the purpose of immunization or for gene therapy. Infection with the virus would lead to the production of the substance encoded by that foreign gene, for example, a foreign antigen.

Vaccinia virus has been investigated for immunization purposes because of its general effectiveness as a vaccine and its large genome, which can carry several foreign antigen genes at once.[21] Alternatively, the development of viruses called adeno-associated viruses as vectors for gene delivery seems promising, as these viruses are defective by nature and have thus never been shown to have any pathogenic effects in humans.[22]

In any case, it is evident that cytokines can be delivered quite effectively by viruses engineered to carry the cytokine genes. In the mousepox experiment previously mentioned, introduction of the

gene for the cytokine interleukin 4 into an otherwise relatively harmless virus had the devastating effect of suppressing an essential arm of immunity, making that virus into a killer.[23] Conceivably, super-antigens as well as other toxins and regulators of complement activation might also be successfully delivered by this means.

Another prime example of a targeted delivery system is an *immunotoxin*. Immunotoxins are molecules that consist of a toxin molecule coupled to an antibody that can bind specific antigens on the surface of particular cells. Most toxin molecules have two parts: the toxic portion and a binding portion. In the case of immunotoxins, the part of the toxin molecule that can bind its usual target has been removed and replaced with an antibody molecule. This permits the antibody to dictate a new target and redirect the molecule. The toxins that have been used to produce immunotoxins include ricin, *Shigella* toxin and diphtheria toxin. Immunotoxins have, for example, been used in tumour therapy. The aim is to target the toxin activity to specified tumour cells in a tumour therapy protocol; in this case, the antibody specificity is directed against tumour cell antigens.[24] A number of clinical trials using immunotoxins have been completed, while others are still going on. To-date, results have been promising in leukaemia and lymphoma patients, but responses in patients with large tumours have been disappointing. In any case, it is conceivable that biologically active substances might be directed to particular targets in combination with an antibody molecule.

Alternatively, molecules can be engineered to contain the toxic portion of a toxin linked to an antigen specific for a particular cell receptor. This antigen would direct the toxin to cells having that receptor. Such engineered molecules are called *fusion proteins*.

Aerosolization of vectors carrying foreign genes could represent an effective delivery system, especially if the vector is a virulent micro-organism, as most infections begin at the mucosa. If the bioregulator is not a micro-organism, such as in the case of cytokines, super-antigens or immunotoxins, successful delivery by the aerosol route depends greatly upon the physical and chemical properties of that vector. The US Army has apparently investigated the absorption of endogenous bioregulators through the aerosol route. It has reported, for example, that the hormone insulin and the proinflammatory cytokine IL-1 were effective in aerosol form in basic pulmonary absorption studies.[25]

There are still many technical problems involved with the use of targeted delivery systems that would serve to limit their application. However, there is tremendous interest in developing these systems further for therapy purposes and we can expect great advances in this area in the near future. As our understanding grows concerning targeted delivery systems, so should our concern regarding their misuse.

As our understanding grows concerning targeted delivery systems, so should our concern regarding their misuse.

Vulnerability of the immune system to modulation after immunization

Activation of the immune system in response to an infection is a vital step in countering the threat posed by the causative agent. Nevertheless, activation of components of the immune system is invariably associated with the enhanced production or exposition of predictable markers that could serve as targets for the delivery of a biological weapon to those sites.

B and T lymphocytes are produced during development of the immune system and prior to encountering antigens to yield an enormous number of cell clones, each being able to respond to a particular antigen.[26] Initially, only a small subset of these clones is able to recognize any one antigen. As previously mentioned, normally less than 0.01% of B or T lymphocytes can recognize a particular antigen.[27] To generate effective immunity, these “resting” B cells and T cell clones must multiply in

response to an antigen challenge in order to amass the numbers required to counter an infection. Depending on the strength of the challenge and the type of antigen, the lymphocytes are activated and then driven to divide ten to twenty times before they cease proliferation and proceed into a phase of differentiation, after which they are able to execute their functions. This represents a considerable expansion of antigen-specific lymphocytes in response to immunization, especially when a vaccine is given in several doses over period of time.

These expanded clones of B and T lymphocytes carry receptors specific for a particular antigen and therefore have an enhanced vulnerability, for example, to being targeted with constructed toxins as discussed earlier. For delivery to B cells, a delivery system might be an engineered or constructed *fusion protein* consisting of the specific antigen (against which the B cells are directed) fused or linked to the toxic portion of a toxin molecule. However, since B cells release antibodies directed against the antigen, the construct might be neutralized and cleared by these antibodies before it could do much damage.

T cells might be a more vulnerable target, as they do not secrete their antigen receptors. However, the delivery system containing the toxin would have to be constructed in such a way as to include the specific foreign antigen fragment bound to the part of a MHC molecule that could be recognized by the T cell. This would be a tall order to achieve at present, particularly in view of the fact that T cells can recognize only self MHC molecules. Nevertheless, new studies are providing greater insight into the fine points of the recognition of antigens presented by MHC molecules to T cells[28] that could make this approach more cause for concern in the future.

In addition to the expansion of specific antigen receptors, immunization also increases the expression of other molecules on the surface of lymphocytes and macrophages. Because of this enhanced expression, these markers could make the cell more vulnerable to attack, for example with immunotoxins.

Assault on the immune system in interaction with the neuroendocrine system

In the preceding article in this issue of *Disarmament Forum* the possibility of the malign misuse of neuroscience was discussed. It is increasingly recognized that the immune system interacts intricately and extensively with the nervous and the endocrine systems. There is a fine network of checks and balances exerted on the operation of all three systems by the elements within them. The perturbation of one system will invariably affect the operation of the others. All three systems are interconnected through the hypothalamus-pituitary-adrenal (HPA) axis via cytokines, hormones, neurotransmitters, peptides and their receptors, and also through hardwiring of neural and lymphoid organs.[29]

To illustrate how one system can affect another, with possible detrimental effects on both, the interaction of bioregulators of the immune system (cytokines) and the neuroendocrine system (hormones and neurotransmitters) within the HPA axis will be taken as an example. First of all, we will take a look at what occurs normally during an infection. Proinflammatory cytokines are produced by cells of the immune system after contact with micro-organisms or their products.[30] These cytokines gain entry into circulation from sites of the immune response in tissues and organs. Normally, they are of sufficiently large size that would prevent them from passing the blood-brain barrier. However, an area of the hypothalamus (the part of the brain involved in the control of such diverse functions as eating, drinking, sleep, thermoregulation, cardiovascular regulation and hormone secretion) represents a window in the barrier, allowing the entry of the cytokines into this region.[31] They subsequently bind to receptors on cells in the hypothalamus and trigger reactions collectively known as sickness behaviour, which is characterized by fever, drowsiness, lethargy and loss of appetite.[32] In this way, the immune system is signalling the brain that rest is needed to help speed recovery.

However, if the reaction is too strong, it could be very debilitating. To keep the actions of the proinflammatory cytokines from getting out of hand, these same bioregulators have another effect on the hypothalamus, which is to induce the production of *corticotropin-releasing factor* (CRF).[33] This is a hormone that is involved in immune regulation. It causes the pituitary to produce adrenocorticotropic hormone (ACTH). This hormone enters the circulation and acts on the adrenal gland cortex to induce the production of glucocorticoids, which have a profound effect in suppressing immune responses, thus turning off the production of proinflammatory cytokines before they are overproduced.

Yet again, balance is key. CRF can have a potentially detrimental effect on the central nervous system if it is overproduced. CRF has been associated with major depression, anorexia nervosa and Alzheimer's disease.[34] Overproduction of CRF has also been implicated with damage to brain cells in animal studies. In these investigations, a stroke was induced in the animals. It could be shown that the damage to brain cells (neurons), which occurred as a result of the stroke, could be prevented, if certain specific substances inhibited the action of CRF. [35]

Normally, these interactions within the HPA axis work as a check and balance system to keep reactions from getting out of hand. However, it is easy to see that a selective overproduction of proinflammatory cytokines could tip the balance to enhance detrimental effects on both the immune and the neuroendocrine systems, leading to debilitating sickness behaviour, significant immune suppression and even damage to brain cells.

Conclusions

In this article, the dual-use dilemma of modern biotechnology has been viewed within a broader scope of consequences by focusing on biological systems as the target of potential malign intent, using the immune system as an example. The possibility of the perturbation of this system not only with micro-organisms designed to evade immune defences, but also with bioregulators that can profoundly affect its function, raises the dual-use dilemma to a higher order of concern. This becomes even more complex when interactions of such vital biological systems as the immune and neuroendocrine systems and their vulnerability to manipulation with bioregulators are considered.

The overwhelmingly rapid advances in biotechnology are pitted against a Biological and Toxin Weapons Convention that has no treaty organization and inadequate mechanisms for verifying compliance.

The overwhelmingly rapid advances in biotechnology are pitted against a Biological and Toxin Weapons Convention that has no treaty organization and inadequate mechanisms for verifying compliance. This situation highlights the need for additional control measures. Preventive arms control criteria emphasize the need for monitoring research to provide possible early warning of potentially dangerous developments. In this regard, serious consideration should be given to the improvement of research oversight, at the least as a contribution to raising awareness of the dual-use problem inherent in biomedical research in the scientific community.

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Non-lethal technologies—an overview

Nick LEWER and Neil DAVISON

Whilst the focus for this issue of *Disarmament Forum* is on chemical and biological weapons, sight should not be lost of the spectrum of non-lethal technologies that are being deployed or under development. These technologies will have an increasing impact on war fighting, peace support operations, civil policing and prison control. It is our purpose here to briefly review the non-lethal field so that biochemical incapacitating agents can be placed in a broader context. There is an extensive literature associated with non-lethal weapons, and readers are directed to this for more detailed information and discussion.[1] We will only highlight the key characteristics and concerns associated with these non-lethal technologies.

There has been a growing interest in non-lethal weapons over the last decade. It has been argued, and in some cases operationally demonstrated, that non-lethal technologies are particularly useful in conflict situations such as when combatants and non-combatants are mixed together (sometimes deliberately); when there is a requirement for alternatives to lethal methods in military peace support operations; when civil law enforcement agencies and prison services have to manage violent lawbreakers; and for riot control. There has also been increasing pressure to develop methods of being able to fight a "bloodless and humane" war, and increasing resistance by domestic constituencies to accept deaths in war operations. Advances in non-lethal technology have been made possible by additional investment both by governments and private companies, and the fact that many of the technologies have dual-use military/civilian applications. Other factors that have fuelled this attention to non-lethal weapons have been debates concerning the revolution in military affairs and the revolution in military technology.

Some analysts have argued that the term "non-lethal" is a misnomer, and that "less lethal" is a more appropriate and accurate description of the weapons described in this paper. We would agree, of course, that there is no guarantee that any weapon can be 100% non-lethal. But we think that the label "non-lethal" has a useful generic function and that the criteria laid out in our following definition clearly set the parameters to what we would call a non-lethal weapon. Non-lethal weapons are specifically designed to incapacitate people or disable equipment, with minimal collateral damage to buildings and the environment; they should be discriminate and not cause unnecessary suffering; their effects should be temporary and reversible; and they should provide alternatives to, or raise the threshold for, use of lethal force. Existing non-lethal weapons include rubber and plastic bullets, entangling nets, irritant sprays such as pepper or tear gas, and electrical stunning devices such as the "Taser" gun. New non-

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Table 1. Non-lethal technologies

Technology	Type(s)	Description	Delivery	Target
Kinetic energy	Impact projectiles	Airfoil; baton (foam, plastic, rubber, sponge, wooden); drag-stabilized (beanbag); encapsulated (water, dye, RCAs, malodorant); fin-stabilized; pads; pellets (single, multiple small/large)	Gun, shotgun, launcher, mortar	AP, AM
	Water cannon	High-pressure jets (may be marked with dye, electrified or have chemical irritant additive)	Vehicle mounted, backpack or fixed-in-place systems	AP
Barriers and entanglements	Nets, chains, spikes	Spikes/strips of spikes, caltrops, barrier to stop vehicles; launched nets to snare people or tangle boat propellers; rigid foams to block windows or doorways	Net launchers; for foam: hand-held, backpack or vehicle mounted tank with spray device	AP, AM
Electrical	Stun weapons	Electrical incapacitation; stun guns, electrical baton, shield, net, water cannon, stun belt, mine/grenade; "wireless" systems under development for use against people or vehicle electronics	From device: either direct contact with electrodes or remotely via wires and barbs; wireless systems will use projectiles with capacitor or pulsed laser for delivery of shock	AP, AM
Acoustic	Acoustic-optical	Flash-bang/stun grenades produce loud noise and bright light	Grenades	AP
	Acoustic generators	Devices that project audible, ultrasonic or infrasonic sound frequencies; may cause pain/discomfort, nausea, disorientation	Acoustic generator devices (fixed, portable or hand-held)	AP
	Vortex generators	Generator that projects a vortex of air at high speed ("acoustic projectile"); may also be used as a carrier of other substances such as chemical agents	Vortex generator devices	AP
Directed energy	High-power microwave (HPM)	Radiofrequency (RF) energy designed to degrade or destroy electronic equipment; electrical or explosive generation of energy	Bomb/missile, fixed or portable device	AM
	Millimetre wave	"Beam" directed at people heats up water molecules in surface of skin causing burning sensation, e.g. "Active Denial System"	Vehicle or aircraft mounted system	AP
	Laser (low energy)	Red and/or green diode lasers to temporarily blind or obscure vision known as "dazzlers" or "illuminators"	Torch-like device (handheld or weapon mounted)	AP
	Laser (high energy)	Chemical laser systems for use against materiel, lethal if used against humans (e.g. "Advanced Tactical Laser"); pulsed chemical lasers to produce "shock wave" to incapacitate people (e.g. "Pulsed Energy Projectile")	Aircraft or vehicle mounted systems under development; desire for handheld systems in the future	AP, AM
Chemical	Riot control agents (RCA)	Irritant chemicals (tear gas) such as CS, CN and CR; OC (pepper spray of biological origin; PAVA is a synthetic version); aerosols or powdered form; cause irritation of eyes and upper respiratory tract	Shotgun cartridges, mortar shells, grenades, and spray devices; frangible projectiles containing powdered RCA fired with launcher or existing gun; airburst munitions under development	AP
	Malodorants	Foul-smelling chemicals used as RCA or to discourage access to an area	As for RCA	AP
	Anti-traction materials (ATM)	Lubricating polymers spread on ground or other surfaces to prevent access by people or vehicles	Backpack or vehicle mounted tank with spray device	AP, AM

Technology	Type(s)	Description	Delivery	Target
Chemical (cont.)	Obscurants	Smokes to obscure vision; dyes for underwater use	Grenades, mortar shells	AP
	Foams	Rigid or sticky foams as a barrier (not for use directly against people because of risk of blocking airways); aqueous foams as personnel barrier (chemical irritants could be added)	Spray devices	AP
	Anti-materiel chemicals	For use against structures or vehicles; combustion modifiers, fuel contaminants, super-corrosives, embrittling agents, super-adhesives and depolymerization agents have been proposed	Direct deployment, spray device, or projectile containing substance	AM
	Defoliants/herbicides	Chemicals to kill crops or vegetation; used in Viet Nam (Agent Orange); dangerous to human health (e.g. cancer causing dioxins in Agent Orange)	Sprayed from aircraft / crop duster	Anti-plant; extreme danger to human health
Chemical / biochemical	Incapacitants ***Illegal under CWC and BTWC***	Toxic chemical or biochemical agents acting on neuroreceptors in the central nervous system to cause sedation, disorientation, hallucination, mood changes, unconsciousness and death; delivered as aerosol; distinct from RCAs	Aerosol delivery directly over an area with an aerosol generator or munitions/projectiles of a similar type to RCAs; also possibility of injection as with sedation darts; other routes (e.g. transdermal) have been suggested	AP
Biological	Anti-material micro-organisms ***Illegal under BTWC***	Bacteria that degrade various materials (e.g. plastics, metal, etc.)	Direct application with aerosol spray most likely	AM
	Anti-crop agents ***Illegal under BTWC***	Fungi to kill drug crops such opium or coca plant	Application with aerosol spray, most likely from aircraft/crop duster	Anti-plant
Combined technologies	Combining various non-lethal technologies	Frangible projectiles containing chemicals (kinetic and chemical); laser delivered "wireless" electrical weapons (DE and electrical); modified water cannon (kinetic and chemical/electrical); "multi-sensory grenade" (acoustic-optical and chemical)	Various described above	AP
Delivery systems	Non-lethal munitions	Non-lethal munitions (e.g. mortar shells) to disperse various payloads (aerosol, liquid, solid, powder); airburst munitions	Gun, launcher, mortar	Depends on payload
	Encapsulation / micro-encapsulation	Encapsulation ("paintball"-type projectiles) and micro-encapsulation (minute capsules) for delivery of chemical agents, such as RCAs, malodorants, dyes, and anti-traction materials	Encapsulated projectiles from launcher; micro-capsules from munition or direct application	Depends on payload
	Unmanned vehicles	Aerial vehicles, surface watercraft, underwater vehicles, ground vehicles	Deployed from unmanned platform	Depends on payload

Note: AP = anti-personnel; AM = anti-material

lethal weapons are on the way, which will include acoustic and microwave weapons, non-lethal landmines, and malodorants (see Table 1). Many analysts would agree that there is a "legitimate" role for non-lethal weapons, both for civil and military applications. However there is considerable disagreement as to the operational effectiveness of non-lethal weapons, and the threat such weapons pose to arms conventions and international law. As usual, a balance has to be achieved where the

benign advantages of developing and deploying non-lethal weapons are not outweighed by their more malign effects. In particular, emerging non-lethal technologies offer an increasing opportunity for the suppression of civil dissent and control of populations—these are sometimes referred to as the "technologies of political control".

Emerging technologies

Kinetic energy

Kinetic energy (KE) weapons, such as baton rounds (plastic and rubber bullets), truncheons, shot-filled beanbags, small rubber balls and water cannons, have been used by police and military forces for many years. Despite long experience of operational use, these weapons have their limitations. A US National Research Council[2] report points out that their short range, together with a deteriorating accuracy at longer distances, limits their use to situations of close engagement. Of more concern are safety considerations, and the control of trauma level from blunt projectiles remains a serious problem. Recent developments in KE technology include sophisticated water cannons, for example "… an Israeli version has been developed which fires 'bullets' of water, very small quantities of water at high pressure. A variety of configurations exist with some recently developed options enabling ultra-cold slugs of water to be fired, or for the jets to be electrified."[3] The water can also have a dye added allowing for easy identification of rioters or a chemical irritant. Several types of plastic bullet are in use, including the L21A1 plastic baton round in the United Kingdom, and foam-tipped plastic bullets that have been designed to minimize injuries. The latter were field tested by the US Marine Corps in Iraq but rejected as being ineffectual.

Barriers and entanglements

Vehicle barrier systems currently available include the Portable Vehicle Arresting Barrier and the X-Net (or Vehicle Lightweight Arresting Device, VLAD), which has been successfully used by US Marines in Haiti. The X-Net is made from a strong polyethylene called Dyneema. Nets are also available to capture individuals; these nets can be electrified or have sticky substances added to them. Current research into new barrier systems includes work based on the principles of gas-generated airbags.[4] Researchers are looking into the use of spider silk as a non-lethal "entanglement" material for disabling people; a method for producing large quantities of recombinant spider silk protein using *E. coli* is being developed.[5] The Running Gear Entanglement System (RGES) is a net deployed to stop propeller-driven watercraft that is in use with the US Coast Guard.

Electrical

Electrical weapons include stun guns, stun batons, electrified shields, electrified nets, electrified water cannon, "sticky shockers", stun belts, landmines and grenades. Amnesty International has identified manufacturers of electro-shock weapons in twelve countries[6] and their list indicates the largest group of manufacturers being located in Taiwan, China, South Korea and the United States. Probably the best known electrical gun is the Taser, which fires out two barbs attached to fine wire. These catch in

the clothing or skin of the target and an incapacitating electrical shock is administered. Concerns have been raised about the safety and abuse of Taser guns including: its potential use for torture and other human rights violations;[7] that some people are more vulnerable to serious injury or death; and that adequate rigorous medical research related to the safety of the more powerful Tasers has not been carried out.

The safety evaluations of weapons are often produced by the manufacturers themselves and independent scientific research and evaluation is scarce.

The safety evaluations of weapons are often produced by the manufacturers themselves and independent scientific research and evaluation is scarce. In the United Kingdom, the Defence Science and Technology Laboratory carried out an assessment of the medical effects of the M26 Taser and, although they concluded from the available literature that the risk of death or serious injuries appeared to be low, they noted that:

> The body of manufacturers' experimental evidence from biological models of the hazardous and intended effects of Taser on excitable tissues is not substantial, particularly with regard to the M26; the peer-reviewed evidence is even more limited.[8]

Several companies are developing weapons that can deliver incapacitating shocks without the need for wires. Some of these are essentially combination directed energy/electrical weapons. The underlying principle is to use a laser beam to produce an ionized gas or plasma through which an electrical charge can be conducted to the target person or vehicle. The "Close Quarters Shock Rifle" (CQSR) is one such prototype weapon. The company claims that it "will be able to fire a stream of electricity like water out of a hose at one or many targets in a single sweep".[9] The CQSR bought a swift response from human rights organizations, such as Amnesty International, who again highlighted the fact that, in their view, inadequate research has been carried out on the potential biomedical and psychological effects of such a weapon. There is also a danger of innocent bystanders being affected when such an "indiscriminate" weapon is used.

Wireless electrical projectiles are also being designed to get round the range limitations of the Taser (around six metres) and offer the increased "stand-off capability" that military and police desire. But, as with all projectiles, there is still the problem of decreased accuracy at longer ranges, and this means that people are more likely to be struck in unintended places such as the head and neck. It is also unclear how the projectiles will cause electrical incapacitation. The Taser, for example, can only remain effective whilst the trigger is held down and the electrical current flowing into the body is maintained. Some questions remain: what will be the duration of electrical incapacitation? If it is only momentary does it confer any advantage? If it lasts longer, will the need for increased electrical shock incur increased health risks?

Acoustic

Acoustic weapons, employing audible sound, infrasound or ultrasound represent one emerging non-lethal technology that is beginning to mature. In the audible range, one company has developed High Intensity Directed Acoustic (HIDA) devices such as the Long Range Acoustic Device (LRAD), designed to deliver audible warning messages over long ranges (up to 1km). However, at closer distances it is considerably more incapacitating and can produce 120db of sound at 60m and peak levels of 130db at 4 metres.[10] Hearing damage can occur at levels as low as 80db if exposure is over a long period, and at levels of 120db and over there is potential for hearing loss even after very short exposures.[11] In addition to ear pain, reportedly some HIDA devices can cause such side effects as loss of equilibrium, vomiting and migraines.[12] A prototype hand-held system based on the same technology,

the "directed stick radiator", has also been demonstrated. It fires high intensity "sonic bullets" or pulses of sound between 125–150db for a second or two. Such a weapon could, when fully developed, have the capacity to knock people off their feet. It has been argued that weapons that utilize infrasonic frequencies can cause nausea, disorientation and bowel spasms. A mobile "infrapulse generator" is being developed that generates low-frequency shock waves that resonate with body organs and that can cause physical damage. The LRAD was acquired by the US Marines for use in Iraq[13] and there have been reports that an acoustic device has also been used in Afghanistan.[14] The New York Police Department acquired two units in the run up to the 2004 Republican Convention in the city. Again, some analysts have voiced concern that "the U.S. is making a serious mistake by trying to quietly deploy a new pain-inducing weapon without first airing all of the legal, policy and human rights issues associated with it".[15]

Directed energy

There are several types of directed energy (DE) weapons under development for non-lethal weapons purposes that employ different sorts of electromagnetic energy: millimetre wave, high-power microwave, low-power diode laser, or high-energy chemical laser. Most are under development and still to be deployed, but there are indications that a new generation of weapons will soon enter into use. The use of DE for non-lethal weapon purposes is only one aspect of a larger "vision" held by the US Department of Defense, which is to exploit the military potential of DE to achieve asymmetric advantage over adversaries. The majority of investment is directed to lethal systems, most notably the Boeing 747-mounted Airborne Laser for missile defence, which has received around US $2 billion in funding.[16] The US Marine Corps *Joint Concept for Non-Lethal Weapons* emphasized the need for a non-lethal to lethal "rheostatic capability"[17] and it has been argued that "... the ideal NLW [non-lethal weapon] would be a system with continuously visible intensity and influence, ranging from a warning tap to a stunning blow to a lethal effect."[18]

The US Marine Corps* Joint Concept for Non-Lethal Weapons *emphasized the need for a non-lethal to lethal "rheostatic capability" and it has been argued that "... the ideal NLW [non-lethal weapon] would be a system with continuously visible intensity and influence, ranging from a warning tap to a stunning blow to a lethal effect."

Directed energy is seen as the most promising opportunity to develop a "tuneable" weapon akin to the oft-cited, but fictional, Star Trek Phaser.

The Active Denial System (ADS) is a weapon that uses millimetre wave energy to heat up water molecules in the subcutaneous layers of the skin, causing a painful burning sensation. The radiation acts in a dose-dependent manner and so exposure duration is critical in terms of safety.[19] The US Army has exhibited a Humvee-mounted prototype, which will be given to the armed forces for evaluation before a decision on deployment expected by the end of 2005.[20]

High-power microwave (HPM) weapons deliver a burst of radio-frequency energy designed to degrade or destroy the circuits of electronic equipment. There are two main types of HPM weapons: wide-band weapons that release a burst of radiation over a broad frequency range generated by a high explosive or an electromagnetic generator; and narrow-band weapons that are electrically driven and are directed at specific targets.[21] Concern has been expressed over their potential for destruction of civilian electronic infrastructure—including hospital equipment and heart pacemakers—that would be in contravention of international humanitarian law. HPM weapons have not been described by the military as "non-lethal" and can be seen as an extension of lethal force. For example, a recent US Army announcement called for proposals to enhance the lethality of conventional munitions with a

HPM directed energy component.[22] Other applications for HPM weapons include their potential for stopping vehicles by disabling onboard computer control systems.

Laser weapons include low- and high-power systems. Devices called "illuminators" or "dazzlers", which are already available, use a low-power diode laser to temporarily blind or obscure vision. There are worries over eye safety in relation to these devices. High-energy lasers are also being investigated for non-lethal applications. For example, the Advanced Tactical Laser is a chemical laser system being developed by the US military, which would be lethal if used against humans. Planned anti-materiel non-lethal uses include "… bursting automobile tires, rupturing fuel tanks, selectively cutting through electrical or communications lines, or setting fires".[23] Some types of high-energy laser are also under consideration for anti-personnel purposes. One such weapon in the early stages of development is the Pulsed Energy Projectile (PEP), the effects of which have been described as follows:

> PEP would utilize a pulsed deuterium-fluoride (DF) laser designed to produce an ionized plasma at the target surface. In turn, the plasma would produce an ultrasonic pressure wave that would pass into the body, stimulating the cutaneous nerves in the skin to produce pain and induce temporary paralysis.[24]

Riot control agents and malodorants

Riot control agents (RCAs) include synthetic chemicals CS, CN, and CR as well as Oleoresin Capsicum (OC) or "pepper spray", which is biological in origin. RCAs are defined in the US Army's *Textbook of Military Medicine* as follows:

> Riot control agents are compounds that cause temporary incapacitation by irritation of the eyes (tearing and blepharospasm), causing them to close, and irritation of the upper respiratory tract. They are often called irritants, irritating agents, and harassing agents; the general public usually calls them tear gas.[25]

PAVA, a synthetic version of OC, has become more popular for use in law enforcement since it is more potent than the natural product. There are a variety of shells, grenades and spray devices for delivering RCAs and recent weapons development has focused on new methods of delivery such as the paintball-type PAVA, OC or CS powder-filled projectiles fired by the PepperBall System or the FN 303 launcher. The UK Defence Science and Technology Laboratory are developing a frangible projectile called the Discriminating Irritant Projectile containing powdered CS.

There is concern over the desire of the United States to use RCAs outside of permitted law enforcement applications. In the run up to the war in Iraq, Secretary of Defense Donald Rumsfeld testified to the US Congress House Armed Services Committee, admitting that the US was attempting to "fashion rules of engagement" to enable their use.[26] Subsequently President Bush authorized their use in Iraq in certain circumstances, and CS and pepper spray were shipped to the Gulf. This is legal in US law under Executive Order 11850, which was signed by President Ford in 1975 and permits the use of RCAs under specific conditions such as in "riot control situations in areas under direct and distinct US military control, to include controlling rioting prisoners of war" and in "situations in which civilians are used to mask or screen attacks and civilian casualties can be reduced or avoided".[27] However, it is illegal under international law. Article I of the 1993 Chemical Weapons Convention (CWC) clearly states "Each State Party undertakes not to use riot control agents as a method of warfare".[28] RCAs do not appear to have been used in the Iraq conflict but such an intention is a serious threat to the international prohibition against the use of chemicals in war.

Malodorants are foul-smelling chemical compounds that are seen as having potential use for controlling crowds, clearing facilities and area denial. The US military do not consider the development of malodorants to be restricted by the Chemical Weapons Convention:

> Malodorants are not considered toxic chemicals, since they do not cause—or are not specifically designed to cause—death, temporary incapacitation, or permanent harm to humans or animals.[29]

However, a Council on Foreign Relations report on non-lethal weapons stated that malodorants are "probably also classed as riot control agents" and could not therefore be used in warfare.[30] From a policing standpoint, a recent UK government report stated that "… malodorants do not appear to offer any tactical advantage over existing incapacitants already available to the police".[31]

Biochemical incapacitating agents

One of the most controversial areas of non-lethal weapons research and development is that related to incapacitating agents, which have also been called "calmatives", "knock-out gas" or "immobilizing agents". They are distinct from RCAs due to their mechanisms of action. RCAs are chemicals that cause *local* irritation to the eyes and other mucous membranes. Incapacitating agents, on the other hand, have *central* effects, acting on cell receptors in the central nervous system to produce various effects including sedation, disorientation, unconsciousness and death. The boundaries of chemistry and biology become blurred in this area since substances that can exert influence by action on specific cell receptor sites can have either a synthetic chemical origin (i.e. toxic chemicals/drugs) or a natural biological origin (i.e. bioregulators).[32] Wheelis has termed these substances potential *biochemical weapons*.[33]

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LEGAL ISSUES

These weapons agents fall somewhere in between "traditional" chemical agents (nerve, blood and blister agents) and "traditional" biological agents (bacteria, viruses and rickettsia). In this context Pearson's Chemical-Biological Weapons Spectrum is a useful concept (see Table 2).

For toxic agents in the mid-spectrum there is overlap between the legal prohibitions of the CWC and those of the Biological and Toxin Weapons Convention (BTWC). Synthetic chemicals such as the fentanyl derivative used by authorities during the 2002 Moscow theatre siege would fall into the theoretical "Industrial Pharmaceutical Chemicals" category and, as toxic chemicals, are covered by the CWC alone. However the superficial boundaries between this category and that of "Bioregulators" and "Toxins" are blurred. As Wheelis points out, the analogues of bioregulators and toxins are covered by the BTWC. He argues, therefore, that synthetic chemical analogues (i.e. drugs) that bind to the same specific cell receptor sites in the body as the corresponding natural ligands (i.e. bioregulators) are also covered. The significance of this "double coverage" is that would-be developers of such agents should not be able to exploit the loophole in the CWC that permits the use of certain chemicals for "law enforcement including domestic riot

Table 2. The chemical-biological weapons spectrum

Classical CW	Industrial Pharmaceutical Chemicals	Bioregulators Peptides	Toxins	Genetically modified BW	Traditional BW
Cyanide Phosgene Mustard Nerve agents	Aerosols	Substance P Neurokinin A	Saxitoxin Ricin Botulinum toxin	Modified/tailored bacteria and viruses	Bacteria Viruses Rickettsia Anthrax Plague Tularaemia
Chemical Weapons Convention ◄——————————►					
		Biological and Toxin Weapons Convention ◄——————————►			
Poison ◄——————————►			Infect ◄——————————►		

Source: G. Pearson, 2002, "Relevant Scientific And Technological Developments For The First CWC Review Conference: The BTWC Review Conference Experience", *CWC Review Conference Paper No. 1,* Department of Peace Studies, University of Bradford.

control purposes". This is particularly important given conflicting interpretations of both the CWC's definition of RCAs and its provisions on the acceptable situations for use of such agents.

Lethality

Currently available incapacitating agents and associated delivery systems cannot be termed RCAs, which are defined by the CWC 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.[34] [emphasis added]

The reversibility of effects, with no permanent deleterious change to the victim may be seen as a key aspect of any non-lethal weapon targeted at humans. However, a model developed by Klotz et alia suggests that no existing agents would be able to perform this role.[35] New compounds are likely to present similar problems. If a compound is extremely potent it will tend to have a poor safety ratio. If a compound has a good safety ratio it will tend to have a long onset time or not be sufficiently potent. The former problem was devastatingly illustrated when Russian authorities ended the Moscow theatre siege using an aerosolized fentanyl derivative, most likely carfentanyl,[36] and at least 120 of the 800 hostages died as a result of exposure to the agent, whose major side effect is respiratory depression. Even with an "ideal" compound (high safety ratio and high potency), there would be significant obstacles to "non-lethality", that is the delivery of an effective but safe dose to all individuals in a given area, notwithstanding the differences in age, size and health and the problems of uneven concentrations and cumulative intake of agent.[37]

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SCIENCE AND TECHNOLOGY

Neurotransmitters mediate chemical transmission in the nervous system through their interactions with specific receptors. In the central nervous system these neurotransmitter-receptor interactions have a major role in regulating consciousness, mood, anxiety, perception and cognition. Table 3 gives some of the clinical effects of neurotransmitters.

Neurotransmitters are of primary interest for this discussion because their sites of action, i.e. neuronal receptors, are the exact targets of proposed "non-lethal" incapacitating agents. One study examining potential "calmatives" defined them as "compounds known to depress or inhibit the function of the central nervous system"—suggesting that these might "include sedative-hypnotic agents, anesthetic agents, skeletal muscle relaxants, opioid analgesics, anxiolytics, antipsychotics, antidepressants and selected drugs of abuse". [38]

The same study recommended that partnerships be formed between weapons developers and the pharmaceutical and biotechnology industries to identify new incapacitating agents. There is already a significant research focus in the pharmaceutical industry to develop more effective drugs to treat a variety of mental illnesses, and many of the receptor targets are the same as those of interest to incapacitant developers. In addition, there have been considerable advances in recent years of techniques for discovery of new compounds.

Table 3. Neurotransmitters and their clinical effects

Bioregulator category	Agent	Clinical effects
Neurotransmitters	Catecholamines	Consciousness, mood alterations, anxiety, hypertension, tachycardia, sexual dysfunction
	Amino acids	Effects on learning, memory, cognition, pain sensitivity
	Neuropeptides	Effects on cognition, sensory processing

Source: E. Kagan, 2001, "Bioregulators as Instruments of Terror", *Clinics in Laboratory Medicine,* vol. 21, no. 3, pp. 607–18.

MILITARY AND LAW ENFORCEMENT INTEREST

Military interest in incapacitants has a long history. The glycolate agent BZ was weaponized by the US in the 1960s as part of its chemical weapons programme, and there are reports that the Former Soviet Union developed a derivative of BZ as an incapacitating weapon. Iraq's chemical weapons programme is thought to have incorporated a glycolate compound known as Agent 15. Biological agents have also been considered for use as incapacitating rather than lethal weapons. [39]

In the US, military research in this area is co-ordinated by Joint Non-Lethal Weapons Directorate (JNLWD) and there have been recommendations for increased research on incapacitants, or "calmatives", and their delivery systems.[40] Objectives listed in the JNLWD's Technology Investment Project for "Front End Analysis of Non-Lethal Chemicals" for the fiscal year 2001/02 included the need to "… identify advances in the pharmaceutical industry and elsewhere for potential non-lethal applications; conduct military user workshops to identify range of desired operational effects; create a searchable database of potential candidates; provide a list of promising candidates to Judge Advocate General's office for preliminary legal review."[41]

In relation to calmatives, the Pentagon's Defense Science Board in their 2004 task force report on *Future Strategic Strike Forces* notes that:

> Calmatives might be considered to deal with otherwise difficult situations in which neutralizing individuals could enable ultimate mission success;
>
> The principle [*sic*] technical issue is the balance between effectiveness (i.e., the targets are truly "calmed") and margins of safety (i.e., avoiding overexposure and resulting fatalities of neutral bystanders);
>
> The treaty implications are significant.[42]

Research and development is not restricted to the United States. As events in Moscow illustrated, Russia clearly has a programme in this area and so may other countries. Authorities in the UK recently made it clear that no type of agent (RCA or incapacitant) would be used in military operations because of obligations under the CWC.[43] They are also hesitant in endorsing the use of incapacitating agents (as opposed to RCAs) for law enforcement purposes:

> The decision to use any drug whether intended to induce a state of calm or complete unconsciousness requires knowledge of a subject's medical history, particularly the use of any prescribed or non-prescribed medication and any relevant medical conditions. There would also be considerable responsibility in terms of immediate and post-incident aftercare.[44]

IMPLICATIONS

If new biochemical agents are developed under the guise of non-lethal incapacitation it is likely that they will soon appear on the existing threat lists for chemical and biological weapons agents. There have already been warnings of this "double-edged sword".[45] Such research is in danger of legitimizing offensive weapons development that is prohibited by the CWC and the BTWC.

Combined technologies

A significant trend in non-lethal weapons development is the combination of one or more technologies into a single weapon.

A significant trend in non-lethal weapons development is the combination of one or more technologies into a single weapon. Examples of current systems include the paintball-type frangible projectiles (kinetic and chemical) and water cannons (kinetic and chemical or electrical). At the research and development stage wireless electrical weapons seek to combine electrical and directed energy technologies. Aqueous foams may combine a barrier function with the capability to incapacitate with the addition of chemical agents. A "Multi-Sensory Grenade" or "Clear-A-Space Device" employs light, sound and malodorant to overwhelm an individual or group, and "Flash-Bang" devices are also available that combine bright light and painful sound levels. Also proposed is a "multi-sensory incapacitation" approach to weapons development, targeting all five human senses (sight, sound, taste, smell, touch) as well as motor skill and cognition. As a result of the Ottawa Treaty (1997), which banned the use, development, production, stockpiling and transfer of anti-personnel landmines, there has been accelerated research into non-lethal alternatives. A range of mines are now being developed[46] including ones which fire out sticky entanglement nets, electrical stunning wires (Taser landmine), small rubber balls (Claymore type), chemical incapacitants, or a combination of these.

Delivery systems

Accurate targeting and delivery of a non-lethal weapon defines their operational utility, and effort is going into the design of more effective delivery systems to enable increased stand-off distances and more discriminate delivery to the target. Advanced munitions, including shells or mortars for delivering chemical agents are being developed with the objective of dispersing the agent near the target whilst minimizing injury from the munition casing. Encapsulated projectiles, such as the paintball-type frangible capsules, are already deployed by law enforcement agencies for delivering OC/PAVA. The use of micro-encapsulation technology has been proposed for delivery of a variety of chemical substances since it has the advantage being able to achieve controlled or remote release of a given substance, or to compartmentalize multiple component systems. Delayed dispersal mechanisms enabling the release of material from the capsule over a period of time include: thermal release, mechanical rupture, water-activated release and photolytic release. Unmanned air vehicles are being increasingly deployed by the US military in their operations. Other unmanned systems include surface watercraft, underwater vehicles and ground vehicles. Whilst unmanned platforms have primarily been developed for use in sensing, surveillance or lethal weapons delivery, they are seen as having great potential for delivering non-lethal weapons at large stand-off distances.

Impact on health

We have already noted some of the health effects of non-lethal weapons. It seems that often more urgent operational needs take precedence over a thorough evaluation of non-lethal weapon technologies. For example, in the case of Tasers, the National Research Council report on non-lethal weapons noted that "the actual mechanism of action is not well studied, but the commercial devices are effective".[47] One study has reviewed the open literature on the effects of seven different non-lethal weapon technologies (acoustic weapons, entanglers, flash-bang non-lethal hand grenades, laser dazzlers, malodorants, non-penetrating projectiles, and oleoresin capsicum) with the objective of building a model to understand the effects of non-lethal weapons on humans. The ability to reach conclusions on the human effects of non-lethal weapons was hampered by the quality of the literature available for review:

> empirically speaking, most of the studies were of a particularly non-scientific nature, including those sources which portray themselves as being objective and controlled. It is often difficult to extrapolate exactly what tests were used to assess the technology, what was measured, and—quantitatively speaking—what effects found.[48]

In 1999 the JNLWD established the Human Effects Process Action Team, which recommended the formation of a Human Effects Review Board (HERB) to review non-lethal weapon health effects and make recommendations, and a Human Effects Center of Excellence (HECOE) to carry out health-effects analysis. Both were set up in 2000.[49] However, the National Research Council study discovered that "HECOE is not funded to perform fundamental research on human effects. In fact, there is no place in the human effects characterization process, as established, where that research is supported."[50]

There are other groups working on non-lethal weapon human effects. The Human Effects Advisory Panel is a group of experts formed in 1998 by the Institute for Non-Lethal Defense Technologies (INLDT) at Pennsylvania State University under contract with the JNLWD to provide advice on human effects.[51] INLDT is also closely involved with the JNLWD in weapons research and development. NATO

has a panel working in this area, the Human Factors and Medicine Panel, which is due to report at the end of 2004 on the human effects of non-lethal technologies.[52]

Conclusion

We have noted that the military and police are interested in weapons that have a rheostatic capability, that is they can operate along a lethal to non-lethal continuum. A number of the non-lethal weapons described in this paper clearly have such a characteristic. At the same time existing weapons are being adapted to have a dual-use purpose. For example, the US Army has developed a "Lightweight Shotgun" that can either be attached underneath a standard automatic rifle or used as a stand-alone weapon. It can fire lethal or non-lethal rounds and has already been deployed in Afghanistan.[53] Rapid progress is being made in delivery systems that can dispense non-lethal weapons more accurately and discriminately from greater stand-off distances, and the development and use of unmanned vehicles and airburst munitions is important in this respect. Whilst the Taser electrical incapacitating weapon has been a "success" with thousands being sold worldwide to both civil and military users, analysts are concerned about the number of deaths associated with their use, and the lack of independent and scientific testing of health effects.[54] Although some of the other newer technologies are beginning to be field tested (such as the LRAD and ADS), it is the older and more established non-lethal weapons that are mostly in operational use. With regard to the military this is due to many factors including an uncertainty about the real utility of non-lethal weapons in combat. As a recent Council on Foreign Relations report notes:

> The question remains: Where do the Department of Defense (DOD) and the armed forces stand on the road to acquiring and integrating these capabilities? We found little evidence that the value and transformational applications of nonlethal weapons across the spectrum of conflict are appreciated by the senior leadership of the Department of Defense. Despite successes on the small scale, NLW have not entered the mainstream of defense thinking and procurement.[55]

Another factor is the potential for quick development of countermeasures by opposition forces.

We would particularly want to highlight dangers posed by biochemical incapacitating weapons: both existing agents that do not fit the definition of "non-lethal", and novel agents that may be developed to incapacitate, damage the nervous system, alter moods, trigger psychological changes and even kill.[56] Classifying this new generation of weapons under the non-lethal umbrella must be resisted since it can give them "acceptability". They must be considered as weapons, which if developed and deployed, would contravene the international prohibitions of the CWC and the BTWC. The Council on Foreign Relations panel recognized the very significant dangers associated with such weapons development:

> Nonmilitary research in biology and medicine will lead to understanding that can greatly facilitate the development, production, and use of lethal and largely nonlethal chemical and biological agents. But NLW-focused research will hasten the day that such materials are available not only to the United States but also to those who would use them against us.[57]

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Biological weapons and the life sciences: the potential for professional codes

Brian RAPPERT

> Two items in this issue of *New Scientist* … re-emphasize a theme which is now always recurring in our pages. This is the responsibility which the scientist bears towards society for the new and often awesome powers which he generates in his laboratory. … Throughout civilized history it has been recognized that certain groups which exercise a special influence and wield a peculiar power within the community must, for the common good, abide by certain rules and accept certain limitations and restrictions. … But except in special cases, scientists as a group have no such corporate law to help the individual act in a way that will preserve the health and reputation of the whole. … [U]nless some principles of conduct are established for the men and women who manipulate the materials of nature, anarchy will develop, and with anarchy, disaster.

So argued the journal *New Scientist* in February 1968 in an editorial entitled "Wanted—a code of conduct".[1] The quote illustrates both the relatively long-term interest in formulating a code of conduct for scientists[2] and the importance of the threats of biological weapons as part of that. In their most basic form, codes seek to formalize existing or idealized standards of practice. Recently, as part of a renewed concern about the dual-use possibilities afforded by molecular biology, neuroscience and immunology vis-à-vis bioweapons (BW), the calls for a code have once again intensified. The adoption of a code is being offered as both a complement and an alternative to traditional international arms control regimes.

This article briefly traces current initiatives to formulate a BW-related code. It does so with a view to highlighting the diversity of proposed codes. Lessons from the analysis of professional codes more generally are referenced to suggest some of the problems and possibilities associated with the adoption of a BW code. Building on this, the outline of a "code matrix" is presented to suggest a range of possible activities that might be taken up under the name of a code. Finally, this article proposes content for a code of conduct and lays out the reasoning behind it. In doing so, the argument seeks to present ideas for discussions under the Biological and Toxin Weapons Convention (BTWC) work programme for 2005.

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BW codes today

Since 2001, with the growing concern about BW threats, many governments, NGOs and professional bodies have forwarded the notion that a code of conduct introduced in conjunction with other initiatives might be useful.[3] Box 1 lists many of the calls made. Moreover, the adoption of a code has entered into the formal agenda of key institutions. "The content, promulgation, and adoption of codes of conduct for scientists" will be discussed as part of the annual meeting of the BTWC States Parties in 2005. The US National Science Advisory Board for Biosecurity has as one of its central aims the development of "Professional codes of conduct for scientists and laboratory workers that can be adopted by professional organizations and institutions engaged in life science research".[4] Following on from decisions by the UN General Assembly and the Security Council,[5] the InterAcademy Panel and the International Centre for Genetic Engineering & Biotechnology are formulating a code of conduct for the life sciences.

Box 1. A biological weapons-related code of conduct could:

include "general safety and ethical standards such as potential conflicts of interests, plagiarism and misrepresenting or exercising bias in recording and publishing state [as well as potentially specific elements] of safety and security such as the handling of potentially dangerous materials. … Good practice should also include the responsibility of scientists to be aware of and comply with the requirements of international conventions and treaties in their research areas. This needs educational and research institutions to put in place the appropriateness measures to enable this requirement to be met."

—British Royal Society, 2004, *The Individual and Collective Roles Scientists Can Play in Strengthening International Treaties,* April

"aim to prevent the involvement of defence scientists or technical experts in terrorist activities and restrict public access to knowledge and expertise on the development, production, stockpiling and use of weapons of mass destruction or related technologies."

—Policy Working Group on the United Nations and Terrorism, 2002, *Measures to Eliminate International Terrorism,* annex

be set up for "those who do laboratory work with pathogenic organisms [and] could underscore that scientists, clinicians, and laboratory workers have personal responsibility to prevent accidental and deliberate releases of such organisms into the environment. Such a code could be an element within a multi-faceted approach to promoting responsible handling and use of pathogenic microorganisms."

—US Department of State, 2001, *New Ways to Strengthen the International Regime Against Biological Weapons,* October

be established as a means of "self-regulation for scientists working with dangerous pathogens and toxins."

—Wellcome Trust, 2003, *Position Statement on Bioterrorism and Biomedical Research*

"be developed by academic and professional bodies to lay out standards internationally for work relevant to the prohibition of the Convention. Such codes could include, *inter alia*, a statement that scientists will use their knowledge and skill for the advancement of human, animal, and plant welfare and will not conduct activities directed towards the use of micro-organisms or toxins or other biological agents for hostile purpose or in armed conflict."

—UK Foreign Office, 2002, *Strengthening the Biological and Toxin Weapons Convention,* April

Despite the widespread endorsement given to the formulation of a code (or codes), at the time of writing, its aims and audiences have not been developed in detail. A close reading of the quotes in Box 1 indicates a variety of aims and audiences. Many other calls for codes could be listed that would indicate a still greater degree of diversity.[6]

The lack of agreement on these issues is of some importance because existing professional scientific codes vary greatly in terms of their functions and content. Codes of conduct (the term is often used interchangeably with "codes of ethics" or "codes of practice") vary from brief statements that lay out aspirational aims in the desire to raise awareness of key issues or establish principles; to educational/ advisory guidelines that suggest considerations to be borne in mind when considering appropriate action; to detailed enforceable rules that specify what should and should not be done.[7]

The need to mind the diversity of codes is all the more important because social scientists and ethicists have often expressed scepticism about the utility of codes. This has been the case particularly for those codes that just aim to aspire, educate or guide action. Problems identified include the manner in which codes are often open to numerous interpretations; the limitations of codified rules to guide action in complicated cases; the limited practitioner referral to the provisions of codes; and the "public relations" potential of codes to act as way of staving off other forms of regulation.[8] To the extent that codes take the form of binding regulations, then the proper topic for examination is not so much the code itself, but the underlying forms of regulation that it embodies. More positive analyses of codes in professional life suggest they can heighten awareness of issues, enable individuals to re-interpret their situations, clarify how individuals and groups share responsibility, and influence action in areas where standards have not yet formed.[9]

Whatever assessment one makes about the value of codes, different types of code options exist (i.e. aspirational, educational/advisory, or enforceable) and there are important differences between them in terms of their goals. Table 1 indicates the range of codes possible, how they are often designated by name, what overall aims each could serve, what types of objections have been made about them,

Table 1. A typology of codes

Type	*Aspirational*	*Educational/ Advisory*	*Enforceable*
Common name	Code of Ethics	Code of Conduct	Code of Practice
Main aims	Alert; set realistic or idealistic standards	Provide guidelines, raise awareness and debate; foster reflective moral agents	Prescribing or proscribing certain acts
Principal criticisms	Standards too broad to guide action; lack of adherence	Often contain conflicting ethical demands and therefore ambiguous; of limited utility with enforcement mechanisms, yet guidelines rarely list definitive do's and don'ts; mainly function as public relations device	Formal codes not able to specify ethical conduct in diverse situations; regulation burden on science base; existing national regulations for the physical and biological containment of pathogens
Functioning	Establish an organizational basis for future action by initially affirming the prohibition against the development of bioweapons	Provide elaboration of individual and collective responsibilities of those associated the life science work; set a basis for long term discussion about what needs to be done, in part by challenging existing agenda and framing of issues	Incorporate BW and biosecurity concerns within day-to-day work procedures
Principal agents	Policy makers in funding and professional organizations	Life science professionals	Administrators, regulators, funders, and practitioners associated with scientific and medical practice

how they would function in more practical terms, and who could be the likely main agents to take their adoption forward.

The lack of codes directly relevant to matters involving biological weapons despite the long-term interest in developing them should alert us to the potential difficulties of agreeing and implementing them. While codes might seem a fairly non-controversial option, particularly relative to other issues associated with biological weapons, if codes are to go beyond reiterating platitudes about the abhorrence of using modern biology toward malign ends, then they are likely to confront major issues of controversy. For instance, codes could comment on the acceptability of disputed attempts to develop "non-lethal" incapacitating agents or the permissibility of contentious biodefence activities. Determining the responsibilities of scientists for the future implications of their work raises many demanding questions about the foreseeable consequences of science and what should be done about them (and by who). To indicate a sense of the range of potential issues that could be raised, Box 2 lists a variety of possible questions about efforts to develop codes.

The lack of codes directly relevant to matters involving biological weapons despite the long-term interest in developing them should alert us to the potential difficulties of agreeing and implementing them.

A code of conduct in a code matrix

In order to cover a broad range of aims and the deficiencies of individual types of codes, one idea that has been put forward is to strive for a "matrix of codes".[10] This would entail the adoption of different aspirational, advisory and enforceable codes that could meet a variety of goals for diverse audiences.[11] This matrix should not only be relevant to individual bioscientists, but researchers in related fields, regulators, policy makers and others associated with conducting and commercializing the life sciences. Elsewhere I have suggested something of the elements of such a matrix. It could include aspirational codes that raise the profile of biological weapons with funding, professional, regulatory and other bodies in order to raise awareness and facilitate future action. Enforceable codes could be devised that further existing controls on the physical and biological containment of pathogens and toxins by incorporating them within the routine practices of researchers and others.[12]

Because working examples of aspirational and enforceable codes are already in place as models for future action, the remainder of this article concentrates on elaborating a possible code of conduct. Although enforceable or aspirational BW-related stipulations might be incorporated within existing codes and regulations, arguably a distinct document is needed in the case of an educational code to elaborate a "thick" appreciation of the possible issues at stake. The main aim of this type of code could be to promote widespread discussion regarding what threats are posed by the dual-use capability of the life sciences and the appropriateness of responsive measures. Codes can seek to encourage individuals and groups to assume a position of responsibility as moral agents, though their ultimate ability to do this is highly dependent on the process of their adoption, promotion and revision.

Box 3 gives an example of a code for those that conduct, fund, administer and regulate work in the biosciences and biomedicine. It has been assembled, in part, by directly drawing on varied declarations, codes and conventions; this including the *Ethical Principles of BIOTECanada,*[13] a statement by Matthew Meselson,[14] the IEEE-CS/ACM Joint Task Force on Software Engineering Ethics and Professional Practices' *Software Engineering Code of Ethics and Professional Practice*,[15] the 2002 World Medical Association's *Declaration of Washington,*[16] the Preamble to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction[17] and the International Committee of the Red Cross's *Responsibilities of Actors in*

the Life Sciences to Prevent Hostile Use.[18] It includes a wide range of stipulations, some which might be classified as "advisory", others as "enforceable" and others as "aspirational".

The code is intended as a modest contribution in a few important respects. First, offering such content is not meant to render superfluous the process of debating what any code should be. Rather it serves as an example of what could be done, i.e. to promote grounded discussion. The adoption of

Box 2. Some key questions for codes

Who is the relevant community to make decisions about what codes should be adopted? Should the scientific communities alone determine the composition of codes intended for them? In what ways is the "prevention against biowarfare and bioterrorism … too important to leave to the scientists and politicians"?*

How will a code combine both individual and collective responsibilities?

Will codes consist of standards that go beyond existing regulatory provisions in terms of their rigor or specificity?

What is the question to which codes are being sought as an answer? As part of this, what is the potential for current scientific developments to facilitate the development of BW?

Does a long-term and widespread commitment exist among the relevant organizations to turn codes into more than pieces of paper? If this is lacking, should codes be pursued at all?

By what measures might a code be deemed effective? Is "keeping the conversation going" about the potential security problems of science sufficient?

To what extent are differences in the adoption of codes as well as other regulatory measures acceptable?

Should codes seek to elaborate and clarify existing international conventions or should discussions undertaken as part of such conventions elaborate and clarify the meaning of codes? Related to this, is the purpose of codes to resolve or reflect international disagreements about the advisability of some actions?

Who are codes for: workers on the bench, professional organizations, government negotiators, those in industry, the public or others?

Are codes being brought in to stave off other controls?

Is it realistic to expect common standards in practice for scientific communities across sub-disciplines and nations?

Can guiding principles for setting and interpreting codes be agreed?

What positive commitments exist for scientists to consider the social and ethical implications of their work?

Is calling for "compliance" to existing national legislation and international agreements sufficient? To what extent is it possible?

How can the effectiveness of codes be gauged? Is it realistic or helpful to assume that common criteria should apply across disciplines and countries?

Are governments, professional organizations, funders, NGOs and others willing to take a stance on the proper interpretation of international weapons agreements?

Could new codes alleviate or exacerbate the deficiencies of existing codes?

Irrespective of questions about scientists' knowledge of international prohibitions, is there sufficient recognition of the dual-use possibilities stemming from research? Is there a significant problem to be recognized at all?

Is the discussion of a code a way of engaging with potentially contentious political questions or a way of avoiding them?

* Pax Christi International, 2004, *Pax Christi International Calls for Ethical Approach to Biological Weapons,* statement at General Assembly Pax Christi International in Brussels, June, at <www.paxchristi.net/PDF/SD08E04.doc>.

a code should be viewed as an occasion for asking questions about the place of science in society at a given time, and how that might change. Second, and a related point, at this stage the stipulations seek to evoke deliberation rather than to provide definitive answers. This orientation is taken on the basis that in these relatively early days of widespread concerted action to define and address the security risks stemming from "fundamental" work in the life sciences and elsewhere, the emphasis should be placed on provoking dialogue about what needs to be done rather than inhibiting dialogue. This discussion should include assessments of the criteria by which codes are judged to be "useful" or "ineffective", which themselves are likely to change over time. Certainly a further elaboration of many of the terms and stipulations listed is needed, for instance, the meaning of "potentially dangerous consequences" or just how work should be "reviewed".[19] Some organizations have already made detailed elaborations of possible do's and don'ts.[20] The purpose here is not to resolve debates, but to raise them as topics of concern that need to be addressed in future discussions. The working through of what particular terms entail could be treated as part of the process related to identifying the benefits of any code. Third, this code is pitched in a largely negative tone regarding the possible detrimental consequences of scientists' work rather than their role in reducing threats from BW. While this or other deficiencies may well need correcting, the rationale in my devising a code has been to flag possible issues of concern rather than resolving its final content.

Box 3. A proposal for a code of conduct for the life sciences

Preventing the Hostile Use of the Life Sciences

Every major technology—metallurgy, explosives, internal combustion, aviation, electronics, nuclear energy—has been intensively exploited, not only for peaceful purposes but also for hostile ones. The rapid developments across the life sciences today not only bring the possibility of improving human health, but the risk that the knowledge and techniques gained will be turned towards the deliberate spread of disease.

This risk is not confined to traditional pathogens and toxins of concern; rather the fields of molecular biology, neuroscience, biological control and many others are offering novel ways of manipulating basic life processes. For instance, through deliberate or inadvertent means, genetic modification of micro-organisms could create organisms that are more virulent, are antibiotic-resistant, or have greater stability in the environment. Advances in gene therapy may allow modification of the immune response system of the target population to increase or decrease susceptibility to a pathogen or disrupt the functioning of normal host genes.

Those of us who conduct, fund, administer and regulate work in the biosciences and biomedicine have an ethical and social responsibility to honour international agreements that we will use our knowledge and skill for the advancement of human, animal and plant welfare and will not conduct activities directed towards the use of micro-organisms, toxins or other biological agents for hostile purposes. In addition, as individuals, collectively as members of professions, and in discussions with other segments of society, we have an obligation to actively deliberate what measures are necessary to minimize the risk that our work will be employed for hostile ends.

Today and in the future, an effective response to the threats from biological weapons can only come from concerted international action by those in governments, the medical and scientific communities, non-governmental and professional organizations, the biotechnology and pharmaceutical industries and others. The history of life science research contains many instances—laboratory biosafety and vivisection to name but two—where standards have transformed and controls have been negotiated out of widespread social concern.

This Code is intended to provoke reflection, dialogue and action regarding the advisability of response measures. The list of points included is not meant to be exhaustive. An understanding of the threats posed from the hostile use of biological weapons from states, groups or individuals will evolve over time and thus so will the necessary responses. The provisions included should not be read as separating the acceptable from the unacceptable in all practical situations. The Code is not a simple algorithm that generates definitive determinations about what needs to be done. In some situations, standards may be in tension with each other or with standards from other

sources. Such situations require that medical and scientific professionals and related individuals consider for themselves and discuss with others what constitutes appropriate action. The provisions of this Code should influence those associated with the life sciences to consider broadly who is affected by their work; to examine if they and their colleagues are acting with due regard; to consider how the public, if reasonably well informed, would view their actions; to analyse how the least empowered will be affected by their actions; and to consider whether their acts would be judged worthy of the ideal working of professionals.

In keeping with this, those that work in the biosciences and biomedicine should:

- acknowledge that minimizing risks from the hostile use of advances in the life sciences is of concern to them and part of their responsibility as professionals;
- recognize their personal benign intent is an insufficient justification for setting aside such concerns;
- strive to become aware of the "dual-use" applications of their work;
- consider the direct and indirect benefits and harms of their work to colleagues, their profession, their communities and society at large;
- be aware of the work of associates;
- ensure they are knowledgeable about and comply with respective national and international regulations regarding the physical and biological containment of agents. Where existing measure are thought inadequate such concerns should be raised with relevant policy officials and professional organizations;
- take actions within their own sphere of influence that will contribute to risk reduction;
- ensure that their actions are known amongst and complement the actions of others; and
- acknowledge they have a responsibility to consider the interests and ideas of all segments of society in assessing what needs to be done.

Responsibility for minimizing the risk that life sciences will be used for hostile purposes is not just a matter for individuals, but one for the scientific and medical communities operating as a whole. Collective activities should be undertaken to monitor the threat of biological weapons and to identify actions likely to prevent BW proliferation. As part of this, acting in concert, those representing and funding work in the biosciences and biomedicine should:

- recognize that their expertise means they have a responsibility to contribute to efforts to reduce the risks associated with biological weapons;
- set up procedures whereby those concerned about possible dual-use applications can seek guidance and report any concerns, including whistle blowing on suspicious activities;
- educate their members and the public about the potential for and responses to biological weapons, including through increasing awareness of this Code;
- establish the expectation that where there is disagreement about the implications of experiments and findings, then these should be debated openly;
- institute measures to scrutinize all work with potentially dangerous consequences and to ensure it is submitted to rigorous and independent peer review;
- put in place procedures to survey overall developments in the life sciences to identity emerging areas of concern;
- call for funding to be further directed at alleviating the causes of insecurity and poverty worldwide (e.g. the spread of infectious disease);
- reinforce existing international commitments on states to achieve effective progress towards general and complete disarmament, including the prohibition and elimination of all types of weapons of mass destruction;
- recognize that international agreements are often written in a vague and abstract manner that leaves standards of appropriate conduct ill-defined. Efforts should be made to actively engage governments to elaborate the meaning of prohibitions; and

- call for states to pursue in good faith disarmament negotiations leading to strict and effective international control that are equitable to the multiple concerns in the international community, including the development of a legally binding verification instrument to strengthen the Biological and Toxin Weapons Convention.

In undertaking these measures, individuals and collective bodies should further recognize that concerns about biological weapons are not limited to activities directly contributing to the stockpiling of agents as part of manifestly offensive programmes. For instance, the recurring interest in some quarters for so-called incapacitating agents threatens to undermine international efforts to prohibit the development, production and retention of biological agents of types and in quantities that serve no prophylactic, protective or other peaceful purpose. In addition, however inadvertently, activities undertaken as part of biodefence programmes to elucidate the mechanism of virulence or assess biological threats can undermine international confidence in and in themselves violate prohibition regimes. To prevent this, efforts should be made to strengthen the confidence between peoples and the general improvement of the international atmosphere. The presumption should be that the details of biodefence programmes should be open for public scrutiny.

Several points about the code are worth stressing. In its terms, following the *Software Engineering Code of Ethics and Professional Practice*, the code recognizes the importance and limitations of trying to establish rules specifying proper conduct on many of the difficult dual-use questions. Rather than setting out certain standards and expectations, it seeks to initiate a process of critical reflection and dialogue. The provisions also seek to challenge narrow focuses on biological and physical containment, the responsibilities of individuals, extensive offensive programmes, or non-proliferation agendas. The disarmament focus is meant to link with initiatives in other areas to reinforce efforts against nuclear, chemical and other proscribed weapons. Furthermore, it not only encourages individuals and associations to be aware of and comply with the requirements of international conventions but to actively work towards the clarification of their meaning. As a final point of emphasis, the code does not seek to just make the issue of responsibility a matter for individuals, but rather highlights the importance of collective action. These are just some of the considerations that might fit into codes of conduct in order to take forward discussions about the dual-use threats stemming from the life sciences.

Conclusion

In response to threats from BW, questions are being asked today in some countries about the implications and appropriateness of activities undertaken in the life sciences. Many organizations and governments have suggested that bioscientists adopt a code of conduct to reduce the security concerns associated with their work. Whatever the widespread interest in such a code, however, little has been offered by way of specific information about its possible content or plans for its promulgation.

This article has briefly surveyed the potential contribution of professional codes—including codes of ethics, codes of conduct and codes of practice. In light of the possible contributions and limitations of each type of professional code, an integrated "matrix of codes" was suggested that would consist of different types fulfilling a range of aims for varied audiences. It has not settled questions about what sorts of matrix would be most beneficial, but instead indicates the significance and general outline of one potential approach for further reflection and debate. The ultimate utility of codes depends on the practical commitments made by organizations in promoting and implementing them, matters which cannot be dictated by analyses.

Notes

1. New Scientist, 1968, "Wanted—A Code of Conduct", *New Scientist,* 29 February, p. 453.
2. For further precedents see: W. Pigman and E. Carmichael, 1950, "An Ethical Code for Scientists", *Science,* vol. 111, pp. 643–47; C. Hedén, 1968, "Perspective on an Identity Card or Certificate for Scientists", *Scientific World,* vol. 12, nos. 4/5, pp. 24–28; and A. Cournand, 1977, "The Code of the Scientists", *Science,* vol. 198, pp. 699–705.
3. For information about the recent history of biological weapon codes, see <www.ex.ac.uk/codesofconduct/>.
4. United States, National Science Advisory Board for Biosecurity, at <www4.od.nih.gov/nsabb/>.
5. See <www.un.dk/doc/A.57.0273_S.2002.875.pdf>.
6. See <www.ex.ac.uk/codesofconduct/Chronology/index.htm>.
7. See <www.codesofconduct.org> for many written examples; also C. Soskolne and L. Sieswerda, 2003, "Implementing Ethics in the Professions: Examples from Environmental Epidemiology", *Science and Engineering Ethics,* vol. 9, no. 2, pp. 181–90.
8. M. Iverson, M. Frankel and S. Siage, 2003, "Scientific Societies and Research Integrity: What Are They Doing and How Well Are They Doing It?", *Science and Engineering Ethics,* vol. 9, no. 2, pp. 141–58; A. Doig and J. Wilson, 1998, "The Effectiveness of Codes of Conduct", *Journal of Business Ethics*, vol. 7, no. 3, pp. 140–49; N. Higgs-Kleyn and D. Kapelianis, 1999, "The Role of Professional Codes in Regulating Ethical Conduct", *Journal of Business Ethics,* vol. 19, no. 4, pp. 363–74; K. Shrader-Frechette, 1994, *Ethics of Scientific Research,* Lanham, Rowan & Littlefield.
9. M. Davis, 1998, *Thinking Like an Engineer,* Oxford, Oxford University Press; M. Meselson, 2000, "Averting the Exploitation of Biotechnology", *FAS Public Interest Report* 53, p. 5; S. Unger, 1991, "Code of Engineering Ethics", in D. Johnson, *Ethical Issues in Engineering,* Upper Saddle River, Prentice Hall, pp. 105–30; S. Reiser and R. Bulger, 1997, "The Social Responsibilities of Biological Scientists", *Science and Engineering Ethics*, vol. 3, no. 2, pp. 137–43.
10. A term originally forwarded by Vivienne Nathanson of the British Medical Association.
11. B. Rappert, 2004, "Responsibility in the Life Sciences", *Biosecurity & Bioterrorism,* September, at <www.biosecurityjournal.com>.
12. G. Pearson, 2004, *Some Additional Considerations Regarding a Possible Biological and Toxin Weapons Convention (BTWC) Code of Conduct,* 12 February, at <www.ex.ac.uk/codesofconduct/Publications/Reflections%20on%20SeminarFeb04.doc>.
13. At <www.biotech.ca/EN/ethics.html>.
14. At <www.hir.harvard.edu/articles/?id=919&page=4>.
15. The Institute of Electrical and Electronics Engineers–Computer Society and the Association for Computing Machinery, at <www.acm.org/serving/se/code.htm>.
16. At <www.wma.net/e/policy/b1.htm>.
17. At <disarmament2.un.org/wmd/bwc/BWC%20text-English.pdf>.
18. At <www.icrc.org/Web/eng/siteeng0.nsf/html/5VDJLW?OpenDocument>.
19. Models of this as provided by National Research Council, 2004, *Biotechnology Research in an Age of Terrorism,* Committee on Research Standards and Practice to Prevent the Destructive Application of Biotechnology Washington, DC, National Academies Press, and J. Steinbruner and E. Harris, 2003, "Controlling Dangerous Pathogens", *Issues in Science and Technology,* vol. 19, no. 3 (Spring), at <www.nap.edu/issues/19.3/steinbruner.htm>.
20. See, for example, <fas.org/bwc/papers/code.pdf> and <www.gene-watch.org/programs/biowarfare/call-for-ban.html>.

OPEN FORUM

Lessons from the implementation of the anti-personnel Mine Ban Convention

The First Review Conference of the Anti-Personnel Mine Ban Convention[1] closed in the Kenyan capital, Nairobi, on 3 December 2004 with recognition from more than 1,200 delegates—governmental and non-governmental alike—of the many achievements of the convention and a resounding call for continued efforts to end the scourge of landmines. In the five-year Action Plan adopted by the Review Conference, states parties noted their "unqualified commitment to the full and effective promotion and implementation of the Convention", and recorded their determination, "in full cooperation with all concerned partners … to spare no effort to meet our challenges in universalizing the Convention, destroying stockpiled anti-personnel mines, clearing mined areas and assisting victims."[2]

Although it is only seven years since the convention was opened for signature in Ottawa in December 1997, the result of a bold initiative by Canada, already more than three-quarters of the world's states have adhered to the convention, formally binding themselves to ending the development, production, stockpiling, transfer and use of anti-personnel mines; to clearing emplaced anti-personnel mines; and pledging to assist the rehabilitation and reintegration of the victims of these indiscriminate weapons.

Since its entry into force on 1 March 1999, the convention has contributed directly to the destruction of tens of millions of stockpiled mines, and hundreds of thousands of buried mines across dozens of blighted countries have already been cleared. Although the number of new victims is still far too high, fewer civilians are being killed or injured by landmines than a decade ago, as the worst of the world's contamination is systematically addressed.

In seeking to benefit from these successes, many of the lessons of the negotiation and adoption of the convention have already been identified by experts. However, to date, far less attention has been paid to reviewing the innovative approaches to the implementation of its provisions. How have the states parties sought to maintain commitment and progress towards their common goals, and what more must be done to ensure that the world has brought the mine problem under control once and for all? This article discusses some of the possible responses to these questions by looking in turn at three key interconnected principles underpinning the implementation of the convention: promotion, participation and partnership.

The promotion of the convention

PROMOTING ADHERENCE

Universalizing the convention was a clear and obvious objective from the outset. Effective ratification campaigns were organized by the International Campaign to Ban Landmines (ICBL), the International Committee of the Red Cross (ICRC), and the United Nations, especially the UN Children's Fund (UNICEF), seamlessly transitioning from campaigning in favour of the adoption of a total ban treaty, to promotion of adherence to one. Key states, especially those that had formed the "core group" of governments driving forward negotiations, engaged their diplomatic services to encourage states to join the convention sooner rather than later. Thus, in only fifteen months after its signature, not only had the requisite forty ratifications been secured but the convention was also already in force as binding international law.

To sustain momentum, states parties subsequently decided to create an informal "contact group" of concerned actors to promote universalization. Meeting regularly, this contact group, as is the case with other, similar groups discussed below, has helped to ensure that the efforts of a disparate range of actors, within and outside governments, have been pooled, coordinated and ever more effectively targeted.

Furthermore, the Review Conference itself has proved to be the occasion for a further push towards adherence to the convention, with Estonia and Papua New Guinea joining in 2004, and Latvia, Poland and Sri Lanka moving towards full adherence. In addition, Ethiopia, a signatory to the convention since December 1997, finally handed over its instrument of ratification at the Review Conference itself. The result is that Sub-Saharan Africa, the Americas (with one significant exception), and Western and Central Europe are almost universal in their formal rejection of anti-personnel mines as a weapon. As the Review Conference acknowledged,[3] continued efforts need to be made over the coming years to make these regions unanimous in foreswearing forever this indiscriminate means of warfare. If greater adherence in Eastern Europe, Asia and the Middle East and North Africa can also be secured, the day in which a truly worldwide prohibition of anti-personnel mines exists will draw ever nearer.

PROMOTING COMPLIANCE

But universal acceptance of any treaty does not necessarily translate into universal respect. Indeed, a number of states were concerned during the negotiation of the Anti-Personnel Mine Ban Convention that its provisions would not be sufficiently vigorously monitored, nor any transgressions effectively punished. For this reason, Article 8 of the convention allows for clarification of compliance, including compulsory fact-finding missions in certain, specific circumstances. To date, no state party has deemed it necessary to formally invoke such procedures.

Universal acceptance of any treaty does not necessarily translate into universal respect.

In fact, although since entry into force of the convention the ICBL has alleged violations by a small number of signatories and states parties, the record of its implementation has been remarkable for its consistency of respect. On no occasion has there been any state party engaged in significant production, stockpiling, transfer or use of anti-personnel mines. Quite the contrary, for a great many states have already adopted the necessary domestic measures referred to in Article 9 of the convention—legal, administrative and other—to ensure that this does not occur.

Of course, implementation has been facilitated by the unambiguous obligations inserted in the convention by its drafters. "No exceptions, no reservations, no loopholes!" was the clarion call of the ICBL, and the world can justly be proud that the instrument that emerged from the Oslo Diplomatic Conference was in some ways even stronger than the one that was presented to it as the basis for negotiation. In particular, the undertaking in Article 1, paragraph 1 of the convention "never under any circumstances" to use, develop, produce, stockpile or transfer anti-personnel mines is a sound basis for promoting compliance.

Moreover, states parties have been alert to any developments that might undermine those obligations—rejecting suggestions that a signatory might somehow be allowed to use anti-personnel mines without frustrating the convention's object and purpose, and declining a request by a state party to delay implementation of the requirement to destroy anti-personnel mine stockpiles beyond the allotted four years. The sanctity of the legal instrument—and its intent—has been preserved as a consequence.

Similarly, the ICBL and the ICRC have moved to ensure that the possibility to retain a small quantity of anti-personnel mines for the humanitarian purposes of training in mine detection and clearance and testing of equipment does not serve as a subterfuge for other, unwelcome intent. As a consequence, prevailing legal opinion among states overwhelmingly reflects the understanding of the drafters at the Diplomatic Conference that parties may retain hundreds or thousands of anti-personnel mines in accordance with Article 3 of the convention, but not tens of thousands.

Monitoring of adherence to the convention has largely been achieved through two mechanisms: formal annual reporting by states parties in accordance with Article 7, and civil-society-based oversight through the *Landmine Monitor*, the annual report presented to states parties by the ICBL. Admittedly, in the case of the former, annual reporting is not uncommon in the case of international treaties. But the admirable decision by states parties, through the auspices of the UN Department for Disarmament Affairs, to make every single report publicly available in its entirety (absent certain technical information that might be misused by non-state actors) has built confidence in the process through such transparency.

UN agencies and bodies, among others, have provided assistance to states parties requesting it to prepare these annual reports—with the process of preparation itself supporting interministerial coordination and cooperation in national implementation. Although some reports have been submitted late, overall the level of respect for the reporting provision has been exceptionally high—a recognition of the significance attached to this by all concerned, and to the work of the contact group on Article 7 reporting—comparing more than favourably with other disarmament treaties.

As ever, the legal excellence and commitment of the ICRC has proved invaluable to states parties in promoting the implementation of the convention. In particular, during and prior to the Review Conference, the ICRC worked energetically to try to persuade states to accept appropriate understandings of Articles 1, 2 and 3 of the convention. As Austrian Ambassador Wolfgang Petritsch, the President of the Review Conference, declared in his statement to the opening press conference: "Undoubtedly organizations like the ICBL and the ICRC will tell you how we can do better. … This is precisely what should happen."[4]

It is also difficult, however, to overestimate the importance of the *Landmine Monitor* in verifying compliance by states parties. This remarkable annual publication has helped to ensure that all states parties are both fully aware of their obligations and conscious that any lowering of the high standards set by the convention will be exposed in the *Landmine Monitor*.

The thoroughness of the research, and the detail with which every state's policy and action are reported, whether party to the convention or not, has made the *Landmine Monitor* the essential reference tool for anyone interested in following progress towards a world free of the hideous effects

of landmines. Although states may not always like, or agree with, what the *Landmine Monitor* writes about them, there is almost unwavering respect for the commitment and professionalism the organizations, coordinated by Human Rights Watch, have shown in this publication. The *Landmine Monitor* stands as a landmark in NGO efforts to promote treaty implementation, and the standard by which other, necessary attempts will be judged.

Participation and partnership in the implementation of the convention

Although the detailed procedure for facilitation and clarification of compliance laid down in Article 8 has never been used, arguably paragraph 1 of the provision whereby "The states parties agree to consult and cooperate with each other regarding the implementation of the provisions of this convention, and to work together in a spirit of cooperation to facilitate compliance by states parties with their obligations under this Convention" has been employed successfully ever since its adoption. Regular discussions have been entertained, among others, within the context of an informal contact group on compliance. Indeed, the spirit of cooperation that has been propagated throughout the life of the convention has been one of the hallmarks of its success.

Certainly there have been disagreements—over the interpretation of certain paragraphs contained in the first three articles of the convention in particular. Their significance should not be played down. But what unites all states parties in their interpretation of what is prohibited by the convention far outweighs the issues that divide them. And unanimity of understanding inevitably fuels unanimity of purpose.

That purpose has been established in both formal and informal mechanisms devised to support the implementation of the convention. The Meeting of the states parties has met annually in accordance with Article 11 to review, inter alia, the convention's operation and status; matters arising from annual reports submitted in accordance with Article 7; and international cooperation and assistance in accordance with Article 6. These meetings enabled states parties to reach important, binding decisions regarding the future of the convention.

But a number of states recognized from the outset that annual meetings would not be sufficient *per se* to maintain momentum towards successful implementation of the convention. For this reason, the First Meeting of States Parties decided to hold a series of "intersessional Standing Committee" meetings to look at key issues involved in the application and implementation of the convention. These meetings, held twice-yearly, and which the Geneva International Centre for Humanitarian Demining (GICHD) hosts, have brought together states parties with UN agencies, international and regional organizations, and NGOs from around the world. This partnership between the diplomats, campaigners and, of enormous significance, organizations working in the field, has proved to be a touchstone for the convention, as discussions have been pragmatic and have involved all interested states and other actors.

To support the intersessional process, states parties volunteered to serve as co-chairs and co-rapporteurs for the various Standing Committees, ensuring that both donor and affected states are fully engaged in the implementation of the convention. The Second Meeting of the States Parties in 2000 recognized that the work of the Standing Committees would require a high degree of coordination between the co-chairs to ensure that their work would facilitate the successful implementation of the convention. In this context the states parties established a Coordinating Committee, which meets on an ad hoc basis under the chairmanship of the President of the Meeting of the States Parties for the year.

Genuine participation has been further supported by the Sponsorship Programme, which, to date, has received voluntary contributions of more than US $2 million from over a dozen states parties.

This programme has enabled representatives of states parties needing financial assistance (and, under certain circumstances, other states, such as those designated a priority for universalization efforts) to attend and participate actively[5] in decisions and discussions that affect them at the intersessional meetings and meetings of states parties.

Partnership and participation has been further facilitated by the creation of the Implementation Support Unit (ISU), set up following a decision by the Third Meeting of the States Parties in Nicaragua in 2001, and which the GICHD also hosts. We believe that the ISU has proved a valuable resource for all states parties, helping them to focus on the core aims of the convention.

The ISU has operated through a number of different avenues. First, by working directly with the co-chairs and co-rapporteurs of the Intersessional Standing Committees as well as the Coordinating Committee as a whole, the ISU has facilitated detailed preparation for the Meetings of the States Parties and other fora for dialogue and discussion. Second, the ISU has responded to states parties with suggestions on ways to make best use of the machinery—formal and informal—set up under the auspices of the convention to promote its implementation. In particular, the ISU has given advice on the so-called "4P" approach to implementation. In this, affected states parties are called on to expound the *problems* they are facing, their *plans* for addressing them, the *progress* they have made, and the *priorities* they have identified for urgent action. This enables states parties in a position to do so, to allocate resources and assistance more effectively, on the basis of need. Third, and of no less importance, the ISU has helped to raise the voices of affected states parties in exchanging views on the implementation of the convention.

For the future, states parties at the First Review Conference agreed that they would continue to hold meetings of states parties annually until the Second Review Conference, due in 2009, but that they would reduce the number of weeks of intersessional meetings each year from two to one[6]—ample recognition of the maturity of the process of education and sharing of information among all concerned actors.

Of course, participation and partnership would not be enough to ensure effective implementation, without the requisite mobilization of resources. States parties have taken extremely seriously their obligations under Article 6 to provide adequate resources to support implementation—more than US $250 million is provided each year for mine action, the majority by states parties to the convention.

Sustaining this level of resources in the future, or at least ensuring that needs can be effectively met, was the subject of considerable discussion in the lead-up to the First Review Conference. At the Conference itself, states parties recognized that fulfilling their obligations during the period 2005–2009, including the implementation of the agreed-upon Action Plan, would demand substantial political, financial and material commitments. To this end, states parties in a position to do so pledged to "fulfill their obligations under Article 6 by promptly responding to calls from those States Parties in need", and all states parties agreed "to encourage the international development community … to play a significantly expanded role in mine action …".[7] Undoubtedly, mainstreaming mine action into development activities, for example by incorporating mine action explicitly into a national development plan or a poverty reduction plan in support of the Millennium Development Goals, will be a major challenge for all in mine action over the coming five years.

The future implementation of the convention

As the First Review Conference has closed, so the states parties to the Anti-Personnel Mine Ban Convention have already begun looking forward to the second, due to be held five years from now. By

then, some fifty states parties will have reached the deadline for implementation of Article 5, paragraph 1—"to clear all anti-personnel mines in mined areas under their jurisdiction or control". The challenge remains a huge one. For despite improvements in techniques and equipment, research and development has thus far failed to uncover a cheap and affordable technological solution that will make the slow, laborious nature of mine clearance for humanitarian purposes a thing of the past.

Until that day, the three watchwords of the convention that have brought us so far in so short a time—promotion, participation and partnership—must continue to resound as we strive collectively to end the tragedies caused by anti-personnel mines. We must never resort to "business-as-usual" diplomacy: innovation and flexibility must continue to characterize work to implement the convention. For assistance to the victims of landmines, mine-risk education and stockpile destruction, supported by ever-increasing efforts to universalize the convention, will all have to be pursued relentlessly. For its part, the Geneva International Centre for Humanitarian Demining will pursue its mandate to assist the international community in reducing the impact of mines and unexploded ordnance. As it has for the past five years, the Centre remains committed to support the impressive efforts of the international community to implement the Anti-Personnel Mine Ban Convention.

Ambassador Stephan Nellen
Director
Geneva International Centre for Humanitarian Demining

Notes

1. The formal title of the treaty is the *Convention on the Prohibition of the Use, Stockpiling, Production and Transfer of Anti-Personnel Mines and on their Destruction*.
2. First Review Conference of the States Parties to the Convention on the Prohibition of the Use, Stockpiling, Production and Transfer of Anti-Personnel Mines and on their Destruction, *The Final Report of the First Review Conference of the States Parties to the Convention on the Prohibition of the Use, Stockpiling, Production and Transfer of Anti-Personnel Mines and on their Destruction*, APLC/CONF/2004/5, Part III, "Ending the Suffering Caused by Anti-Personnel Mines: Nairobi Action Plan 2005–2009", Nairobi, 3 December 2004.
3. "We remain gravely troubled that anti-personnel mines continue to kill or maim, adding new victims to the hundreds of thousands of landmine survivors requiring life-long care. … And we call upon those states that have not joined our efforts, and in particular those that possess vast stocks of anti-personnel mines or continue to use this insidious weapon, to adhere to the Convention without delay." First Review Conference, op. cit., Part IV, "Towards a Mine-Free World: the 2004 Nairobi Declaration".
4. Statement by Ambassador Wolfgang Petritsch, President of the Nairobi Summit, to the Nairobi Summit Opening Press Conference, Nairobi, 29 November 2004.
5. Indeed, there is an element of conditionality involved in sponsorship for participation: assisted states are expected, for instance, to present details of their progress towards implementation.
6. First Review Conference, op. cit.
7. First Review Conference, op. cit., Part III.

UNIDIR FOCUS

ACTIVITY

European action on small arms, light weapons and explosive remnants of war

At the request of the European Parliament and the European Commission, UNIDIR is undertaking the study "European Action on Small Arms, Light Weapons and Explosive Remnants of War".

The project takes place against the background of recent European Union involvement in small arms, light weapons and explosive remnants of war (ERW) programmes in key conflict regions. After the last round of enlargement, the EU represents an influential group of twenty-five European nations. The European Community itself has a wide range of instruments at its disposal to promote arms reduction and disarmament. Increasingly, EU Member States act together in a number of multilateral disarmament fora.

The first phase of work is to map and analyse global and EU-level activities related to small arms, light weapons and ERW. This research will determine where there are gaps, overlaps or divergences that could be ameliorated by the EU. The second phase of work is to develop a conceptual framework for addressing these matters. The third phase is to formulate recommendations for the EU. The research findings will be presented to the EU at a conference in late 2005. The fourth phase of work is a field validation study that will test some of the key research results in the field.

The project will be carried out over the next eighteen months by a dedicated team at UNIDIR, working closely with the International Security Information Service-Europe as an implementing partner. The project will also benefit from the expertise of a number of specialized agencies and institutes, contributing research papers on specific topics of relevance to the EU.

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In each issue of *Disarmament Forum*, UNIDIR Focus highlights one activity of the Institute, outlining the project's methodology, recent research developments or its outcomes. UNIDIR Focus also describes a new UNIDIR publication. You can find summaries and contact information for all of the Institute's present and past activities, as well as sample chapters of publications and ordering information, online at <www.unidir.org>.

NEW PUBLICATION

Implementing the United Nations Programme of Action on Small Arms and Light Weapons: Analysis of the Reports Submitted by States in 2003

In 2001 the United Nations General Assembly called on Member States to submit reports to the Secretary-General on the progress made in implementing the UN Programme of Action on Small Arms and Light Weapons (PoA), adopted earlier the same year. This national reporting provides an opportunity for states to review their progress made in national implementation efforts and identify the challenges remaining.

The United Nations Development Programme (UNDP), the United Nations Department for Disarmament Affairs (UNDDA), the United Nations Institute for Disarmament Research (UNIDIR) and the Small Arms Survey analysed the national reports submitted in 2003 to identify major developments in the implementation of the PoA and highlight issues of concern for states. This was undertaken in the context of the project entitled "Capacity Development for Reporting to the UN Programme of Action on Small Arms".

Entitled *Implementing the United Nations Programme of Action on Small Arms and Light Weapons: Analysis of the Report Submitted by States in 2003*, the goal of the study is to ascertain current levels of state commitment to the PoA by reviewing the various national, regional and international initiatives related to small arms underway, as well as identifying the strengths and weaknesses of the reporting process.

Overall, the findings are encouraging—103 out of 191 Member States submitted reports in 2003. The national reports show that notable progress has been made in implementing the PoA, especially in regard to national legislation, weapons collection and destruction, and awareness-raising activities. Regional and international cooperation is growing and involves an increasing number of governmental actors, regional and international organizations and elements of civil society. Moreover, national reports have proven to be an invaluable resource for information exchange and serve as an important reference for countries affected by illicit small arms proliferation as well as countries funding disarmament programmes around the globe.

However, there is still a need for enhanced implementation efforts if states are to prevent, combat and eradicate the menace posed by illicit small arms and light weapons. Tackling this problem effectively requires a comprehensive and inclusive approach in all related thematic aspects, incorporating national, regional and global dimensions. This publication is already contributing to reflection in Member States on how to make their next reports more comprehensive and thereby further improve implementation of the PoA.

Implementing the United Nations Programme of Action on Small Arms and Light Weapons: Analysis of the Reports Submitted by States in 2003

Elli Kytömäki and Valerie Yankey-Wayne

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