Strengthening the Chemical Weapons Convention

First CWC Review Conference Paper No 4

The Danger to the Chemical Weapons Convention from Incapacitating Chemicals

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THE DANGER TO THE CHEMICAL WEAPONS CONVENTION FROM INCAPACITATING CHEMICALS

Malcolm Dando*

Introduction

1. On 23 October 2002 a group of some 50 Chechens took over 700 people hostage in a Moscow theatre. Three days later Russian forces stormed and retook the building after two hostages were killed. The action by Russian forces was preceded by large quantities of 'gas' being pumped into the building with the intention of incapacitating the hostage-takers. The hostage-takers and over 120 hostages died, and many others were hospitalised because of the effects of the gas. In January 2003 some of the hostages were taking legal action against the authorities and complaining of persisting neurological problems.[1]

2. The 'gas' used was stated by the Russian Health Minister to be a derivative of fentanyl, an opiate chemical related to morphine,[2] perhaps mixed with other agents.[3] Reports suggesting that atropine, an antidote to anticholinergic nerve agents, did not reverse the effects of the gas whereas naloxone, an antidote to opiates, did supported the conclusion that a fentanyl derivative was used in the attempt to incapacitate the hostage-takers.[4] [5]

3. These events and their consequences raise much wider questions about human rights than will be discussed here.[6] In regard to the Chemical Weapons Convention (CWC), it might, at first sight, appear that there is little to be discussed. The Russian Health Minister stated that the hostage deaths from the gas had been the result of their weakened state and insisted that the Chemical Weapons Convention had not been violated. The US President was reported to feel *"very strongly that responsibility for this [the hostage deaths] rests with the terrorists who took these people hostage"*.[7] It might also be argued that the use of an agent that was believed to be an anaesthetic which *"could not cause death"*[8] falls under the "Purposes not

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[1]CBS News.com (2002) *Moscow Theater Victims Sue City*. Available at http://www.cbsnews.com/stories/2002/10/31/world/main527614.shtml

[2]CBS News.com (2002) *Russia IDs Theater Gas: Fentanyl*. Available at http://www.cbsnews.com/stories/2002/10/31/world/main527614.shtml

[3]Van Damme, B. (2002) Moscow theatre siege: a deadly gamble that nearly paid off. *The Pharmaceutical Journal*, **269** (7224), 723-724.

[4] Fox News (2002) U.S. *Questions Use of Chemical Gas.* Available at http://www.foxnews.com/story/0,2933,66911,00.html

[5]Fox News (2002) *Gas Russia Used in Hostage Siege was Fentanyl, U.S. Officials Say.* Available at http://www.foxnews.com/story/0,2933,669,88,00.html

[6]Amnesty International (AI) Index [2002] *Russian Federation: Update on the situation regarding Chechens and in the Chechen Republic following the October hostage taking incident in Moscow.* Available at http://web.amnesty.org/802568F7005C4453/0/42BF43279E3E80880256C8500408F2F?Open

[7]CNN.com/WORLD (2002) *Russia names Moscow siege gas.* Available at http://europe.cnn.com/2002/WORLD/europe/10/30/moscow.gas/

[8]CBS News.com (2002) *Russia IDs Theater Gas: Fentanyl*. Available at http://www.cbsnews.com/stories/2002/10/31/world/main527614.shtml

Prohibited" exemption of paragraph 9 (d) of Article II of the CWC which allows use of chemicals for *"Law enforcement including domestic riot control purposes"*.[9]

4. As with any chemical incapacitants, the concentration of fentanyl in any particular part of the building will have been difficult to control, the effects of any given concentration of fentanyl on any particularly susceptible individual would not have been known, and achievement of a certain separation between the incapacitating and lethal effects of the drug -- in other words, discriminating between making people unconscious without stopping them breathing -- is very difficult.[10] Yet it can be argued that the rescue operation in Moscow was a success as *all* of the hostages could have been killed if the Chechens had been able to use all the explosives they had available.

5. In the wake of the Moscow incident, other security and military forces may have analysed what happened in Moscow and decided that chemical incapacitants, whatever their limitations, could have a genuine advantage in such difficult operations. It is well known[11] that in April 1997 the US Senate ratified the Chemical Weapons Convention with specific exemptions[12] that would allow the use of riot control agents in operations other than war - for example, to deal with mixed groups of hostile combatants and non-combatants - outside of domestic territory. However, these exemptions were not tabled by the United States as reservations to the Convention.

6. This Review Conference Paper recognises that any such interests on the part of security and military agencies may have been given significant enhancement by the scientific and technological developments during the 1990s that might be seen to allow improved differentiation between the incapacitating effects of some chemical agents and their other, more dangerous, effects. Clearly, if such opportunities are seen to exist, and are widely exploited, erosion of the General Purpose Criterion[13] at the heart of the Convention is highly probable. For that reason the issue of novel non-lethal chemicals cannot be ignored by the Review Conference which, according to paragraph 22 of Article VIII[14]:

"...shall take into account any relevant scientific and technological developments..."

7. Fentanyl, which was discovered in the late 1950s[15] and has been widely used in medicine[16] and as a drug of abuse (with numerous derivates)[17], is widely known. This Paper goes on to

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[9]The Chemical Weapons Convention (text). Available at http://www.opcw.org/html/db/cwc/eng/cwc_article_II.html

[10]CNN.com/WORLD (2002) *Russia names Moscow siege gas*. Available at http://europe.cnn.com/2002/WORLD/europe/10/30/moscow.gas/

[11]Dando, M. R. (2002) Future incapacitating chemical agents: The impact of genomics, pp 167-181 in N. Lewer (ed.), *The Future of Non-Lethal Weapons*. Frank Cass, London.

[12]Gordon, A (1997) *Implications of the US Resolution of Ratification*, CBW Conventions Bulletin, December, No. 38, pp. 1-6. Available at http://fas-www.harvard.edu/~hsp.pdf.html

[13]Pearson, G.S. (2003) *Implementing the General Purpose Criterion of the Chemical Weapons Convention*. First CWC Review Conference Paper No. 3, University of Bradford, January. Available at http://www.brad.ac.uk/acad/scwc .

[14]The Chemical Weapons Convention (text). Available at http://www.opcw.org/html/db/cwc/eng/cwc_article_VIII.html

[15]Street Drugs (2003) *Fentanyl*. Available at http://www.streetdrugs.org/fentanyl.htm

[16]Medline Plus Health Information (2003) *Fentanyl*. Available at http://www.nlm.nih.gov/medlineplus/druginfo/supdi/203780.html

[17]Drug Facts (2003) *Street Terms: Drugs and the Drug Trade: Fentanyl*. Available at http://www.whitehousedrugpolicy.gov/streetterms/ByType.asp?intTypeID=30

consider the recent advances in drug development and the expanded understandings of the effects of drugs on the body, and examines how such new knowledge might be subject to misuse. Finally, consideration is given to the origin, nature and implications of paragraph 9 (d) of Article II and what action needs to be taken by the Review Conference to ensure that there is no erosion of the purpose and objective of the Convention.

Modern Drug Development

8. There was certainly considerable interest in the development of chemical incapacitants during the early and middle Cold War periods. According to the original SIPRI study of *The Problem of Chemical and Biological Warfare*, means were sought, for example, to induce hypotension, emesis, alterations in body temperature, loss of balance, temporary blindness, uncontrollable muscular tremors and numerous psychotropic effects.[18] Whilst the evolutionary process had produced some chemicals with reliable effects -- for example, staphylococcal enterotoxin B, which is now known to overstimulate the immune system and thereby cause illness (and which was weaponised as an incapacitant) -- producing new synthetic agents remained very difficult. Once a compound was found which had an interesting effect, much medicinal chemistry expertise was expended to try to enhance the effect by modification of this 'lead' compound. Moreover, whilst there were many mechanisms by which the operation of the central nervous system could theoretically be disrupted, in the opinion of the SIPRI authors much more would need to be known about the workings of the nervous system and the actions of psychochemicals on the brain before effective intervention would be possible.

9. Since then, the enormous burden of unhappiness and economic costs caused by major mental illnesses such as inappropriate anxiety, dysregulation of mood, disturbances of perception and thought (psychoses), and cognitive dysfunction, in both the developed and developing worlds, have driven the search for new means to help the mentally ill.[19] The serendipitous discovery of some chemical agents that were of help, in the years following the Second World War,[20] has helped to ensure that the search for new and more effective drugs plays a major part in this effort. Success in that enterprise has been greatly facilitated by the steadily increasing improved understanding of the brain and of the way in which drugs act upon it.

10. Transmission of information from sense organs of the body and of information to effector organs, and information processing in the brain and spinal column are carried out by specialised cells called neurons. Within each neuron information is transmitted by electrical means (nerve impulses that can be experimentally recorded). However, transmission of information *between* neurons and between neurons and effector organs is overwhelmingly by chemical means. Junctions between neurons and between neurons and effector organs like muscles are called synapses. When a nerve impulse reaches the end of a neuron it causes the release of a neurotransmitter chemical. This chemical affects the post-synaptic cell in such a way as to either enhance the likelihood that a nerve impulse will be generated in the post-synaptic cell (excitation) or to reduce the likelihood (inhibition). Drugs for the treatment of

[18]SIPRI (1973) *The Problem of Chemical and Biological Warfare: Volume II CB Weapons Today.* Almqvist and Wiksell, Stockholm

[19]World Health Organization (2001) *Mental health: New understanding, new hope.* World Health Report 2001, World Health Organization, Geneva.

[20]Barondes, S. H. (1993) *Molecules and Mental Illness.* Scientific American Library, New York.

mental illness have been designed to affect such processes. As a report in 1999 by the US Surgeon General noted[21]:

> *"Put simply, most antidepressants are designed to heighten the level of a target neurotransmitter at the neuronal synapse. This can be accomplished by one or more of the following therapeutic actions: boosting the neurotransmitter's synthesis, blocking its degradation, preventing its reuptake from the synapse into the presynaptic neuron, or mimicking its binding to postsynaptic receptors..."*

Whilst there is obviously much more to learn about these processes the Surgeon General's report makes clear that enormous progress is being made. In particular, the recent development of new means of neuroimaging has helped to elucidate which parts of the brain are active when certain behaviours are undertaken. The report notes:

> *"...Ultimately, however, the goal is not only human self-understanding. In knowing eventually precisely what goes wrong in what circuits and what synapses and with what chemical signals, the hope is to develop treatments with greater effectiveness and with fewer side effects..."*

These laudable aims have been made much more achievable also by the revolution in our understanding of the human genome - the genomics revolution.

11. Most communication between neurons is through the production and reception of chemical signal neurotransmitters, but the reception system is complex and **it is the elucidation of the receptors for neurotransmitters that has been facilitated by the genomics revolution.** The receptors for neurotransmitters are protein molecules embedded in the cell wall of the neuron. The receptors are of two main types. One type is involved in fast actions and the neurotransmitter binding to the receptor opens a pore in the receptor molecule through which ions can pass to effect change in the second nerve cell. The second type is involved in slower and often more complex actions. These slower G protein-coupled receptors do not operate by the neurotransmitter's binding directly opening a pore in the receptor molecule, but instead by the neurotransmitter interacting with the receptor to cause a change in the associated G protein located inside the cell wall. The change in the G-protein may then initiate a variety of further changes in the cell. The genomics revolution is crucial because[22]:

> *"...the genome sequence information will allow us to make a short-list of proteins with a high probability of becoming drug targets. In the neuroscience area, G protein-coupled receptors (GPCRs) and ion channels are obvious candidates because most existing drugs for neurologic and psychiatric diseases act on these classes of target..."*

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[21]Surgeon General (1999) *Mental Health: A Report of the Surgeon General*. Department of Health and Human Services, U.S. Public Health Service.

[22]Hefti, F. (2001) From genes to effective drugs for neurological and psychiatric diseases. *Trends in the Pharmacological Sciences*, **22** (4), 159-60.

Indeed, so fast has been the flow of information on GPCRs that there are now many 'orphan' GPCRs for which no natural neurotransmitter is currently known. An estimate in 2001 gives some idea of the drug development opportunities available[23]:

> *"...At present ~300 full open reading frames that encode putative members of the GPCR super family can be identified from the public databases. Of these 191 are classified as known receptors, activated by around 70 known ligands [natural transmitters], and 108 are described as orphan receptors..."*

An idea of the dramatic rate of change in the 1990s can be gathered from analysing one standard source that provides annual information on receptors. In 1990 when the source was first produced there were just 30 pages of information. In 2001, in the 12th edition, this had expanded to 145 pages with a huge amount of detail on the many new receptor types discovered.[24] As a consequence, a medicinal chemist is no longer 'fishing in the dark' but knows a great deal about the receptor structure he is trying to target with a drug - or novel agent.

Potential Misuse?

12. The level of understanding now available to neuroscientists can be appreciated by considering the state of knowledge about fentanyl and its actions. Fentanyl was first synthesised in Belgium in the 1950s.[25] It has an analgesic potency about 80 times that of morphine. It is called an opioid because of the similarity of its effects to those of morphine.[26] Fentanyl and two other related chemicals, alfentanyl and sufentanil, are widely used for anaesthesia and analgesia. Over 12 different analogues of fentanyl are also used as illegal designer drugs.

13. Extracts from the poppy have been used to relieve pain for hundreds of years and morphine was first crystallised from extracts of the plant in 1803.[27] Many chemical modifications of morphine -- for example to produce heroin, methadone and codeine -- were made well before the genomics era in order to try to improve the utility of the drug. Given the potency of morphine, and the specificity of chemical structure required to produce its effects, it was proposed in the 1950s that it must be interacting with a specific receptor and in the 1970s endogenous peptides with similar effects were discovered. There are now thought to be three classical types of opioid receptor for these peptides: ß-endorphin has strongest effects on µ receptors, enkephalins act most strongly at delta receptors and dynorphins at kappa receptors. All these receptors are of the GPCR type. There has also recently been the discovery of a structurally-related opioid-like GPCR receptor N/OFQ. Morphine and fentanyl exert their main actions through their effects on µ receptors[28]:

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[23]Howard, A. D. *et al*. (2001) Orphan G-protein-coupled receptors and natural ligand discovery. *Trends in the Pharmacological Sciences*, **22** (3), 133-140.

[24]Alexander, S. *et al*. (2001) *TiPs Nomenclature Supplement*. Elsevier.

[25]US Drug Enforcement Agency (2003) *Fentanyl*. Available at http://www.usdoj.gov/dea/concern/fentanyl.html

[26]Stone, T. W. (1997) *Neuropharmacology*. W. H. Freeman/Spektrum, Oxford.

[27]Corbett. A., McKnight, S. and Henderson, G. (2003) *Opioid Receptors*. Available at http://opioids.com/receptors/index.html

[28]Stone, T. W. (1995) *Neuropharmacology*. W. H. Freeman/Spektrum, Oxford.

"The μ-receptors are responsible for the induction of analgesia at the level of the brain, but also mediate the respiratory depressant and euphoric actions of opioids..."

14. Rapid progress in the understanding of the circuits involved and of the pharmacology continues, for example through the use of 'knock-out' mice in which particular receptor types have been rendered non-functional.[29] There is also evidence that there may be sub-types of the μ receptor involved in respiratory depression[30] and therefore that more specifically targeted drugs could become available. Additionally, as the International Union of Pure and Applied Chemistry has stressed, there are now techniques to develop and investigate - for good or ill - huge numbers of such chemicals:[31]

"The application of automated syntheses and high throughput screening by pharmaceutical and agrochemical companies has produced databases of physiological properties associated with millions of chemical compounds..."

Clearly, then, we are in a new situation in which there are incredibly rapid developments in our understanding of brain circuits, receptor types and sub-types, and in our ability to synthesise and test novel chemicals that may have effects on such receptors.

15. A straightforward test of how simple it would be to misuse such capabilities is to ask the following question, *"In regard to neurotransmitters where there is some good reason to suspect that there could be interest in abuse, have chemicals with specific actions on specific receptor sub-types been developed?"* If this level of capability is clearly present amongst those striving to achieve benign results and publishing in the open literature, it is a reasonable supposition that those with malign purposes in mind could develop chemicals to attack such receptor sub-types. Should that be the case, we necessarily have to ask what more can be done to prevent misuse. The next sections of this Paper show, by examination of developments in bioregulators and neuroscience, that this level of capability is indeed present.

Bioregulators

16. Although this Paper is focused primarily on the possible misuse of our growing understanding of the circuits, neurotransmitters and receptors of the central nervous system, it needs to be recognised that neurotransmitters are but one class of signalling molecules in the body. Other classes that also act through cellular receptors are the hormones of the endocrine system and the cytokines of the immune system. All these bioregulators are amongst the mid-spectrum agents covered by the prohibitions of both the Chemical Weapons Convention and the Biological and Toxin Weapons Convention. Bioregulators have been described as[32]:

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[29]Sora, I. *et al*. (1997) Opiate receptor knockout mice define μ receptor roles in endogenous nociceptive responses and morphine-induced analgesia. *Proc. Natl. Acad. Sci*., **94**, 1544-1549

[30]Colman, A. S. and Miller, J. H. (2001) Modulation of breathing by μ_1 and μ_2 opioid receptor stimulation in neonatal and adult rats. *Respiratory Physiology*, **127**, 157-172.

[31]IUPAC (2002) *Impact of Scientific Developments on the Chemical Weapons Convention*. Report to the Organisation for Prohibition of Chemical Weapons and its States Parties by the Union of Pure and Applied Chemistry. Available at http://www.iupac.org

[32]Kagan, E. (2001) Bioregulators as instruments of terror. *Clinics in Laboratory Medicine*, **21** (3), 607-618.

"...naturally occurring organic compounds that regulate diverse cellular processes in multiple organ systems. As such, they are produced in very small quantities in a variety of living organisms and are essential for the normal homeostatic functions of the body..."

They may be defined as:

"...structurally diverse compounds that are capable of regulating a wide range of physiologic activities, such as bronchial and vascular tone, muscle contraction, blood pressure, heart rate, temperature and immune responses..."

It is well known that the presence of such substances in unusual quantities, or in forms modified to alter their potency, can be extremely disruptive, leading to illness, incapacitation or death.

17. Against that background it is not surprising to find that some of the mechanisms of incapacitation sought during the 20th century Cold War period could be achieved with much greater ease today. One detailed review[33] deals with endogenous pyrogens that cause fever, eicosanoids that cause bronchoconstriction and excessive mucus production in the lungs, the hormone insulin that can cause hypoglycemia and the blood kinin bradykinin that can cause hypotension. This review is also of interest because it lists some of the advantages to an attacker of using bioregulators. These include:

- non-specific effects that make diagnosis difficult;

- rapid onset of action;

- no vaccines available to immunize potential victims;

- not on any threat list making detection and diagnoses very difficult; and

- the possibility of unusual modes of distribution.

The last point is of particular importance because the review goes on to point out the potential for enormously widespread consequences in using a bioregulator. For example, if a bacterium was engineered to carry the gene for a dangerous cytokine in a plasmid and this bacterium containing the plasmid was dusted across major crops:

"...If the bacterial plasmid was present in sufficiently large numbers to contaminate the food chain supply of a ***country, region, or economic zone****...the adverse health consequences for susceptible groups of individuals could be considerable..."* [Emphasis added]

18. In short, it is important not to view the problem of dealing with non-lethal chemical agents as one solely related to *tactical* military actions. Indeed, it is not difficult to find other ways in which such large-scale effects could be achieved - for example, in the direct contamination of the food or beverage supply chain in developed countries by terrorist groups.

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[33]Kagan, E. (2001) Bioregulators as instruments of terror. *Clinics in Laboratory Medicine*, **21** (3), 607-618.

19. What has also to be understood is the range of potential abuse that will become possible in coming decades. As Professor Matthew Meselson of Harvard University has argued[34]:

> *"...During the century ahead, as our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life but* ***will became able to manipulate it - including the processes of cognition, development, reproduction and inheritance****..."* [Emphasis added

Such developments will have profound implications. As Meselson continued:

> *"A world in which these capabilities are widely employed for hostile purposes would be a world in which the very nature of conflict had radically changed.* ***Therein could lie unprecedented opportunities for violence, coercion, repression or subjugation****..." [Emphasis added]*

The threat to human rights from such a misuse of the life sciences is obvious -- particularly in regard to the potential for the manipulation of brain and behaviour that could lie ahead.

Neuroscience

20. Whilst there has been considerable concern about the impact of modern genetics on our society there has been a strange silence on the implications of growing capabilities in neuroscience. There are some recent indications, however, of an awakening to the threats to civil society. In May 2002, for example, the London *Economist* carried a front page headlined "The Future of Mind Control" and a lead article[35] contrasted the great concern over misuse of genetics with the apparent unconcern over neuroscience: *"If you want to predict and control a person's behaviour, the brain is the place to start"*. A detailed article[36] in the same issue noted:

> *"...pharmaceutical companies are only just beginning to mine the spectrum of psychological ailments that flesh is heir to. Drugs to combat shyness, forgetfulness, sleepiness and stress are now in or close to clinical trials, not to mention better versions of drugs that have already swept society..."*

The authors expressed concern over the lack of regulatory control of such developments which begin to impact on the very conceptions we have of what it is to be human.

21. Such concerns were taken up by Francis Fukuyama in his book, *Our Posthuman Future: Consequences of the Biotechnology Revolution*[37]. In particular, in a chapter on *"Neuropharmacology and the Control of Behavior"*, he pointed out that:

> *"...Long before genetic engineering* [of human beings] *becomes a possibility, knowledge of brain chemistry and the ability to manipulate it will become an important source of behavioral control that will have significant political*

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[34]Meselson, M. (2000) Averting the hostile use of biology. *Chemical and Biological Weapons Conventions Bulletin*, **48** (June), 16-19.

[35]Leader (2002) The future of mind control. *The Economist*, 25 May, p 11

[36]Anon. (2002) The ethics of brain science: Open your mind. *The Economist*, 25 May, 93-95.

[37]Fukuyama, F. (2002) *Our Posthuman Future: Consequences of the Biotechnology Revolution*. Farrar, Straus and Giroux, New York.

implications. We are already in the midst of this revolution and do not have to spin out science fiction scenarios to see how it might unfold."

These authors are all concerned with the implications of the actions of those without hostile intent. What then of Meselson's concerns about those **with** such hostile intent?

22. The first neurotransmitter to be discovered, in the early 20th century, was acetylcholine. This would obviously also be the first target one would consider for abuse because it has been the prime target for modern chemical weapons. Acetylcholine is broken down in the synapse by acetylcholinesterase, which limits the action of the transmitter to the appropriate level. The lethal nerve gases developed in the last century acted by inhibiting the function of the acetylcholinesterase. Thus the synapses were inappropriately flooded with acetylcholine. Even minute amounts of nerve gases like tabun (GA), sarin (GB), soman (GD) and VX were sufficient to kill. That much is well known. Less well known are the considerable efforts that went into producing incapacitating agents which also interfered with transmission at acetylcholine synapses. The United States did, in fact, weaponise one such agent called BZ -- 3-quinuclidinyl benzilate, and Iraq is said to have a similar agent called Agent 15[38]. The currently available drugs for treating the cognitive decline in Alzheimer's disease are also designed to cause a limited inhibition of acetylcholinesterase and thus to try to prevent the loss of acetylcholine which characterises this disease[39].

23. When efforts were being made to produce effective incapacitants like BZ during the Cold War period it was known that there were two different types of acetylcholine synapse. Nicotine mimics the effects of the transmitter at synapses on skeletal muscle so these synapses are termed nicotinic. Muscarine, an extract from a particular type of mushroom, mimics the effects of the transmitter at synapses on heart muscle so these types are called muscarinic. The difficulty those engaged in developing weapons in the Cold War era had was that they did not know what we now know, that there are nine sub-types of nicotinic and five sub-types of muscarinic receptor. The muscarinic sub-types are the most important in the brain. Clearly, without such knowledge, designing a reliable incapacitant was almost impossible and BZ was eventually rejected as too variable in its effects.

24. It is known that the DNA coding sequences of the muscarinic receptors are strongly conserved across the evolutionary sequence of animals. This suggests that they have very important functions and that if mutations occur the affected animals die out. The range of functions in which muscarinic receptors are involved include the following[40]:

"In the periphery...muscarinic receptors mediate smooth muscle contraction, glandular secretion, and the modulation of cardiac rate and force. In the CNS [Central Nervous System]*, there is evidence that muscarinic receptors are involved in motor control, temperature regulation, cardiovascular regulation and memory..."*

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[38]Dando, M. R. Future incapacitating chemical weapons: The impact of genomics. Pp 167-181 in N. Lewer, (ed.), *The Future of Non-Lethal Weapons: Technologies, Operations, Ethics and Law*. Frank Cass, London.

[39]Bartfai, T. and Sellstrom, A. (2002) *Neurobiology, weapons, humanity.* Presentation at the ICRC Symposium on Biotechnology, Weapons and Humanity, Montreux, 23 September.

[40]Caulfield, M. P. and Birdsall, N. J. M. (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacological Reviews*, **50** (2), 279-290.

Clearly, this range of functions is of considerable interest to the medical profession (for example, for treatment of the loss of memory in Alzheimer's disease), and pharmaceutical companies will make great efforts to find drugs which have controllable effects at acetylcholine synapses.

25. Designing drugs to bind to just one of the sub-types of muscarinic receptor was considerably facilitated in the late 1990s when it became possible, through the use of genetic engineering, to breed mice lacking just one of the five different sub-types of muscarinic receptor. From the investigation of such mice it became clear that the M_2 receptor is one sub-type of muscarinic receptor that functions as an inhibitory *auto*receptor - as the neuron produces acetylcholine, the M_2 receptors on that neuron are affected by it and as a consequence production of acetylcholine is reduced. Thus a selective antagonist drug which blocked M_2 receptors without affecting other types should increase the amount of acetylcholine available. A contribution[41] to a recent symposium on muscarinic receptor research described:

> *"...the high M_2 receptor selectivity of SCH72788, which has a reasonable **in vivo** activity, and, in conscious rats, increases ACh* [acetylcholine] *concentrations in the striatum* [part of the brain] *and shows positive effects on a rat model of passive avoidance* [behavioural test]*..."*

Work on such chemicals continues in the hope of finding new means of dealing with Alzheimer's disease[42]. However, if it is possible to design a specific antagonist to block such synapses, it is just as possible for those with malign intent to design a specific agonist to activate such receptors and close down acetylcholine production. So instead of reducing cognitive deficiencies in disease one might induce them in healthy individuals -- perhaps with few other side-effects.

26. Acetylcholine is a simple small molecule that one would intuitively think of as being suitable for a role as a fast-moving signalling chemical and there are others, for example noredrenaline. When neurotransmitters were first being discovered it was thought that a particular neuron would produce only one such type of 'classical' chemical transmitter. Later it was discovered that there are also **peptide** transmitters (peptides are short strings of amino-acids specified by a much smaller series of metabolic stages from the DNA of genes). It also became clear that a particular neuron can produce more than one type of neurotransmitter and it is often the case that a small molecule classical transmitter and a neuropeptide transmitter are produced by the same cell. As for classical neurotransmitters, there are sub-types of receptor for the neuropeptide transmitters. With such degrees of complexity, there are obviously many potential targets for new drugs or chemical agents.

27. Military discussions of such neuropeptides are not often found in the open literature. However, an article[43] entitled *"An Evaluation of Bioregulators as Terrorism and Warfare Agents"* was published in the *Applied Science and Analysis Newsletter* in mid-2002. This

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[41]Birdsall, N. J. M., Nathanson, N. M. and Schwarz, R. D. (2001) Muscarinic receptors: It's a knockout. *Trends in the Pharmacological Sciences*, **22** (5), 215-219.

[42]Lachowicz, J. E. (2002) Selective M_2 antagonists facilitate acetylcholine release and improve performance in behavioural models of cognition. Presentation 115.2 in the Symposium on "Advances in Muscarinic Receptor Research" at the *International Congress of Pharmacology*, San Francisco, 7-12 July.

[43]Bokan, S., Breen, J. G. and Orehovec, Z. (2002) An evaluation of bioregulators as terrorism and warfare agents. *Applied Science and Analysis Newsletter*, **02-3**, June, 1 and 16-19.

article evaluated sixteen peptide bioregulators first against criteria for selection as a warfare agent and then against criteria for selection as a bioterrorism agent. The criteria included the possibility of effective dissemination, toxicity, incapacitation, no effective prophylaxis and therapy, stability in the environment, difficulty of detection and identification and ease of production. All sixteen bioregulators were given high cumulative scores which, the authors suggested, indicates that they need to be given careful consideration by experts. In general, they concluded that:

> *"...Advances in discovery of novel bioregulators, especially bioregulators for incapacitation, understanding of their modes of operation and synthetic routes for manufacture have been very rapid in recent times. Some of these compounds may be potent enough to be many hundreds of times more effective than traditional chemical warfare agents..."*

How then do such neuropeptides fare against the question asked earlier -- whether selective synthetic agents have already been found for particular receptor sub-types. The answer is again that the capability to design selective synthetic agents to target specific receptor sub-types is already available.

28. Endothelin is a 21-amino-acid chain -- a peptide -- which provides a spectacular example of the speed at which discoveries are being made. Until the 1980s it was thought that the tissue which lines blood vessels (the endothelium) functioned only as a barrier to the passage of various nutrients and other substances. It is now clear that this tissue is a widely dispersed 'organ system' with important physiological roles. Indeed, in the mid-1980s it was discovered that the cells of this endothelial tissue could release a peptide which is the most potent and long-lasting endogenous vasoconstrictor yet discovered -- endothelin. Endothelin has a curious structure similar to that of certain snake venoms, and given its known properties, it is little surprise that is has been raised as an agent of potential concern in official documents produced during the negotiations in the 1990s on strengthening the effectiveness of the Biological and Toxin Weapons Convention[44]. In mammals there are three endothelins, ET-1, ET-2 and ET-3. ET-1 is the main vasoconstrictor in humans. The endothelins act through two different GPCR sub-types, ET_A and ET_B. The ET_A receptor has highest affinity for ET-1 while the ET_B receptor has equal affinity for all three endothelins. Many synthetic selective antagonists for ET_A have been developed and both agonists and antagonists for ET_B. Under normal conditions endothelin is not a circulating hormone but acts locally where it is produced. The bioregulator endothelin has complex functions in the regulation of blood pressure, development and central nervous system functions. In the open literature its possible malign misuse has focused on its potential effects on the operation of the blood system[45]. It is perhaps significant that there is already a licensed drug - bosentan - on the market which is a synthetic ET_A/ET_B antagonist used to treat high blood pressure.

29. Substance P has been known since the early 1930s. Again, it is a neuropeptide which is a member of a group of tachykinins comprising, in mammals, substance P, neurokinin A and neurokinin B. Three GPCR receptor sub-types have been discovered so far: these are NK1, NK2 and NK3. Substance P has greatest affinity for the NK1 receptor. Substance P has many

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[44]Russian Federation (1992), Illustrative List of Potential BW Agents, Ad Hoc Group of Governmental Experts to Identify and Examine Potential Verification Measures from a Scientific and Technical Standpoint, BWC/CONF.III/VEREX/WP.23, Geneva, 7 April. Available at http://www.opbw.org

[45]Hamilton, M. G. (1998) Toxins: The emerging threat. *ASA Newsletter*, **98** (3), 1 and 20-26.

functions, but it is of concern to biodefence authorities because it can cause intense bronchoconstriction. One study[46] concluded that:

> *"Exposure to the substance at extremely low air concentrations may result in incapacitation in humans."*

The mechanism causing bronchoconstriction is complex, but synthetic antagonists to NK1 have been tested in clinical trials in an attempt to find means of alleviating asthma. However, substance P is widely distributed in the nervous system and most recently it has been of interest in relation to depression. The synthetic antagonist MK-869 appears to alleviate depression effectively which has obviously sparked intense interest in this new route for helping people with such a major mental illness[47]. It is clearly also at least possible that an effective synthetic agonist could *induce* depression.

30. An idea of the full range of present possibilities can be gained from a study carried out by a group in the United States known to be closely associated with the Joint Non-Lethal Weapons Directorate. The study[48], entitled *"The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique"* makes clear that there are other classes of compounds besides calmatives, such as convulsives, that could be of interest to those seeking such capabilities. Calmatives are defined as agents that induce a calm or tranquil state. Nine different types of neurotransmitter/receptor system are discussed in the report. Not surprisingly, these include opioids and μ receptor agonists, as well as a wide range of classical and peptide neurotransmitters.

31. According to the report:

> *"...The researchers identified several drug classes (eg...alpha$_2$-adrenoreceptor agonists) and individual drugs (...dexmedetomidine) found appropriate for immediate consideration as non-lethal[s]..."*

Such a finding is hardly surprising as the 1994 US Army Chemical and Biological Defense Command Edgewood RDE Center annual research conference had a paper[49] which argued that:

> *"Centrally acting a$_2$-adrenergic compounds show antihypertensive actions with sedative properties. More selective a$_2$-adrenergic compounds with potent sedative activity have been considered to be ideal next generation anesthetic agents which can be developed and used in the Less-Than-Lethal* [Non-Lethal] *Technology program..."*

32. The mechanism underlying this effect is well understood. The brain contains a rather small number of neurons that have the classical transmitter noradrenaline as their

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[46]Koch, B. L. *et al*. (1999) Inhalation of substance P and thiorphan: Acute toxicity and effects on respiration in conscious guinea pigs. *Journal of Applied Toxicology*, **19**, 19-23.

[47]Kramer, M. S. *et al*. (1998) Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*, **281**, 11 September, 1641-1645.

[48]Lakoski, J. M., Bosseau Murray, W. and Renny, J. M. (2000) *The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique*. Applied Research Laboratory, College of Medicine, Pennsylvania State University.

[49]Chronology (1995) 15-18 November. *Chemical Weapons Convention Bulletin*, **27**, 16-17

neurotransmitter, and most of these neurons are clustered in the bilateral locus coeruleus. However, the nerve fibres (axons) which carry the output from these cells spread widely to many parts of the brain. One recent review[50] indicated the function of this system:

> *"...In general terms...it is agreed that noradrenergic neurons influence arousal. This encompasses not only the sleep/waking cycle but also more specific activities, such as selective attention and vigilance..."*

Understanding the mechanisms of disruption of this system could obviously be useful in medicine, but also to those seeking an incapacitant. One particular type of adrenoreceptor, the a_{2A}, is an inhibitory autoreceptor on the neurons of the locus coeruleus. Such receptors again function to limit the output of the locus coeruleus neurons by feedback inhibition. The report notes that the drug clonidine does not have the desired effect because it also affects other adrenoreceptors. However:

> *"Dexmedetomidine acts selectively on the a_{2A} adrenoreceptor...in the locus coeruleus of the central nervous system..."*

Dexmedetomidine was originally developed as a veterinary sedative-analgesic, but was released in the United States in March 2000 as an *"anesthetic"* for sedation of intensive care patients. It has recently been possible to generate knockout mice lacking a_{2A}, a_{2B}, and a_{2C} adrenoreceptor sub-sub-types and to further elucidate their role. Considerable further understanding of the brain's noradenaline system, and how it may be modified, is therefore to be expected.

33. Noradrenaline is a classical small-molecule neurotransmitter. The study of calmatives also deals with the neuropeptide cholecystokinin (CCK) and its receptors. It is well known that there are two sub-types of CCK receptor, CCKA and CCKB. It is also known that natural agonists such as the eight-amino-acid chain CCK8 can cause panic attacks in healthy people[51]. Clearly, given the links between panic attacks and inappropriate anxiety, much effort has gone into developing drugs targeted at this receptor sub-type and a wide range of selective therapeutic agents is available[52].

Analysis

34. The conclusion that must be reached, even from such a limited review of the many possibilities, is that, in regard to body systems and behaviours that could be of interest to those with malign intent, **there is already clear evidence that specific selective agents can be designed to attack particular receptor sub-types.** The situation has therefore dramatically changed since the early Cold War period when these kinds of agents were first sought.

35. The situation is made much more dangerous by two other factors which will become increasingly important in the future. The Human Genome Project demonstrated that many of

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[50]Stanford, S. C. (2001) Noradrenaline. Pp 163-185 in R. A. Webster (ed.), *Neurotransmitters, Drugs and Brain Function*. John Wiley, London.

[51]Noble, F. and Roques, B. P. (1999) CCK-B receptor: Chemistry, molecular biology, biochemistry and pharmacology. *Progress in Neurobiology*, **58**, 349-379.

[52]Kopin, A. S. *et al*. (2000) CCK receptor polymorphisms: An illustration of emerging themes in pharmacogenomics. *Trends in the Pharmacological Sciences*, **21**, September, 346-353.

the relatively small number of genes that separate us from other animals are involved in neural development, structure and function[53]. Moreover, the number of genetic diseases affecting the nervous system is higher than for any other organ system[54], and many of these diseases are caused by defects in transmitter/receptor systems. For example, there are differences relating to the ability to deal with acetylcholinesterase inhibitors[55]. Whilst no such polymorphism (difference in genetic constitution) has yet been found to occur exclusively in one ethnic group, big differences are known between groups and this gives rise to fears of misuse[56]. Secondly, one area of intense work on gene therapy is in relation to dealing with brain tumours.[57] Such techniques will undoubtedly improve and there are well-known examples of viruses which specifically target the nervous system which might be used in treatment. The group of arboviruses (viruses transmitted naturally by arthropods), for example, includes some of those which target the nervous system such as Venezuelan Equine Encephalitis[58] which was weaponised in the former US offensive biological weapons programme. There is thus a distinct possibility that viral vectors could be found which would deliver bioregulators directly into the nervous system.

What Should be Done?

36. In a Congressional hearing[59] on 5 February 2003, the US Secretary of Defense was asked a question about the possible use of a non-lethal technology in a war with Iraq. The Secretary of State said that the US had signed a treaty, *"tangled ourselves up so badly"*, that it was very difficult to write coherent rules of engagement for soldiers to use non-lethal riot control agents. Indeed, Secretary Rumsfeld stated that he and his top commander had spent an hour or an hour and a half trying to write a set of such rules. In his opinion, the issue was very complex and unfortunate because he believed there were many situations where is would be preferable to be able to use such riot control agents. He cited, for example, attempting to remove a mixed crowd of combatants and non-combatants from a cave when US soldiers were being fired on from the cave.

37. The reasons for these difficulties were discussed in some detail in a recent article[60] by Major Ernest Harper of the US Marine Corps. According to Harper the problem facing the Defense Secretary has long roots. When negotiation of the Chemical Weapons Convention began in the early 1980s the US view was that riot control agents *"did not constitute chemical weapons, due to their nonlethal nature"*. Indeed, when President Ford acted in 1975 to ratify

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[53]Bird, T. D. (2001) Thoughts on the relationship of the Human Genome Project to neurology. *Archives of Neurology*, **58** (11). Available at http://archneur.ama-assn.org/issues/v58n11/full/ned1003.html

[54]Tsuji, S. (2001) Neurogenetics in the postgenome era. *Archives of Neurology*, **58** (11). Available at http://archneur.ama-assn.org/issues/v58n11/full/ned1006.html

[55]Shapira, M. *et al*. (2000) A transcription-activating polymorphism in the ACHE promoter associated with acute sensitivity to anti-acetylcholinesterases. *Hum. Mol. Genet*., **9** (9), 1273-1278.

[56]Bartfai, T. and Sellstrom, A. (2002) *Neurobiology, weapons, humanity*. Presentation at the ICRC Symposium on Biotechnology, Weapons and Humanity, Montreux, 23 September.

[57]Brandes, A. A., Lacombe, D. and Vecht, C. (2001) Future trends in the treatment of brain tumours. *European Journal of Cancer*, **37** (18), 2297-2301.

[58]Gubler, D. J. (2002) The global emergence/resurgence of arboviral diseases as public health problems. *Archives of Medical Research*, **33** (4), 330-342.

[59]Rumsfeld, D., Testimony to the U S House Armed Services Committee, 5 February 2003. Audio of testimony available at http://www.house.gov/hasc/schedules/2003.html#Feb03. Non-lethal weapons testimony starts at 1 hr 32 minutes 45 seconds.

[60]Harper, Major E. (2001) A call for a definition of a method of warfare in relation to the Chemical Weapons Convention. *Naval Law Review*, **XLVIII**, 132-160.

the 1925 Geneva Protocol his Executive Order 11850[61] allowed for specific exemptions that permitted the use of riot control agents such as for dealing with the kind of situations confronting the present-day US Secretary of Defense. However, other parties to the CWC negotiations, including many of America's allies, wanted riot control agents included in the definition of chemical weapons because[62]:

> *"They believed that any use of a RCA* [riot control agent] *could all too easily escalate to the use of lethal chemical weapons, and viewed RCAs as a large loophole in the effort to eradicate chemical warfare. A loophole they were determined to close."*

According to Harper, in the endgame of the negotiations in the early 1990s neither side wished to give up its position but each wished to conclude the Convention. Thus a compromise was reached in paragraph 5 of Article I which states that *"Each State Party undertakes not to use riot control agents as a method of warfare".* In Harper's view this seemingly straightforward text is *"intentionally undefined and ambiguous"* as it was designed as a compromise between two polarised positions. His concern, given that the Senate enacted the exemptions of Executive Order 11850 when it ratified the Convention and that no reservations are allowed, is that US soldiers could end up being perceived as breaking international law. His paper is therefore an attempt to clarify the meaning of *"a method of warfare".* Recently released US military legal reviews[63] have also attempted to show that common riot control agents are subject to a quite different legal regime than chemical weapons in the Chemical Weapons Convention on account of their limited physiological impact on the victim.

38. Despite such complexities there is clearly evidence[64] that the US military is still attempting to discover new forms of chemical incapacitant. Moreover, some might argue that the peaceful purpose exemption of Article II.(9)(d) of the Chemical Weapons Convention, which allows for "Law enforcement including domestic riot control purposes", would allow quite new law enforcement chemicals with complex physiological effects on humans to be developed - particularly as no definition is offered for what chemicals are permitted for law enforcement other than that Schedule 1 chemicals may not be used.

39. At the time of the negotiation of the Convention an editorial[65] in the *Chemical Weapons Convention Bulletin* pointed out the dangers:

> *"The Chemical Weapons Convention in no way limits use of tear gas or other temporarily disabling chemicals by police forces for purposes of domestic riot control.* ***But the language used to exempt other law enforcement purposes has created ambiguity in the heart of the Convention****..." [Emphasis added]*

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[61]US Executive Order 11850, *Renunciation of certain uses in war of herbicides and riot control agents*, 8 April 1975. Available at http://www.archives.gov/federal_register/codification/executive_order/11850.html

[62]Harper, Major E. (2001) A call for a definition of a method of warfare in relation to the Chemical Weapons Convention. *Naval Law Review*, **XLVIII**, 132-160.

[63]Department of the Navy (1998) *Legal Review of Oleoresin Capsicum (OC) Pepper Spray*, (Ser 103/353). Office of the Judge Advocate General, Alexandria, Virginia.

[64]Joint Non-Lethal Weapons Directorate (2003) *Front End Analysis for Non-lethal Chemicals.* Available at http://www.sunshine-project.org/publications/nlwdpdt/feachemical.jpg

[65]Editorial (1994) New technologies and the loophole in the Convention. *Chemical Weapons Convention Bulletin*, **23**, March, 1-2.

In particular, the editorial noted that:

> *"**What is at stake is the ability of the treaty regime to withstand technical change.** For new chemical agents and technologies have begun to emerge whose attractions for weapons purposes may eventually drive them through the loopholes which the ambiguity has created."* [Emphasis added]

The evidence presented in this paper shows that we have now reached that point as, in regard to a number of systems that could well be of interest to those with a malign intent, **it is clearly now possible to create specific chemicals that target specific receptor sub-types and thereby cause specific behavioural effects.**

40. It is certainly possible to find strong advocates of non-lethal chemical weapons who believe that it is necessary to consider selective changes to current international legal agreements. As Fidler has noted[66]:

> *"The selective change perspective uses changes in military operations and technologies as a basis for advocating selective, case-by-case reforms in international law to allow NLW* [Non-Lethal Weapons] *development and use..."*

But, he argued, inherent in that selective change position is a much more radical position that could upset the current international legal system that we have developed over centuries to constrain warfare. He noted, for example, that:

> *"Arguments in favour of developing and deploying NLWs often rely on the new capabilities such weapons give military forces and suggest that such capabilities affect how we evaluate the ethics of weapons' use..."*

As an example, at present soldiers are clearly not allowed to directly target civilians with their lethal weapons. If we agree that civilians can be targeted directly with non-lethal weapons (when with such weapons there will always be a risk of deaths[67]) where does that leave the principle of discrimination between combatants and non-combatants?

Conclusions

41. With the extremely rapid current rate of development in the life sciences it would be **dangerous** to leave this matter unattended to at the 2003 Review Conference. It is likely that the scientific possibilities will be even more tempting to those seeking new weapon systems after five more years. The bioregulators and synthetic analogues such as fentanyl considered here are mid-spectrum agents covered -- and correctly so -- by both the Biological and Toxin Weapons Convention and the Chemical Weapons Convention. A NATO Advanced Research Workshop held in the run-up to the 2001 Review Conference of the Biological and Toxin Weapons Convention considered the scientific changes carefully and recognized that the

[66]Fidler, D. P. (2001) "Non-lethal' weapons and international law: Three perspectives on the future. *Medicine, Conflict and Survival*, **17**, 194-206.

[67]Klotz, L, Furmanski, M and Wheelis, Mark (2003) *Beware the Siren's Song: Why "Non-Lethal" Incapacitating Chemical Agents are Lethal*, Available at http://microbiology/ucdavis.edu.faculty/mwheelis/sirens_song.pdf

scope of the Convention should be reaffirmed as at previous Review Conferences by a consensus statement in regard to Article I, along the following lines[68].

> *"The Conference...reaffirms that the Convention unequivocally covers all microbial or other biological agents or toxins, naturally or artificially created or altered, as well as their components, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.* ***Consequently, prions, proteins and bioregulators, and their synthetically produced analogues and components are covered.****"* [Emphasis added]

Unfortunately, no Final Declaration was agreed by the 2001-2002 Review Conference of the Biological and Toxin Weapons Convention and consequently the opportunity for such a consensus statement was missed.

42. As was shown in our First CWC Review Conference Paper[69] this system of reaffirmation and developed understanding of the scope of Biological and Toxin Weapons Convention has come about through the Final Declarations agreed at successive Review Conferences since 1980. There is much to be said for the Review Conferences of the Chemical Weapons Convention to gain similar benefits from extended understandings agreed in their Final Declarations. Appropriate language would be to state that:

> *"The Conference also reaffirms that the Convention unequivocally covers all chemicals, regardless of whether they are produced in facilities, in munitions or elsewhere, of types and in quantities that are consistent with purposes not prohibited under this Convention."*

In order to avoid any possible misunderstanding, it was suggested that an explanatory sentence should be added to state that:

> ***"Consequently, toxins, prions, proteins, peptides and bioregulators and their biologically or synthetically produced analogues and components are covered."*** [Emphasis added]

43. The Review Conference **must** address this issue to prevent a dangerous erosion of the purpose and objective of the Convention. The risks are real as a recent US military legal review[70] noted:

> *"Convulsives and calmatives may rely on their toxic properties to have a physiological effect on humans. If that is the case, and these two NLWs [Non-Lethal Weapons] are not considered RCAs [Riot Control Agents], in order to avoid being classified as a prohibited chemical weapon, they would have to be used for the article I(9)(d) "purpose not prohibited" the law enforcement purpose.*

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[68]Pearson, G. S. (2002) *New Scientific and Technological Developments of Relevance to the Fifth BTWC Review Conference,* Review Conference Paper No. 3, University of Bradford, October. Available at http://www.brad.ac.uk/acad/sbtwc .

[69]Pearson, G. S. (2002) *Relevant Scientific and Technological Developments for the First CWC Review Conference: The BTWC Review Conference Experience*. CWC Review Conference Paper, No. 1, University of Bradford, August. Available at http://www.brad.ac.uk/acad/scwc

[70]Department of the Navy (1997) *Preliminary Legal Review of Proposed Chemical-Based Nonlethal Weapons.* Office of the Judge Advocate General (International and Operational Division), 30 November. Alexandria, Virginia.

*As discussed...**the limits of this "purpose not prohibited" are not clear and will be determined by the practice of states.**"* [Emphasis added]

If the Review Conference does not clearly address this issue novel non-lethal weapons based on the new understanding of the nervous system and its chemical neurotransmitters and receptors could well have been deployed and used before there is an opportunity for the next CWC Review Conference to address the issue. The events in Moscow in late 2002 would then be seen as a harbinger of a much more dangerous future with a seriously eroded chemical weapons prohibition regime rather than as an isolated hangover from the military developments of the Cold War period which has served as a useful signal to strengthen the understanding that all such chemicals are prohibited under the Chemical Weapons Convention.

44. Although it is true that the CWC is, in a sense, under continuous review through the annual Conferences of the States Parties and the regular Executive Council meetings, it would be irresponsible if the States Parties at the forthcoming Review Conference in April 2003 -- given the mandate of the Review Conference specified in the Convention to *convene in special sessions to undertake reviews of the operation of this Convention. Such reviews shall take into account any relevant scientific and technological developments.* -- were to fail to address the real and present danger to the Chemical Weapons Convention from incapacitating chemicals. The outcome should be a clear reaffirmation of the comprehensive prohibition of toxic chemicals in the Convention making it clear in the reaffirmation that all incapacitating chemicals are covered. Consideration could also be given to an action placed on the annual Conference of States Parties and the Executive Council to be vigilant to ensure that there is no erosion of the chemical weapons prohibition regime through incapacitating chemicals.