PART ONE (OF THREE)

"In the Know": Why the well-informed are concerned about the possible misuse of advances in neuroscience in novel chemical and biological weapons*

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Introduction

States are unlikely to spend the time and effort required to negotiate and implement international multilateral arms control and disarmament agreements unless there are serious problems that require the use of such complex methods. Multilateral negotiations can take years to conclude, result in the need for extensive national implementation, and ongoing multilateral engagement in order to assess the operation of the agreement and how it might need further elaboration.

Therefore the fact that over the last century three such international multilateral agreements were negotiated and implemented in relation to the control of chemical and biological weapons leaves little doubt that many States perceived that such weapons were a significant threat. During the terrible war-torn twentieth century[1] the 1925 Geneva Protocol, the 1975 Biological and Toxin Weapons Convention (BTWC) and the 1997 Chemical Weapons Convention (CWC) progressively brought tighter and tighter control over the proliferation of these weapons.

The 1925 Geneva Protocol was negotiated following the large-scale use of chemical weapons, and the initial crude attempts to use (anti-animal) biological weapons,[2] during the First World War. Now that most of the many reservations that were lodged at the time have been removed the Protocol bans the use of chemical and biological weapons, stating, in part:[3]

> Whereas the use in war of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices, has been justly condemned by the general opinion of the civilized world; and
>
> Whereas the prohibition of such use has been declared in Treaties to which the majority of Powers of the World are Parties; and
>
> To the end that this prohibition shall be universally accepted as part of International Law, binding alike the conscience and the practice of nations.

and then leading on to the 'Declaration' that:

> ...the High Contracting Parties, so far as they are not already Party to Treaties prohibiting such use, accept this prohibition, agree to extend this prohibition to the use of bacteriological methods of warfare and agree to be bound as between themselves according to the terms of this declaration.

In 2012 the United Nations General Assembly once again reaffirmed the 'vital necessity' of States upholding the provisions of the Protocol and called upon States still holding reservations to withdraw them.[4]

The Biological and Toxin Weapons Convention was opened for signature in 1972 and entered into force in 1975. Its first article adds a series of further prohibitions to the ban on use stating, in part, that:[5]

> Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or other wise 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...

Thus, under this - what has become known as - 'General Purpose Criterion' any peaceful uses of biological and toxin agents are allowed but non-peaceful purposes are banned. Like the 1925 Geneva Protocol, the BTWC continues to be developed, the BTWC through its five-yearly Review Conferences, the latest of which took place in 2011.[6]

Whilst Article IX[7] of the BTWC recognized the 'objective of effective prohibition of chemical weapons' and States Parties undertook 'to continue negotiations in good faith with a view to reaching early agreement,' it was not until the end of the East-West Cold War that the Chemical Weapons Convention was agreed. It opened for signature in 1993 and entered into force in 1997.

Like the BTWC, the CWC has a 'General Purpose Criterion,' Article I stating, in part, that:[8]

> 1. Each State Party to this Convention undertakes never under any circumstances:
> (a) To develop, produce, otherwise acquire, stockpile or retain chemical weapons, or transfer, directly or indirectly chemical weapons to anyone;

Reinforcing the 1925 Geneva Protocol, the Article directly goes on to add, '(b) To use chemical weapons'. The CWC is also subject to a review every five years and the latest such review took place in 2013.[9]

The Responsible Conduct of Research

Why should a practising neuroscientist carrying out benignly-intended civil research be interested in such international arms control issues? Surely, it might well be

argued, there is enough to do keeping up with this rapidly advancing field and making a reasonable research contribution in his or her own area of cutting-edge research. That, however, would be to ignore the evolution of the scientific community's conception of Responsible Conduct of Research (RCR). As Rebecca Carlson and Mark Frankel of the American Association for the Advancement of Science (AAAS) explained recently, the scientific community is getting better at teaching and observing the necessities of responsible conduct in regard to the internal operations of science such as dealing with human and animal subjects, data acquisition and its management, and publication practices and responsibilities.[10] However, they also argue that there is a long way to go before the scientific community can be said to have dealt adequately with its external research responsibilities. These cover aspects of the societal impacts of research such as communication, advocacy and emerging technologies.

Two questions that really need to be asked are these. What evidence is there that, as the growing sciences of chemistry and biology have been applied to the development and use of chemical and biological weapons over the last one hundred years, advances in neuroscience have contributed to these hostile purposes? And what are the possibilities that such distortions of civil science might continue in the future? One way to approach those questions is to look at the weapon systems that have been produced by States and the extent to which they affect the nervous system.

The nervous system is made up of individual cellular units including the numerous neurons that are specialized for the transmission of information to and from, and within, the central nervous system. Information transmission within a neuron is by electrical means, but transmission between neurons is predominantly by chemical means. Specialized neurotransmitter molecules are released from one neuron into the synaptic cleft and latch onto specific receptor molecules on the next cell in order to affect the operation of that following neuron or effector system (such as muscle). This, of course, opens up the possibility of manipulation of the nervous system by the introduction of other chemicals like drugs for benign purposes or chemical agents for hostile purposes. It should be understood, however, that the nervous system does not act in isolation and is intimately linked to the endocrine (hormonal) system and the immune (defence) system.[11] Thus stress registered in the brain can lead to hormones being released that then cause the release of glycogen and glucose - readily available substrates for energy metabolism, while amazingly small

amounts of some bacterial toxins can induce elevation of body temperature in the fever response to infection. Given that there are many different neurotransmitters, hormones and cytokines (of the immune system) and numerous cellular receptors for bioregulatory chemicals in the nervous system, it follows that as our knowledge becomes more detailed, more and more specific targets for manipulation - for benign or malign purposes - are likely to be revealed.

Chemical Weapons

Michael Faraday is, of course, best known for his groundbreaking work on electricity in the first half of the nineteenth century. It is less well known that Faraday was also a significant chemist and, for example, the discoverer of benzene which was to be of fundamental importance in the growth of organic chemistry later in the century.[12] In later life Faraday was frequently consulted by officialdom for his views on scientific issues and during the Crimean War he was asked for his opinion on a proposed scheme to attack and capture Cronstadt through the use of a chemical weapon. As his biographer[13] noted, "Faraday was sceptical of the plan and his report could not be interpreted as a favourable one." Indeed, it was not until the First World War, after the growth of industrial chemistry in the latter part of the nineteenth century, that large-scale chemical warfare became possible.

Chemical weapons can reasonably be divided into lethal and disabling agents (Table 1).[14] Lethal agents such as phosgene and mustard gas were used in large quantities in the First World War, but it was not until the 1930s that nerve agents were first discovered, in Germany. Disabling incapacitating agents like BZ that affect the central nervous system, were developed after the Second World War as drugs began to be discovered that could help people suffering from some mental illnesses.

Acetylcholine (ACh) the first neurotransmitter molecule discovered resulted from research by Loewi early in the twentieth century.[15] ACh is manufactured in some neurons and stored in vesicles on the presynaptic side of the synaptic cleft between such an ACh neuron and a postsynaptic neuron. When a nerve impulse (an electrical signal) in the presynaptic neuron reaches the synapse the ACh is released into the cleft, attaches to receptors on the postsynaptic neuron, and affects the electrical activity of that cell. However, precision in the information transfer is ensured because an enzyme called acetylcholinesterase quickly breaks down the ACh

in the synaptic cleft. The constituent parts of the ACh molecule are then taken up for reuse in the presynaptic neuron.[16]

Nerve agents are deadly because their main action is to inhibit the action of acetylcholinesterase and thus excessive amounts of ACh accumulate in the synaptic cleft and continue to affect postsynaptic cells. As there are ACh synapses in the skeletal muscles, the autonomic nervous system and the brain it is no surprise that agents such as GA (tabun), GB (sarin), GD (soman) and the even more toxic V agents cause extensive disruption of bodily functions and can lead to death.[17] The original G series of nerve agents were discovered by civil scientists working on pesticides in Germany before the Second World War[18] and then, as shown clearly in a recent study, the V agents were discovered through later civil research after that war.[19]

The example of the initial development of the V agents is of particular interest because of the involvement of UK civil scientists. As the authors explain:[20]

> Although defence research and development laboratories achieved incremental improvements in chemical warfare agents, major breakthroughs such as the discovery of the G [original series] and V-agents were spin-offs of civil technologies. The transfer of Amiton from PPL [Plant Protection Limited] to Porton Down [Chemical Defence Experimental Establishment] demonstrated how the British defence establishment interacted with the domestic chemical industry to develop a new family of nerve agents.

We will have cause to return to this point - of crucial breakthroughs in weapons developments resulting from *civil* not military research. It should also be noted that even such dangerous agents as sarin, once developed for military purposes, were also eventually produced and used by terrorists in the Tokyo subway attack of 1995.[21]

It should also be noted that the lethal chemical agents used during the First World War could also have effects on the central nervous system. As the US *Textbook of Military Medicine* notes:[22]

> Although the effects are not usually prominent clinically, mustard affects the CNS [central nervous system]. Reports of World War I casualties described apathy, depression, intellectual dullness and languor. Of 233 Iranian casualties sent to various western European hospitals for medical care during the Iran-Iraq War, about 83% had CNS complaints; most complaints, however, were mild and nonspecific.

The account goes on to say that large amounts of mustard gas administered by various routes to animals caused 'convulsions, and other neurological manifestations' and that they died a 'neurological death' a few hours after being given a lethal dose.

The effect of a chemical agent is a function of dose, so not everyone will be killed by release of a nerve agent or other lethal chemical but the World Health Organization (WHO) defines lethal chemicals as those:[23]

> ...intended either to kill or injure the enemy so severely as to necessitate evacuation and medical treatment...

On the other hand, it defines disabling chemicals as those:

> ...used to incapacitate the enemy by causing a disability from which recovery may be possible without medical aid.

The WHO also points out that when the industrial developments of the nineteenth century allowed the large-scale use of chemical weapons in the First World War chemical warfare began with the use of sensory irritants such as tear gases, mainly to drive enemy combatants out of protective cover. The use of lethal chemicals then followed and escalated as systematic surveys indicated more potential agents, and as the WHO points out:[24]

> The chemical industry, not surprisingly, was a major source of possible agents, since most of the new chemical warfare agents had initially been identified in research on pesticides and pharmaceuticals.

So the critical link between civil research and military uses is again made quite clear.

The link to the pharmaceutical industry is important because as drugs that could help people with some mental illnesses began to be discovered after the Second World War, the military became interested in the development of more incapacitating chemicals. As the US textbook on military medicine commented:[25]

> Virtually every imaginable chemical technique for producing military incapacitation has been tried at some time...

and it went on to state that between 1953 and 1973, in the United States:[26]

> ...many of these were discussed and, when deemed feasible, systematically tested. Chemicals whose predominant effects were in the central nervous system were of primary interest and received the most intensive study...

The text suggests that virtually all drugs with prominent psychological or behavioural effects - psychochemicals - can be placed in four classes: stimulants (for example, amphetamines), depressants (for example, barbiturates), psychedelics (for example, D-lysergic acid diethylamide), and deliriants[27] that cause 'an incapacitating syndrome, involving confusion, hallucinosis, disorganized speech and behavior.' Amongst many such deliriants, chemical compounds that interfered with the ACh system - anticholinergics - were regarded as the most likely to be used as military incapacitating agents.

One of these anticholinergic deliriants, BZ (3-quinuclidinyl benzilate), was eventually weaponized by the United States, and, as the text again makes clear, the process involved a transfer of civil research findings to the military:[28]

> BZ was first experimentally studied for therapy of gastrointestinal diseases. However, reports were received of confusion and hallucinations, suggesting that even small excesses of dosage were likely to cause problems. BZ was quickly withdrawn from commercial study and turned over to the U.S. Army as a drug of possible interest as an incapacitating agent.

BZ was produced between 1962 and 1965 and by 1970 there was a stockpile of 49 tons of the agent held by the United States. Although BZ had many shortcomings as an agent, and the stockpile was destroyed, eventually numerous other compounds with similar characteristics were investigated, for example by the United States and the United Kingdom.[29]

There are two main sub-classes of receptors for ACh in the nervous system, those affected by nicotine (nicotinic) and those affected by muscarine (muscarinic). BZ and similar agents latch on to the muscarinic type of receptor and thereby block the action of the ACh transmitter. As the US textbook of military medicine[30] noted, 'The term anticholinergic used in the context of this discussion refers more specifically to compounds that selectively block the brain's muscarinic receptor (now known to consist of several subtypes).'

More generally, the report of the Scientific Advisory Board (SAB) of the Organization for the Prohibition of Chemical Weapons (OPCW) to the Third Review Conference summarized the origins of candidate incapacitating chemicals as follows:[31]

> ...The types of chemicals and pharmaceuticals, known to have been considered as incapacitants from open literature sources, were discussed. Most are

> centrally acting compounds that target specific neuronal pathways in the brain. All of them emerged from drug programmes undertaken from the 1960s to the 1980s, as far as can be judged by the research that has been published.

So the SAB, using only open sources, was able to show the strongest possible link between civil research and military developments in this field of neuroscience.

There is a clear consensus amongst many experts[32] that an operationally effective chemical incapacitant is not available at the present time but there is also a concern that as our understanding of the chemistry of the brain - and how to manipulate it - develops some will believe that such an agent is possible and will therefore continue to seek to misuse civil research for hostile purposes.

Riot control agents act on the external sensory systems rather than the central nervous system, but there is also a concern that several States are seeking means for the long-range delivery of larger quantities of riot control agents[33] and of thereby producing weapon systems which might be loaded also with an incapacitating agent in other situations than riot control.

Biological Weapons

Biological agents such as bacteria and viruses are capable of multiplying in the affected victim and thus differ crucially from chemical agents (and toxins, which are discussed later). So, many biological agents will be much more fragile in the environment than a chemical agent and thus more difficult to deliver effectively. On the other hand, a very small amount may need to be delivered in order to cause an infection. Additionally, some biological agents can be contagious from the first victim to other people. Therefore, in addition to thinking about categories of lethal and non-lethal agents we have to think of contagious and non-contagious agents (Table 2).[34]

The link between civil research on infectious diseases and the development of biological weapons hardly needs stressing. The huge advances in our understanding of microbial pathogens resulting from the work of people like Pasteur and Koch in the late nineteenth and early twentieth centuries were made for beneficial purposes,[35] but were then applied in numerous State-level offensive biological weapons programmes in the twentieth century. The hostile applications would obviously not have been possible without the civil work that characterized the bacteria in the first place. Similarly, the growing understanding of viruses was taken up in offensive

programmes later in the twentieth century. Whilst the discussion here is focused on anti-personnel agents, it has to be said that the same argument can be made in regard to anti-animal and anti-plant biological warfare agents and offensive programmes.[36]

As we all know too well, when we are infected by a pathogen and become ill, our behaviour may change a good deal. As the WHO notes in regard to anthrax:[37]

> Inhalation anthrax begins with nondescript or influenza-like symptoms that may elude correct diagnosis. These may include fever, fatigue, chills, non-productive cough, vomiting, sweats, myalgia, dysponea, confusion, headache...followed after 1-3 days by the sudden development of cyanosis, shock, coma and death...

Given the intimate connections between the immune (defence) system and the nervous system such behavioural outcomes are to be expected. Similarly, tularæmia, caused by infection with *Francisella tularensis*,[38] results usually in 'an abrupt onset of fever, accompanied by chills, malaise and joint and muscle pain. Ulceroglandular tularæmia, caused by virulent strains, if untreated, has a case-fatality rate of about 5%...'.

Other pathogens that have, like anthrax and tularæmia, been developed as biological warfare agents directly target the nervous system. Venezuelan equine encephalitis (VEE) virus is a member of the Alphavirus group and is transmitted by mosquitoes naturally but can also be infectious in a biological weapons aerosol. The related eastern equine encephalitis (EEE) and western equine encephalitis (WEE) viruses, which were also identified in the 1930s, cause more severe illnesses:[39]

> ...In contrast, severe encephalitis is rare in humans infected with VEE virus - except in children. In adults, the usual VEE syndrome is an acute, febrile, incapacitating disease with prolonged convalescence.

Considerable work with animals[40] has shown that in such models '[t]he lymphatic system and the CNS appear to be universal target organs ... as was seen in humans.' As VEE is infectious in low doses by aerosol, possible to produce at low cost and in large quantities, and is quite stable, it is not surprising that it was developed as an incapacitating agent during the twentieth century. So here again we can see the cycle of civil science advances being taken up and applied to other, hostile, purposes.

Toxins

It is necessary to begin here by noting that the understanding of the word 'toxin' in relation to the BTWC and CWC prohibition is different from that held by scientists. As the WHO explained:[41]

> In the sense of the Biological and Toxin Weapons Convention, 'toxin' includes substances to which scientists would not normally apply the term. For example, there are chemicals that occur naturally in the human body that would have toxic effects if administered in large enough quantity. Where a scientist might see a bioregulator, say, the treaty would see a poisonous substance produced by a living organism, in other words a toxin...

Of course, as such a substance would be a chemical, and toxic, it would automatically also fall under the CWC prohibition.

There are, of course, many different types of toxin and these can be lethal or incapacitating. Examples of both kinds have been developed in offensive programmes as they specifically attack the nervous system. The bacterium *Clostridium botulinum* produces neurotoxins that have often caused food poisoning. The WHO stated:[42]

> ...Botulinum toxins are the most acutely lethal of all toxic natural substances. As a dry powder, they may be stable for long periods. They are active by inhalation as well as ingestion...

Not surprisingly, it then adds, '[t]hey have long been studied as warfare agents of the lethal type, particularly, though not exclusively, types A and B.'

The US textbook of military medicine explains the neurotoxic action of botulinum as follows:[43]

> The extreme toxicity of the botulinum toxins would led us to believe that it must have some highly potent and efficient mechanism of action. This probability made botulinum toxin the subject of work by many laboratories, especially after we learned that it is a neurotoxin. Experiments with *in vitro* neuromuscular models established that the toxin acts presynaptically to prevent the release of acetylcholine...

It also notes that one of the legacies of the military research on these toxins during the Second World War[44] was the development of 'the botulinum vaccine that is used even today.'

Staphylococcal enterotoxins are produced by the bacterium *Staphylococcus aureus* are a very common cause of diarrhoeal food poisoning. The WHO stated that:[45]

> ...The toxins are known in at least five antigenitically distinct forms, of which type B is the most studied. It is heat-stable and, in aqueous solution, can withstand boiling. It is active by inhalation, by which route it causes a clinical syndrome markedly different, and often more disabling, than that following ingestion. It has been studied as a warfare agent of the incapacitating type...

The US textbook of military medicine describes the mechanism of action as follows:[46]

> ...When inhaled as a respiratory aerosol, SEB [staphylococcal enterotoxin B] causes fever, severe respiratory distress, headache, and sometimes nausea and vomiting. The mechanism of intoxication is thought to be from a massive release of cytokines...

SEB is, in fact, a superantigen that provokes this massive response from the immune system and thus indirectly affects the brain and behaviour.[47]

Toxins can be obtained from bacteria, marine organisms, fungi, plants and animal venoms. They come in many different types and sizes of molecule and attack diverse targets in the victim's body. Historically, bacterial toxins were the most important potential weapons agents because of their toxicity but the US textbook of military medicine commented that animal venoms 'must be considered potential future threats...as largescale production of peptides becomes more efficient.'[48] This is of interest here, of course, because many such venoms attack the nervous system of the victim in order to achieve rapid effects. However, the reference to peptide production is of most interest.

Concerns about novel peptide agents have been made clear by States Parties to the BTWC for over twenty years. The contribution of the United States to the background paper on relevant scientific and technological developments for the 1991 Third Review Conference stated, in part, that:[49]

> ...peptides are precursors of proteins made up of amino acids....They are active at very low concentrations....Their range of activity covers the entire living system, from mental processes (e.g. endorphins) to many aspects of health such as control of mood, consciousness, temperature control, sleep, or emotions, exerting regulatory effects on the body...

The text on these bioregulatory peptides, some of which clearly are involved in the operation of the nervous system, continues directly:

> ...Even a small imbalance in these natural substances could have serious consequences, including fear, fatigue, depression or incapacitation. These substances would be extremely difficult to detect but could cause serious consequences or even death if used improperly.

As if to reinforce the point, the Canadian Government took the unusual step of producing a separate document titled *Novel Toxins and Bioregulators: The Emerging Scientific and Technological Issues Relating to Verification and the Biological and Toxin Weapons Convention*[50] and sending it to all States Parties to the Convention. This reiterated the point made by the United States[51] that '[b]ecause bioregulators have many different sites of action, this gives rise to the possibility of selectively affecting mental processes and many aspects of health, such as control of mood, consciousness, temperature control, sleep or emotions.'

The Canadian study also noted that, given the evolutionary pressures for survival, toxins are likely to have reached an endpoint of selectivity for a particular target but:[52]

> ...with bioregulators, this is not the case since these compounds are involved in modulating cellular activities. They do not have a single endpoint of functions as neurotoxins do. The significance of this is that, while it is unlikely that research may lead to more toxic lethal agents, it may be possible to make more effective incapacitating agents.

The document goes on to discuss a wide range of toxins, and bioregulators such as Substance P, which subsequently were the subject of considerable discussion.[53,54,55] Indeed, the UK considered putting Substance P on the Schedules of the CWC verification system to serve as a marker for such bioregulators in the same way as saxitoxin and ricin serve as markers for toxins and ensure that it is understood that all come under the General Purpose Criterion.[56]

In the last decades of the twentieth century the revolution in the life and associated sciences continued apace and was applied in the large-scale, illegal, offensive biological weapons programme of the former Soviet Union. One focus of this programme was precisely on the hostile misuse of bioregulators. There is much that remains unknown about this programme, but a recent major study by Leitenberg and Zilinskas shows how dangerous such misuse could become. They argue that the 'most advanced and frightening research done in this area involved human myelin...that acts as a type of insulator for nerves.'[57] The aim of the work was to engineer a bacterium so that it would produce a protein like myelin when it infected a

human victim. The host's immune system would then mount an attack on myelin including that surrounding its own neurons to destroy the myelin. The authors explained:[58]

> ...Without their myelin, nerve cells gradually lose their ability to send electrical signals. The result would be an artificial version of multiple sclerosis...

However, there would be a major difference from the natural disease:[59]

> ...The difference between natural multiple sclerosis and the autoimmune disease induced by the genetically engineered *L. pneumophila* [bacterium] would be that the first takes years to kill its victims, whereas the second would progress to death in a matter of weeks.

Alibeck had given a brief account of this work previously,[60] but made the crucial point that '[a] new class of weapons had been found.' Clearly, this opened up numerous different possibilities for getting foreign bioregulators produced in the victim in order to carry out hostile manipulation.

Conclusion

With that history, it would be reasonable to expect that, even if they had ignored the possible misuse of their work before the 9/11 attacks and the subsequent sending of anthrax letters in the United States, neuroscientists would quickly have responded thereafter to ensure that they could engage in the process of preventing such misuse.[61] They could, for example, have ensured that biosecurity became part of the standard education given to all students of neuroscience. As the UK Royal Society recommended in its 2012 study, *Neuroscience, conflict and security*:[62]

> Recommendation 1: There needs to be fresh effort by the appropriate professional bodies to inculcate the awareness of the dual-use challenge (i.e., knowledge and technologies used for beneficial purposes can also be misused for harmful purposes) among neuroscientists at an early stage of their training.

The available evidence strongly suggests that a great deal remains to be done to achieve that objective.[63]

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Table 1: Chemical weapons agents*

Lethal	
	Lung irritants e.g. Phosgene
	Blood gases e.g. Hydrogen cyanide
	Vesicants e.g. Mustard gas
	Nerve gases e.g. Sarin, VX
Disabling	
	Incapacitants e.g. Lysergide, Agent BZ
	Harassing agents and other irritants e.g. Agent CN, Agent CS, Agent OC

*From reference 14

Table 2: Biological weapons agents*

Potentially infectious from first victim	
	Incapacitating -Influenza virus
	Lethal -*Yersinia pestis* (plague)
Not infectious from first victim	
	Incapacitating -*Coxiella burnetii* (Q-fever)
	Lethal -*Bacillus anthracis* (anthrax)

* From reference 34