Biotechnology, weapons and humanity II

Board of Science and Education
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For further information about the editorial secretariat or board members please contact the science and education department (info.science@bma.org.uk).

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ACRONYMS

ABW	Advanced Biological Warfare Agents
AHG	Ad Hoc Group
ARCAD	Advanced Riot Control Agent Device
BMA	British Medical Association
BTWC	Biological and Toxin Weapons Convention
BW	Biological weapons/warfare
BWC	Biological Weapons Convention (US version of BTWC)
BWPP	Bioweapons Prevention Project
CBMs	Confidence Building Measures
CBRN	Chemical Biological Radiological Nuclear
CBW	Chemical and biological warfare
CDC	Centers for Disease Control and Prevention
cDNA	Complementary DNA
CIA	US Central Intelligence Agency
COSHH	Control of Substances Hazardous to Health Regulations
CWC	Chemical Weapons Convention
DPTs	Dangerous pathogens and toxins
FOIA	Freedom of Information Act
GAO	General Accounting Office
HA	Hemagglutinin
IAPO	Importation of Animal Pathogens Order
ICRC	International Committee of the Red Cross
IHL	International Humanitarian Law
IUPAC	International Union of Pure and Applied Chemistry
JNLWD	Joint Non-Lethal Weapons Directorate
MIT	Massachusetts Institute of Technology
NA	Neuraminidase
NGOs	Non-governmental organisations
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NS	Nonstructural gene
OPCW	Organisation for the Prohibition of Chemical Weapons

PDE	Programme for the Preparedness for Deliberate Epidemics
RNAi	RNA interference
SAPO	Specified Animal Pathogens Order
SARS	Severe Acute Respiratory Syndrome
SIPRI	Stockholm International Peace Research Institute
SNPs	Single nucleotide polymorphisms
SPICE	Smallpox inhibitor of complement enzymes
USDA	US Department of Agriculture
VCP	Vaccinia complement control protein
WHO	World Health Organisation
WMA	World Medical Association
WMD	Weapons of mass destruction

FOREWORD

In the early years of the 21st century mankind stands at a crossroads. We have access to increasing technical ability and knowledge, to unprecedented levels of information about the genetics of a variety of life forms on this planet, including viruses and bacteria, as well as a better understanding of the processes by which the human body is regulated. The development of tools and techniques to manage, control and limit what we do with this knowledge has been slower. With knowledge comes power, in this case the ability to manipulate the human and the external environment. All of these are extraordinary tools that could be used for good or for ill. We could manage the technology and the information to reduce the toll of human suffering. Equally, we could allow their unfettered use. All of them are similarly open to abuse and we must recognise the possibility of their use to produce new weapons with either an immediate or a delayed impact.

We must start this report by emphasising that the developments in technology and in knowledge acquisition offer us real hope for better medical care for many with chronic diseases, for enormous improvements to public health and for opportunities for sound environmental policies. We must safeguard these potential benefits and not lose them because of the chance of harm; however, we cannot afford to ignore the potential for abuse.

The realisation that these powerful tools and this knowledge could drive the production of new, improved biological weapons was recognised five years ago by the BMA and was a major reason for the production of our 1999 report *Biotechnology, weapons and humanity*. Since that time, the technology has continued to improve and develop apace. The global situation in terms of the willingness of states and of so called 'non-state actors', including terrorists, to use and misuse technology, whether sophisticated or simple, has also increasingly been demonstrated.

It should be recognised that the boundary fences of International Humanitarian Law (IHL), including the Geneva Conventions, the Biological

and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC) have afforded us considerable protection over a number of years. But the very existence of these laws and norms is being questioned. Some are arguing that IHL arose out of consideration of wars between nations, formally declared and with combatants fighting in distant fields away from the general population. Modern wars are often not declared and are usually fought in and around centres of population. But dismissing IHL because the nature of wars has changed is to miss the essential facts. IHL exists to define the limits that will apply to what armies and governments can do in war. It protects combatants and non-combatants. It is based upon international consensus. These boundaries are under threat; their preservation must be of importance to all.

The use of biological weapons is no longer an interesting – and frightening - historical memory, but instead a relatively recent event. The release of anthrax in Washington DC and elsewhere in the United States at the end of 2001 may be regarded in many ways as a 'success' for the perpetrators if their aim was to cause disruption to government and a significant cost to the United States. It was also a wake-up call to those who had been confident that existing international law and a repugnance to use banned weapons presented us with some level of security. Global awareness, from government down to the person in the street, about the possibility that biological weapons could be used is now high. Our ability to prevent the manufacture of such agents, or if we fail in this, our ability to prevent their release, has not kept pace with either the scientific or the geopolitical developments.

Indeed, it can be said that since 1999 the situation has got worse politically in that one major plank of many experts' hopes for prevention has been irretrievably damaged by the collapse of the negotiations on a system that would increase compliance with the BTWC and make it truly effective. This new report looks at developments since 1999 in two areas. These are the developments in scientific terms with our increased understanding of the way in which technology and information may allow us to potentially produce biological weapons, and the political effects of major geopolitical events on

the processes designed to protect us from the production of offensive biotechnology developments.

To understand the issues it is important to iterate the developments in these two areas since 1999. In terms of science we have increasingly developed our ability to genotype organisms in an automated or semi-automated fashion. As an instrument of 'good' this allowed rapid typing of the SARS virus, helping the development of appropriate containment and management strategies, as well as secondary prevention. We know more about the similarities and dissimilarities between individual human beings. Every day we understand more about disease sensitivities and predispositions. Technology allows us to manipulate the genetic make-up of organisms. This work may well lead to better vaccines – more effective and with fewer side effects – as well as allowing the development of entire new categories of drug treatments. Increasingly, the future of medicine includes the idea that we will fundamentally alter the management and indeed the outcome of chronic diseases by action at the level of body regulators. This knowledge is still specialised, but is widely available – inevitable in this 'information age'. And the automatic procedures for manipulation at a genetic level are increasingly available and mainstream.

At the same time the world is now immersed in the 'war on terror'. Regardless of personal views of this conflict, the world has witnessed actions against states and against individuals by other states or 'non-state actors'. Attempts to produce coherent, constructive and comprehensive strategies, based upon international law and international agreements and understanding, have run into serious difficulties. There are still opportunities to strengthen the BTWC through the on-going inter-review conference process. This process does not address the major issue of preventing state-level offensive biological weapons programmes, but it could help prevent or at least reduce the likelihood of terrorism by sub-state groups by toughening up national legislation in some key areas. The scientific community has an opportunity to contribute to this process over the next two years, and to emphasise the need for deeds and not just words, in the run-up to the 2006 conference to review the BTWC.

When these two sets of factors are put together it becomes clear that the risk of the abuse of biotechnology is significant, increasing, and in need of urgent attention by the global community. If political will is lacking, or when international political considerations make progress difficult, alternatives must be sought. Whilst the concept of scientists attempting to limit such scientific abuse is increasingly important, it is not an effective alternative to international political action. But in the absence of such action or of effective progress in developing inter-governmental policy it may become the only active intervention.

Recommendations from the 1999 report are reiterated where appropriate on the basis of up-to-date thinking, and in line with what may now be possible, and details on other, more positive developments are also included. A timetable of the opportunities for development of the BTWC and related international and national actions is set out in appendix I.

The BMA believes that the importance of this issue cannot be overstated. Global security requires action by the international community of nations, by national governments and by those with specific expertise in science, medicine and law. If we accept that the risks are real we must also accept that we all share a responsibility to try to be part of the solution. This report looks in some detail at the scientific developments since 1999, the legal and other control issues and at the emerging evidence of a willingness to push at the boundaries of the controls currently in place. We recognise that it does not make comforting reading, but hope that the conclusions we have drawn and the recommendations we have made will help shape an agenda for action.

Professor Sir David Carter
Chairman, Board of Science and Education
October 2004

CHAPTER 1:

INTRODUCTION: HUMANITY AT A CROSSROADS

The 1999 BMA report

In January 1999 the British Medical Association (BMA) produced a report on *Biotechnology, weapons and humanity* (BMA I).[1] Worried about the dangers inherent in the development of the revolution in biology this stated, in part:

> 'The world faces the prospect that the new revolution in biotechnology and medicine will find significant offensive military applications in the next century, just as the revolutions in chemistry and atomic physics did in the 20th century.'

and:

> ' 'Recipes' for developing biological agents are freely available on the Internet. As genetic manipulation becomes a standard laboratory technique this information is also likely to be widely available. The window of opportunity for developing effective controls is thus fairly narrow.'

Therefore, the report argued:

> *'Urgent action is essential to ensure that the BTWC [Biological and Toxin Weapons Convention] is strengthened, and to reinforce the central concept that biological weapons, whether simple or complex in design and production, are wholly unacceptable.'* (emphasis added)

On any realistic assessment, the situation has not improved since 1999. Negotiations to add a verification protocol to the BTWC, which had been pursued by the states parties for most of the 1990s, broke down in 2001 and there is little hope of significant progress in these negotiations until after the 2006 Sixth Review Conference of the Convention at the earliest. By contrast, many more examples of the ways in which advances in the biological sciences might be misused – mousepox,[2] synthetic polio virus[3] and smallpox inhibitor protein[4] – have received significant public attention. The disruption that could be caused by use of even a small amount of biological agent for hostile purposes was amply demonstrated by the anthrax letter attacks in the United States in late 2001.[5]

The attack on the twin towers in New York on 11 September 2001, the subsequent 'war on terror' with major military invasions of Afghanistan and Iraq, and continuing terrorist attacks around the world have made us all realise that we live in a dangerous new international security system. Rather than the ending of the 20th century east-west cold war leading to a period of constructive peaceful development in which we might hope to find means of preventing the militarisation of the new biology, we seem to be heading in exactly the opposite direction – towards a prolonged period of disruptive, disorganised conflict in which states and non-state actors are likely to resort to increasingly destructive means.

In such a situation, the 1999 BMA I report emphasised the important role that doctors and scientists can play in developing preventive measures. With that in mind, this second report attempts to build on the first by providing an update on the events since 1999, and reviewing the available means that governments and civil society presently have to close down the militarisation of modern biology while there is still time.

The 1999 BMA I report began by recalling that the Board of Science and Education had published previous reports on biological and other weapons of mass destruction such as *The medical implications of chemical and biological warfare* in 1987, and further noted increasing concerns that the new technology of

genetic engineering might be used for malign purposes. That report went on to consider the symposium held by the International Committee of the Red Cross (ICRC) in Montreux in 1996 on 'The medical profession and the effects of weapons.' At that symposium one working group discussed future weapons based on the new biotechnology and genetics research.[6] The symposium concluded that:

> '...weapons of the future, especially those developed on the basis of knowledge of the human genome and of genetic engineering, should be given serious consideration...'

Following the Montreux symposium, similar concerns were expressed at the 48th World Medical Association General Assembly in South Africa in October 1996 and this led to the BMA deciding to commission its first report to investigate the issue in greater detail. Given that one of the restraints on the use of biological weapons was held to be that they would likely be indiscriminate – affecting defender and attacker alike – the BMA was particularly concerned about the possibility that modern biology might facilitate the development of more precise weapons which, for example, might target particular ethnic groups.

The main body of the report, however, began by setting such concerns in the broader context of the development of offensive biological weapons programmes by major states during the 20th century. Chapter 2 of the report accepted that there has long been a strong prohibition against biological weapons because of their relationship to chemical weapons and the abhorrence of the use of poison in warfare. Nevertheless, there were examples of the possible use of biological weapons prior to the 20th century and at least one documented example – the use of smallpox by the British against North American Indians in 1763. Yet, until the elucidation of the nature of bacterial diseases at the end of the 19th century, such use could not be put on a strong scientific basis, but this is just what happened in the offensive biological weapons programmes carried out by a number of major states in the 20th century.

Both sides attempted to use biological weapons to damage the valuable draft animal stocks of the other during the First World War, and a number of states investigated biological warfare in the inter-war years. The massive and gruesome Japanese programme led to numerous attempts to use biological weapons against the Chinese during the Second World War, but it was the British who really brought scientific analysis to bear effectively on the problem. They first developed a retaliatory capability against German livestock by impregnating five million cattle cakes with anthrax spores (which were, of course, never used), and then worked out that the most effective way to attack people was to spread agents on the air so that they were inhaled into the lungs by the intended victims. After the war, the UK's programme was dwarfed by that of the United States, in which a number of anti-personnel and anti-plant agents were developed and weaponised. Subsequently, the US programme was closed down by President Nixon, and the BTWC was agreed in 1972. The Convention entered into force in 1975.

The agents that were weaponised from the many available pathogens were not chosen by chance, but against the necessary criteria for effective use. For example, the highly lethal bacterium *Bacillus anthracis* (anthrax) naturally forms an environmentally resistant spore, which is why it is usually included in an offensive biological warfare programme. Though biological agents and toxins might be used for a variety of hostile purposes, the main concern is based on the very clear evidence that, whilst it would not be straightforward, they could be used as weapons of mass destruction (WMD) to harm very large numbers of people or to wreak enormous damage on crops or animal husbandry.

The impact of the developing biotechnology revolution on this problem was considered in chapter 3 of the BMA I report. It was argued that the initial impact was likely to be the genetic engineering of traditional agents like anthrax – for example, to increase their antibiotic resistance – and it was suggested that some such manipulation appeared to have taken place in the massive Soviet offensive biological weapons programme during the later part of the east-west cold war. The question was then raised as to what novel kinds

of manipulation might become possible as the biotechnology revolution continued, and the possibility of developing ethnic-specific weapons was examined. It was concluded that such weapons did not yet seem technically feasible, but the possibility that they would become available in future decades could not be ruled out (chapter 4).

The report went on to examine what policies were available to prevent the proliferation and possible use of biological weapons. The crucial importance of the norm of non-use of chemical and biological weapons, embodied in the 1925 Geneva Protocol, the 1975 BTWC and the 1997 CWC, was emphasised (chapter 5), as was the need to reinforce this norm with a range of other national and international policies – a veritable 'web of deterrence' (chapter 6). The report concluded with a set of recommendations which then appeared most important for the scientific and medical community, the international community and national governments (chapter 7).

When the report was written it was expected that the Ad Hoc Group (AHG) negotiating a verification protocol to the BTWC would succeed. The report strongly recommended that the protocol be agreed. Unfortunately, the negotiations failed and a verification protocol is unlikely to come back on to the agenda in the near future. However, many of the BMA's other recommendations are still very much under consideration. The BMA argued, for example, that:

> '1. Professional scientists and physicians have an ethical responsibility to reinforce the central norm that biological and genetic weapons are unacceptable. This should be explicitly stated in codes of professional conduct in order to safeguard the public interest in matters of health and safety.'

and:

> '3. The World Health Organization's [WHO] disease reporting network should be expanded, particularly in

> relation to unexplained outbreaks of disease which could potentially arise from the development or use of biological or genetic weapons...'

and:

> '8. The international bioscientific community should support colleagues formerly employed on biological programmes (eg [in] the countries of the former Soviet Union), but who are now unemployed or underemployed...'

As we shall see, these ideas have been pursued in a variety of ways. Indeed, the failure of the protocol negotiations has concentrated many minds on finding different ways of avoiding the hostile use of biology. Governments and civil society are far from lacking the means to make considerable advances on the present situation. With sufficient awareness, organisation and political will there is much that can and should be accomplished.

Evidence of increasing awareness

As the original BMA I report emphasised (see its table 3.3: The chemical and biological warfare (CBW) spectrum, it is important to understand that the current and future threat is best regarded as coming from a biochemical threat spectrum ranging from classical (lethal) chemical weapons, toxic industrial chemicals, toxins and bioregulators through to traditional and genetically modified biological agents. A detailed description and analysis of events related to this biochemical threat can be found in the annual yearbooks of the Stockholm International Peace Research Institute (SIPRI). For example, the anthrax attacks in the United States in late 2001 are covered in the 2002 edition,[7] and the use of a fentanyl derivative to break the 2002 Moscow theatre hostage crisis in that of 2003.[8] Such events will be discussed in later chapters.

What is of interest here, however, is not merely the events, but also the significance of the reactions to them. Concerns about the possible impact of

genetic engineering and the biotechnology revolution generally on biological warfare are not new,[9] but there has been an increasingly obvious official response since the BMA I report. Here in the United Kingdom, the Ministry of Defence issued a report, *Defending against the threat from biological and chemical weapons*, in mid-1999. It argued:[10]

> '...Biological agents are extremely potent. Although meteorological conditions will influence the effectiveness of an attack, even low technology dissemination systems could spread a harmful dose of material over wide areas.'

and:

> '...The potential threat from biological and chemical agents is now greater than that from nuclear weapons...'

Nevertheless, this Ministry of Defence report concluded that the basis for managing the problem had to be diplomacy, 'international pressure to agree acceptable norms of behaviour; disarmament and non-proliferation initiatives; and preventing the supply of materials needed for biological and chemical warfare programmes.'

In mid-1999 the UK Royal Society, along with the National Academy of Sciences in the United States and the Académie des Sciences in France considered biological warfare. The Royal Society went on to publish its own report, *Measures for controlling the threat from biological weapons*, in July 2000. Whilst cautioning against exaggeration of the threat, and emphasising the need for careful scientific analysis, the Royal Society, nevertheless, concluded in part that:[11]

> 'In the past, only naturally occurring micro-organisms and toxins have been considered as potential BW [biological weapons/warfare], *but over the last decade, the derivation of additional agents has become possible through advances in genetic*

> *manipulation and biotechnology, a trend that will continue in the future...*' (emphasis added)

Thus the concerns expressed earlier by the BMA were reinforced.

An interesting sign of the times amongst the scientific community was the publication of an article by the *Annual Review of Microbiology* in 2001 on 'Biological weapons – a primer for microbiologists.' This contribution by the Commander of the US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland, was blunt about the dangers:[12]

> 'Biological weapons are not new, but the technologies of production and delivery have been developed and perfected by nations during the 20th century...'

And an article in the *Scientific American*[13] asked cogently: 'Is enough being done to keep biotechnology out of the wrong hands?'

Significantly, the WHO whose 1970 report, *Health aspects of chemical and biological weapons*, had been so influential in the lead-up to the agreement of the BTWC, put out an internet version of the second edition of its report in November 2001, following events in the United States. This new report did not minimise the changes:[14]

> '...As for biological weapons, the genetic modification techniques foreshadowed in 1972 by the first laboratory-made 'recombinant' DNA, as well as other developments in molecular biology, seem to offer possibilities for producing new biological-warfare agents. The accessibility of biological agents on a militarily significant scale has been substantially increased by advances in industrial microbiology and its greater use throughout the world...'

The medical profession clearly had become alarmed by the proportions of

what it might have to deal with in the event of large-scale use of biological weapons, and detailed analyses of the traditional agents, and recommendations for management after an attack, began to appear in the mainstream literature.[15]

Events such as the foot-and-mouth disease outbreak in the United Kingdom,[16] the SARS epidemic,[17] and the difficulties over Iraq's weapons of mass destruction,[18] did little to reduce the growing feeling in the scientific and medical community that hard questions would be asked about biosecurity and the responsible stewardship of bioscience.[19] And in late 2003, just as this new BMA report was about to be drafted, the United States Central Intelligence Agency (CIA) published a quite startling warning about the dangers ahead, in a report entitled *The darker bioweapons future*. This report stated that:[20]

> 'A panel of life science experts convened for the Strategic Assessments Group by the National Academy of Sciences concluded that advances in biotechnology, coupled with the difficulty in detecting nefarious biological activity, have the potential to create a much more dangerous biological warfare (BW) threat...'

The panel noted, for example, that '*[t]he effects of some of these engineered biological agents could be worse than any disease known to man'* (emphasis added).

In such an environment it is hardly surprising that the international medical community has responded vigorously. In October 2002 a scientific special session of the World Medical Association (WMA) General Assembly[21] considered the problem of 'Responding to the growing threat of terrorism and biological weapons' and the WMA made a declaration in regard to biological weapons. This stated, in part, that:[22]

> 'The WMA recognises the growing threat that biological weapons might be used to cause devastating epidemics that could spread internationally....The release of organisms

> causing smallpox, plague, anthrax or other diseases could prove catastrophic....At the same time, there is a growing potential for the production of new microbial agents, as expertise in biotechnology grows and methods for genetic manipulation of organisms becomes simpler...'

Building in part on this declaration, the ICRC issued its appeal on *Biotechnology, weapons and humanity*,[23] which is given in summary form in box 1.1. As can be seen from the detailed suggestions made by the ICRC (appendix II), the situation was felt to be so serious that a high political level declaration was required from states which should contain 'a renewed commitment to existing norms and specific commitments to future preventive action.'

Box 1.1: Appeal of the International Committee of the Red Cross (ICRC) on *Biotechnology, weapons and humanity* (summary)

Alarmed by the potential hostile uses of biotechnology, the ICRC appeals to:

- all political and military authorities to strengthen their commitment to the international humanitarian law norms which prohibit the hostile uses of biological agents and to work together to subject potentially dangerous biotechnology to effective controls
- the scientific and medical communities, industry and civil society in general to ensure that potentially dangerous biological knowledge and agents be subject to effective controls.

Source: reference 23

The ICRC appeal was considered as part of a meeting on 'International humanitarian law and disarmament: recent developments and prospects for the future,' organised by the Canadian Red Cross in March 2003,[24] and then at a workshop on 'Biotechnology, weapons and humanity' at the 28th International Conference of the Red Cross and Red Crescent Movement in Geneva in December 2003. This conference urged, in its 'Agenda for humanitarian action,' that:[25]

> 'In light of recent advances in biotechnology that could be misused to create new means or methods of warfare, urgent action is taken to prevent the misuse of biotechnology for hostile purposes and the erosion of the prohibitions of poisoning and the deliberate spread of disease contained in international humanitarian law.'

and many of the actions proposed in the ICRC appeal, including the high-level political declaration, were endorsed in the action plan approved by the conference.

However, independent commentators expressed concern about politicians responding to crises by enacting policies too hastily, without paying proper attention to assessing the balance between the risks they are seeking to reduce and the harm the introduced policies might do in the longer term.[26] To what extent, for example, would efforts to prevent terrorist access to materials and information actually inhibit the work necessary to prevent and treat disease? Clearly, as the debate developed following the publication of the BMA I report in 1999, the complexity of the legislative task,[27] and the problems for the biomedical community in responding[28] became increasingly apparent.

Aims and structure of this report

It is essential to understand that not only the scope and pace of change in biotechnology are of concern, but also where this revolution will take humanity in the 21st century. Matthew Meselson, Professor of Natural Sciences at Harvard University, set out the problem succinctly in 1999:[29]

> '...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 also be able to manipulate it – including the processes of cognition, development, reproduction and inheritance.'

He 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...'

Preventing that terrible distortion of the biotechnology revolution, and the appalling threats to human rights it contains, is what the ICRC appeal, properly understood, is asking us to do.

This second BMA report is intended to assist that process. It begins by briefly reviewing the current political situation, in which the effort to strengthen the BTWC with a verification protocol has been abandoned. A series of annual meetings on subsidiary issues was found to be the only way to keep a multilateral process alive between the broken 2001-02 Fifth Review Conference and the 2006 Sixth Review Conference (chapter 2). Current worries about biological research which might easily lead to dangerous malign applications – for example, the mousepox experiment – are reviewed in chapter 3. Chapter 4 assesses the impact of efforts being made by major states to counter possible terrorist use of biological weapons, and whether an offence/defence arms race may already be underway. Then, on the assumption that the prohibitionary norm against hostile use of modern biology may not be maintained, chapter 5 considers what kinds of malign applications might become possible in future decades. The final chapter asks what options are available to prevent such threats to human rights and what are the most important steps that need to be taken now.

CHAPTER 2:

THE CURRENT POLITICAL STAGNATION

The BTWC

The BTWC is a mid-cold war agreement which was negotiated in the early 1970s. It entered into force in 1975 without an organisation to operate it between its five-yearly review conferences or any effective means of verifying that states party to it were living up to their obligations.[1] The realisation that the former Soviet Union had been in serious violation of the Convention for many years and, in the early 1990s, that Iraq had a biological weapons programme, demonstrated all too clearly the weakness of this prohibition on the hostile use of biology. For these reasons, at the Third Review Conference of the BTWC in 1991, a serious effort was initiated to strengthen the Convention that was to last for a decade.

The CWC, with its tough verification system based on declarations, routine inspections (visits) to check declarations, and the possibility of challenge inspections in the event of serious suspicions of violation, had come into force in 1997. At the time of the BMA I report[2] in 1999, the CWC had been in operation to the general satisfaction of the international community for two years. With the exception of the massive problem of destroying enormous stocks of lethal chemical weapons, there are great similarities in the problems of verifying the prohibition of chemical and biological weapons. It could, therefore, be reasonably argued that the BTWC verification protocol emerging from the protracted negotiations in Geneva would form the basis for an integrated, reliable and effective regime since it was of a similar three-pillar form of declarations, visits and challenge investigations.[3] Whilst

accepting that there were political and technical difficulties to be overcome, the BMA I report argued that the protocol being negotiated was the best way to strengthen the BTWC and looked forward to its early completion. Such hopes were dashed in 2001.

By February 2001 the states parties in the AHG negotiating the protocol had met in over 20 sessions. Differences had been aired, and narrowed to such an extent that there were calls for the chairman, Ambassador Tibor Tóth of Hungary, to produce a text which might be used to finalise the agreement. This he duly did in March 2001. The 210-page document had 30 articles which, although somewhat reorganised and renumbered, were clearly derived from the negotiators' most recent version of the 'rolling text.'[4]

A detailed evaluation of the chairman's composite text in July 2001 strongly supported the text as the best compromise available and argued that:[5]

> 'In signing and ratifying the composite Protocol text states parties will be seen to have taken *all possible practicable* multilateral steps to *obstruct* the proliferation of biological weapons...'

From the protracted nature of the negotiations it was clear that not all states parties were strong supporters of the protocol and the evaluation therefore argued that 'rejection of the protocol by an individual state will undermine other efforts that that State might wish to pursue internationally at the bilateral, regional or multilateral level.' Nevertheless, rejection of the protocol by the United States followed, at the July 2001 meeting of the negotiators.

The argument of those who supported the protocol was not, of course, that it would lead to the detection of every possible violation, but rather that, over time, it would lead to greater transparency and therefore greater confidence in compliance. Furthermore, the tougher the compliance measures agreed – declarations, visits, clarification mechanisms and challenge investigations – the better the transparency and the greater the confidence.

Additionally, the other aspects of the protocol, crucially the formation of an international organisation to operate the protocol and take care of development of the Convention between review conferences, would provide major new benefits to everyone's security and peaceful development prospects.

Despite the fact that the protocol text had been watered down during the negotiations from the more stringent forms of compliance monitoring that its supporters, such as the European Union, would ideally have liked, when the AHG met for its 24th session in July 2001, plenary statements were made on the first two days from 50 of the approximately 55 states parties taking part supporting the chairman's composite protocol text as a basis for completion of the protocol prior to the Fifth Review Conference to be held later in the year. A further two states parties spoke in support of the protocol on the third day before the United States presented its position.[6]
US ambassador Mahley stated:[7]

> 'The draft protocol will not improve our ability to verify BWC compliance. It will not enhance our confidence in compliance and will do little to deter those countries seeking to develop biological weapons. In our assessment, the draft protocol would put national security and confidential business information at risk.'

He further concluded that:

> '...the mechanisms envisioned for the protocol would not achieve their objectives, that no modifications of them would allow them to achieve their objectives, and that trying to do more would simply raise the risk to legitimate United States activities.'

In short, not only was the chairman's composite text unacceptable, but so also was the mandate on which it had been negotiated.

During the Clinton administration, the United States had played an ambiguous role in the negotiations of the protocol. Support for the objective was proclaimed; indeed, a year before the rejection 'Mahley had expressed confidence that the draft protocol contained adequate safeguards for sensitive information.'[8] However, strong opposition from the commerce and defence departments and lack of top-level direction led to virtual deadlock in the inter-agency debate in Washington and a lack of US leadership in the Geneva negotiations.[9]

What changed in July 2001 was that there *was* top-level direction, but from a new administration with a different political viewpoint:[10]

> '...Nowhere is this change clearer than in the appointment of John Bolton as undersecretary of state for international security and arms control. A longtime ideological ally of North Carolina's former Republican senator, Jessie Helms, Bolton has seemed no less vehement in his dislike of multilateralism...'

In this perspective there was total opposition to the protocol from the Bush administration because at base it 'saw the protocol as yet another mandatory – and therefore, unpalatable – multilateral regulation.'

There can be little doubt now, at the beginning of 2004, of the nature of the Bush administration's new foreign policy.[11] In late 2001, however, after the anthrax attacks in the United States, it might have been hoped that there had been some reconsideration of the July decision. At the very least, a standard thorough review of the whole of the Convention, article by article, might have been undertaken at its November/December Fifth Review Conference.[12] In its rejection of the protocol the United States had suggested the need to consider alternative means of strengthening the Convention, and on 1 November President Bush indicated seven such alternatives. Given the sympathy for the United States after the September terrorist attacks, these suggestions were not openly opposed by other states parties. Despite the antagonism towards the United States which its July

rejection of the protocol had obviously generated, there still remained hopes for the BTWC regime to be strengthened at the review conference. Considerable background work, for example, in the UK's important paper on science and technology[13] (to which we shall refer in later chapters) was put into preparations for the meeting.

The review conference did not start well, with John Bolton for the United States naming a number of countries which the US considered were operating clandestine biological weapons programmes. John Bolton also continued his attack on the protocol. Reactions to this approach varied:[14]

> 'Ironically, China, Cuba, Iran, Indonesia, Libya and Pakistan – which in 2001 were among those states resisting attempts to propel the AHG process into a final phase...were now (together with Russia, which kept a low profile throughout the AHG negotiations) among those most eager to reconvene the negotiations...'

In view of such manoeuvring, it was a considerable surprise to many observers that on the last day of the meeting the review conference appeared to be reaching a successful conclusion. Indeed, the president of the review conference noted in his press conference[15] after the meeting that it had been quite close to finishing its work 'both in terms of the volume of the elements consolidated and in terms of the understandings which had been reached.' Crucially, he added that 'the draft final declaration was 95 per cent ready.' This declaration, if completed, would have added to those of previous review conferences in reinforcing and strengthening the BTWC by multilateral agreement.

As is now well known, however, a successful outcome was not reached in December 2001 because:[16]

> '...less that two hours before the conference was scheduled to close, the American delegation tabled drastic new language on

> the AHG and follow-up action....the proposal suggested that the conference decide to hold annual meetings...to "consider and assess progress by state parties in implementing the new measures adopted at the Fifth Review Conference".... *In exchange the US demanded the termination of the AHG's mandate.*' (emphasis added)

The introduction of this controversial proposal at such a late stage was widely viewed as a deliberate attempt to disrupt proceedings and derail the conference. The end result of much heated debate was that the review conference had to be adjourned for a year. Stagnation of the political process was plain for all to see.

During the following year, even states parties that supported the protocol began to accept that alternative means of strengthening the BTWC had to be found – and agreed – in order to prevent a potential disintegration of the regime. In the United Kingdom the Foreign Office issued a green paper which identified a range of measures[17] and it was not difficult to find a number of other possibilities in the proposals put forward by a variety of states parties at the 2001 Review Conference.[18]

Strong supporters of the protocol felt, however, that the US rejection of the protocol and prevention of the agreement of a final declaration at the review conference not only left a gaping hole at the centre of the 'web of prevention,' but also totally ignored what was the best way of dealing with the main problem at present. An editorial in the *CBW Conventions Bulletin* in September 2002, in the run-up to resumption of the adjourned review conference, argued:[19]

> 'The fact of the matter is that multilateral international agreements designed to implement the BWC regime effectively will be needed to deal with the main problem of precluding major state-level offensive biological weapons programmes. In order to be effective, these agreements must include a system of declarations, visits to declared sites and challenge inspections...'

Commenting on the kind of measures being put forward instead of the protocol the editorial noted:

> 'So whilst we pursue other necessary avenues, such as the development of better professional standards to avoid inadvertently dangerous research, we must not become distracted from the main goal. The BWC regime has to be strengthened and effectively implemented, as soon as possible, whatever the prevailing winds in Washington...'

Traditionally, decisions in the BTWC review conferences have been taken by consensus, but at least amongst non-governmental organisations (NGOs) there was discussion about using the available voting mechanisms to deal with the obstruction of progress by the United States.

Nicholas Sims, who has written extensively on the legal history of the BTWC, argued in mid-2002 that there were two sets of circumstances where majority voting might be considered:[20]

> '...First, to arrive at a decision on the language to appear in the article XII section of the final declaration in regard to future activities to strengthen the Convention and, if necessary, in any other sections thereby clearing the way to the adoption of a final declaration by consensus or, failing that, by a further vote. Second, to use the Fifth Review Conference to commend a draft protocol to a second Special Conference...'

There are clearly great benefits to be gained from reaching a proper final declaration[21] and a second Special Conference could have led to the adoption of the protocol (the first Special Conference in 1994 having agreed the mandate for the AHG).

The United States, however, was on a decidedly different course. In May 2002 John Bolton made a speech with the title 'Beyond the axis of evil.' To the

original three countries – Iraq, Iran and North Korea – named earlier by President Bush as rogue states he now added Cuba, Libya and Syria. In the speech, given at the right-wing Heritage Foundation, each of these three states was accused by John Bolton of having some form of offensive biological weapons programme.[22] As the London *Financial Times* reported in late 2003, John Bolton considered that categorisation as a rogue state has further potential consequences:[23]

> 'If rogue states are not willing to follow the logic of non-proliferation norms, they must be prepared to face the logic of adverse consequences....It is why we repeatedly caution that no option is off the table.'

The difficulties experienced by the United States in convincing others that Iraq had an offensive biological weapons programme in the late 1990s/early 2000s demonstrates how contentious such designations can be.

In 2002, however, the United States continued to pursue its hard line in regard to what it wanted from the resumed review conference. A US paper for the Western Group of nations in the BTWC in early September stated that the US had reached a series of conclusions regarding the resumed review conference due to take place in November. These included the following:[24]

> '...The US does not support follow-on meetings between November 2002 and 2006 Review Conferences.
>
> Non-compliance: if the RevCon is very short, the U.S. would not 'name names'...
>
> ...We seek the end of the AHG and its mandate...
>
> ...the US prefers a very short RevCon, if any.

> US definition of a "very short RevCon" is one with the sole purpose and outcome of agreeing to hold a RevCon in 2006.'

Against that line from the superpower, it is hardly surprising that when the review conference did resume, the chairman could only propose a document reflecting the United States' proposals for alternative measures – to be agreed by the review conference without any consideration of possible changes. There was no final declaration reflecting a thorough article-by-article assessment of the operation of the Convention and no action on the protocol.

The new BTWC process

The United States paper of September 2002 was reportedly rejected unanimously by the Western Group at a meeting in Geneva. This presumably led to some moderation of the US position, but the United States essentially got what it wanted in the agreed programme of work, which is shown in box 2.1. As one review noted:[25]

> 'This work programme closely resembles the proposals set forth in the United States' opening statement at the onset of the Fifth Review Conference in 2001. Indeed, the topics for the 2003-05 yearly meetings are a subset of the proposals US undersecretary of state for arms control, John Bolton, made at the time.'

Independent commentators considered the agreement a very modest achievement indeed, whilst welcoming the fact that the regime did not fall apart, with no agreement being reached at all or the United States walking away from this multilateral framework.[26,27]

Box 2.1: Draft decision of the Fifth Review Conference of the Biological and Toxin Weapons Convention

1. The conference decides to hold three annual meetings of the states parties of one week duration each year commencing in 2003 until the Sixth Review Conference, to be held not later than the end of 2006, to discuss, and promote common understanding and effective action on:
   i. the adoption of necessary national measures to implement the prohibitions set forth in the Convention, including the enactment of penal legislation
   ii. national mechanisms to establish and maintain the security and oversight of pathogenic microorganisms and toxins
   iii. enhancing international capabilities for responding to, investigating and mitigating the effects of cases of alleged use of biological or toxin weapons or suspicious outbreaks of disease
   iv. strengthening and broadening national and international institutional efforts and existing mechanisms for the surveillance, detection, diagnosis and combating of infectious diseases affecting humans, animals and plants
   v. the content, promulgation, and adoption of codes of conduct for scientists.
2. All meetings, both of experts and of states parties, will reach any conclusions or results by consensus.
3. Each meeting of the states parties will be prepared by a two week meeting of experts. The topics for consideration at each annual meeting of states parties will be as follows: items i and ii will be considered in 2003; items iii and iv in 2004; item v in 2005. The first meeting will be chaired by a representative of the Eastern Group, the second by a representative of the Group of Non-Aligned and Other States, and the third by a representative of the Western Group.
4. The meetings of experts will prepare factual reports describing their work.
5. The Sixth Review Conference will consider the work of these meetings and decide on any further action.

Source: reference 28

As can be seen from the document presented by the chairman of the review conference to the states parties (box 2.1),[28] there were to be two-week meetings of experts and one-week meetings of states parties in each of the years 2003, 2004 and 2005. The topics for discussion were different in each of the years and the results of the meetings were to be considered and further action decided upon only at the 2006 Sixth Review Conference of the BTWC.

Though the main current problem in regard to proliferation of biological weapons is how to prevent state-level offensive biological weapons programmes, there is little doubt that as the biotechnology revolution progresses more means of potential misuse will arise and such capabilities will spread. Instead of having to deal with a focused problem somewhat analogous to that of preventing the proliferation of nuclear weapons, we shall have to deal progressively with a more diffuse problem[29] in which sub-state groups - and eventually, perhaps, deranged individuals – will possess the means to cause great harm. The issues to be dealt with in the new BTWC process are important in the overall aim of building an effective 'web of prevention' against biological weapons, but it would certainly have been better if these supplementary measures had been agreed *in addition* to a protocol. Nevertheless, for anyone wishing to see the prohibition embodied in the BTWC reinforced, it is certainly to be hoped that the meetings leading up to the 2006 Review Conference go well.

On the face of it, the topics for the meetings in 2003 looked well chosen as they were surely unlikely to be controversial. In article IV of the BTWC states parties undertake to adopt the necessary national measures to implement the prohibition embodied in the Convention, and national mechanisms to establish and maintain the security and oversight of pathogenic microorganisms and toxins are surely in everyone's interest. As commentators pointed out, the crucial point in the chairman's paper was in the last lines of the first paragraph which stated that the objective was 'to discuss, and promote common understanding and effective action' on the topics set out for the annual meetings. It was pointed out that the new process would be judged by:[30]

'a. its success in promoting common understanding; and

b. its success in promoting effective action;

and also, informally but importantly, by

c. its ability to achieve sharper focus on key BTWC topics whilst maintaining the integrity and cohesion of the overall regime; and

d. its cumulative effect in steering the BTWC towards a resumption of the review process proper in 2006.'

Judging by what happened in the first round of discussions in 2003, the prospects of significant progress in strengthening the regime do not look good.

Whilst it was possible to set out what needed to be agreed in regard to national implementing legislation[31] and the security and oversight of pathogenic microorganisms and toxins,[32] the gap between what should be done and what was happening on the ground was illustrated by a survey of national implementing legislation. This reported in late 2003 that:[33]

> 'Collectively, 47 per cent of state parties have some legislation in force which implements the BWC, while a further 15 per cent have legislation which may serve to implement the treaty....No information could be identified on the status of measures in 37 per cent of states parties.'

Clearly, even with regard to this basic requirement, there was much to be done in the first round of annual meetings.

The experts' meeting took place in August 2003. In a working paper for the meeting, the United States repeated its view that the new approach had superseded the protocol[34] and argued that in implementing the 2002 decision

'[p]arties should seek solid results each year, "deliverables" that will have a concrete, positive impact on efforts to counter the growing biological weapons threat.' In regard to national implementation, the paper suggested that deliverables included:

- 'a compilation of information on national implementation measures taken by individual states parties
- a list of suggested, basic domestic elements of measures that may, or should, be taken
- a list of contacts in the form of multilateral organizations or national government legal experts that can assist individual states parties in establishing national implementation measures.'

A similar set of deliverables was set out in regard to the issue of pathogen and toxin security. Some sense of the uphill task facing US diplomacy may, however, be gained from a progressive state such as Brazil which began a working paper[35] by noting that: '[t]he new, "ad hoc" and step-by-step method that was adopted at the Fifth Review Conference set back the clock of negotiations to strengthen the BTWC by at least seven years.'

Over 80 states parties were represented at the Experts Group meeting and some 66 working papers were submitted. The report of the meeting was in two parts, a four-page (part I) procedural report with an annexed list of documents such as working papers and a 172-page part II (annex II)[36] compiling all the statements, presentations and contributions made available to the chairman. A great deal of information had obviously been produced by states parties for the meeting.[37] Unfortunately, it is very difficult to analyse the part II document since, for example, there is no indication of whose statements were made as working papers and are therefore not included in the annex II or of where the contributions fitted into the detailed topics and sub-topics of the meeting. Nor was there any attempt to summarise or identify the outcome of the two weeks of meetings.

The follow-up meeting of states parties duly took place in November 2003 and again generated a large amount of paper.[38] The resulting report contains a one-page 'Report of the meeting of states parties' listing three general points (common understandings) that were agreed to be valuable (box 2.2).

Box 2.2: States parties agreement, November 2003

To review, and where necessary, enact or update national legal, including regulatory and penal, measures which ensure effective implementation of the prohibition of the Biological and Toxin Weapons Convention (BTWC), and which enhance effective security of pathogens and toxins.

The positive effect of cooperation between states parties with differing legal and constitutional arrangements. States parties in a position to do so may wish to provide legal and technical assistance to others who request it in framing and/or expanding their own legislation and controls in the areas of national implementation and biosecurity.

The need for comprehensive and concrete national measures to secure pathogen collections and the control of their use for peaceful purposes. There was a general recognition of the value of biosecurity measures and procedures, which will ensure that such dangerous materials are not accessible to persons who might or could misuse them for purposes contrary to the BTWC.

Source: reference 39

However, it had not been possible for the chairman to circulate a draft report (a non-paper) until the middle of the meeting. This draft report, in addition to the three points agreed in the the final report:[39]

> '…also included seven "basic measures" that states parties would agree to undertake on an urgent basis and report to the Sixth Review Conference on progress to date...'

These practical measures (box 2.3) would obviously have served to strengthen the prohibition regime and meet the objective of generating effective action, but they could not be agreed. It appears that having accepted what was effectively the unilateral diktat from the US in the unusual circumstances of 2002 – when the very survival of the BTWC was at stake – many states parties were not prepared to go along with a similar, essentially non-negotiable, suggestion (in view of the late delivery of the non-paper) in 2003. There were consequently no 'deliverables' from the meeting. The superpower could dominate proceedings, but it could not control them.

If that is the net outcome of the states parties' efforts on the non-contentious issues for 2003, it is difficult to be sanguine about what will be achieved with respect to the issues tabled for 2004. Indeed, with the best will in the world, a large question mark hangs over the whole thrust of US diplomacy in regard to the BTWC regime. It is difficult to avoid the conclusion that the BTWC prohibition regime is currently in a weak state and that there is little, without the concurrence of the United States, that the states parties will be able to agree to improve matters.[40] As we shall see in later chapters, this has led civil society organisations to consider what can be done *outside* the state-level process.

Box 2.3: What was not agreed, November 2003

- National penal legislation for each state party incorporating the prohibitions contained in article I (the general purpose criterion) and a prohibition on acts related to BW use by its citizens in any location and by anyone under its jurisdiction. This could include adaptation or enhancement of existing domestic legislation.
- Establishment of a national licensing system governing the export of dual-use biological agents and related equipment and technologies.
- Enforcement of national legislation, including criminal and civil penalties, and utilization of investigative tools for prevention and response.
- Establishment of national programmes to evaluate and implement biosecurity procedures, based on both intrinsic pathogen danger and likelihood of diversion, including oversight of facilities, transport systems and personnel possessing, handling, using and transporting potentially dangerous pathogens and toxins.
- National penal legislation to protect facilities and transport systems that possess, handle, use or transport potentially dangerous pathogens and toxins, including requirements limiting handling, use and transport of such materials to registered facilities and authorised personnel.
- National identification and licensing/registration of facilities and persons, and internal and external monitoring of such facilities.
- Support, as appropriate, for efforts by relevant international bodies, such as the World Health Organisation, the Office International des Epizooties (animal health organisation (France)) and the United Nations Food and Agriculture Organisation, to develop and/or expand voluntary biosecurity guidelines.

Source: reference 39

The CWC

The modern CWC is of interest to us here because it will be recalled that the chemical and biological threat spectrum ranges from lethal chemical agents, through mid-spectrum agents such as toxins and bioregulators, on to traditional and modified biological weapons agents. The BTWC appropriately covers the mid-spectrum agents such as toxins and to ensure that there is no loophole in the total prohibition, so does the CWC.

The CWC, which entered into force in 1997, in part defines chemical weapons as:[41]

> '(a) toxic chemicals and their precursors, *except where intended for purposes not prohibited under this Convention*, as long as the types and quantities are consistent with such purposes.' (emphasis added)

A toxic chemical is defined as:

> '...any chemical which through its chemical action on life processes can cause death, *temporary incapacitation* or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, munitions or elsewhere.' (emphasis added)

Clearly, the CWC differs from the BTWC because some states parties that had accumulated huge stocks of lethal chemical weapons were required to verifiably destroy these agents. However, the CWC is also concerned with ensuring that the prohibition regime continues to be effective in the future as the biotechnology revolution and associated developments in chemistry (such as combinatorial chemistry[42]) draw the chemical and biologically-based industries together. It should be reiterated that the definition of chemical weapons covers agents that cause 'temporary incapacitation' as well as lethal agents that kill. A major problem arises, as we shall see, in regard to those

situations in which chemical agents *may* be used to cause temporary incapacitation under the 'purposes not prohibited' exemption, and those in which they may *not* be used.

Despite carrying out its tasks to general international satisfaction, the CWC has run into management and financial problems. It was reported that at the end of 2001 the director general, Mr. Bustani, was accused of bad management by the United States, which called for a new director general to be appointed.[43] In April 2002 a Special Conference of states parties voted to remove Mr Bustani, but the vote was clearly split along regional lines, and left difficult problems for the new director general to overcome.

Well in advance of the First Review Conference of the CWC in 2003 it was being pointed out that, since there was an Organisation for the Prohibition of Chemical Weapons (OPCW) and a regular meeting of the conference of states parties, the review conference should focus on significant strategic issues relating to the previous years of operation of the Convention and to the future development of the regime. These issues had, at the least, to include a review of the disarmament obligations, the non-proliferation obligations and the potential impact of scientific and technological developments.[44] The latter point was required by the Convention as article VIII paragraph 22 stated, '[s]uch reviews shall take into account any relevant scientific and technological developments.'

The review conference was duly held for two weeks in April and May of 2003. During the previous year there had been a good deal of preparatory work by the states parties, the technical secretariat of the OPCW and a number of interested NGOs. In particular, the International Union of Pure and Applied Chemistry (IUPAC) published a monograph[45] based on a seminar it held on the 'Impact of scientific developments on the Chemical Weapons Convention,' and a report on the same subject was made to the review conference by the Scientific Advisory Board of the OPCW.[46]

The review opened with the United States accusing a number of states of

stockpiling and pursuing chemical weapons and with Iran exercising its right of reply to vehemently deny the accusation. Nevertheless, after two weeks the review conference was able to agree on a political declaration document and a review document.[47] Given the ongoing problems of arms control, this certainly was an achievement. Moreover, the review document contains numerous specific tasks which have to be undertaken, 'by either the conference of states parties at its next regular session, the executive council, the technical secretariat, or two or more of the OPCW's organs working together.' These actions should provide a road map for the development of the CWC over the next five years and ensure that the prohibition regime moves forward.[48]

There is no doubt that the CWC is in far better shape than the BTWC at the present time, but what of the impact of scientific developments? One problem concerns the balance of the verifications system. Verification of the CWC depends on a two-tier framework: states parties have the responsibility to ensure that no violations take place in their territory; the OPCW, through its technical secretariat, checks up on a sub-set of the chemicals that could be of concern.[49] The chemicals are set out in three schedules, with the most dangerous – such as former chemical weapons agents like nerve gases – being in schedule 1 and subject to the most stringent restrictions. Obviously, at the start of operations it was sensible to concentrate verification on straightforward matters such as destruction of chemical weapons stocks, but there is now a need to pay greater attention to what are called 'other chemical production facilities' producing discrete organic chemicals.[50] There are many such facilities and the technical secretariat inspections have shown that they are very relevant to the Convention, particularly where the modern equipment is designed to provide containment and flexibility. However, adaptation of the verification system to provide more focus on these facilities was strongly resisted by some states parties.

A second problem of longer standing concerns the growing interest in military (and police) forces in so-called non-lethal chemical weapons such as the fentanyl derivative used to break the theatre hostage crisis in Moscow in

late 2002.[51] The CWC covers chemicals such as riot control agents which normally would not be lethal. Such chemicals are allowed for domestic use, but *not* as a method of warfare. The United States ratified the Convention with qualifications[52] which some people would argue were dangerously close to use as a method of warfare, but these qualifications were not formally passed on to other states parties, who were therefore unable to formally object. The bigger issue, however, concerns the exemption allowed for the use of toxic chemicals for law enforcement. As was pointed out just after the CWC was negotiated:[53]

> 'Article 11.9(d) states that "law enforcement including domestic riot control purposes" are among those purposes not prohibited....But what is "law enforcement"? Nowhere in the Convention is it defined. Whose law? What law? Enforced where? By whom?'

and, furthermore:

> 'The identity of chemicals which states parties hold for riot-control purposes will have to be disclosed in national declarations....For chemicals intended for law-enforcement purposes other than domestic riot control, there is no provision for any such transparency. The Convention does not even require declaration of their chemical names...'

This issue is important in regard to the future of the CWC, firstly because it is well known that such 'incapacitating' chemicals were sought by both sides during the cold war period. Indeed, one such chemical, BZ, is on the CWC schedules because it was weaponised by the United States, and Iraq was accused by the UK of having large stocks of a similar chemical agent – Agent 15 – in the late 1990s.[54] Secondly, it is clear that because military forces of developed countries expect to have to deal with more operations-other-than-war (interventions) in the developing world, they have become more interested in having a range of non-lethal weapons available. There has been

similar interest in the past, but current technological developments suggest that some such weapons may be effective.[55] In particular, the biotechnology revolution is revealing much more about the molecular targets for these chemicals within the nervous system, leading to the belief that precise non-lethal chemical agents will soon become available if they are not already so.[56] Should states choose to develop such agents, there is quite clearly a huge threat to the entire prohibition regime which will lead to its progressive erosion as others follow suit and institutional interest develops.

Unfortunately, this issue, despite its importance, did not receive explicit reference in the review document. During the conference:[57]

> '...Although two states parties – New Zealand and Switzerland – made explicit reference to "non-lethal" weapons during the General Debate, *the ICRC, whose statement was focusing on incapacitants, was not allowed to address the plenary...*' (emphasis added)

The view amongst some distinguished commentators is this:[58]

> 'It is hard to think of any issue having as much potential for jeopardizing the long-term future of the Chemical and Biological Weapons Conventions as does the interest in creating special exemptions for so-called "non-lethal" chemical weapons...'

It would indeed be a misfortune if our developing understanding of the brain, which could be used to such good purpose in helping people suffering from mental illnesses, should be misused for malign purposes.

Conclusion

The regime designed to prevent the proliferation of biological and chemical weapons is currently far from secure. It seems most unlikely that states parties will be able to do much to improve the BTWC for some years to come. Though the CWC is in better general shape, it again appears unlikely that any action will be taken in the near future with respect to the crucial threat to it from the advance of science and technology – that from non-lethal agents.

CHAPTER 3:

THE ONGOING SCIENTIFIC AND TECHNOLOGICAL REVOLUTION

Introduction

Some biologists have been concerned about the possible misuse of genetic engineering to 'improve' biological warfare agents almost from the time that the techniques were developed in the 1970s. By the mid-1990s, as the BMA I report made clear, official concerns were being publicly expressed. Reference was made in that report to a US Department of Defense study[1] which suggested that agents might be modified, for example, to make them resistant to antibiotics or able to go undetected in standard immunological identification tests. More detailed reviews of such possibilities were also coming from microbiologists,[2] but only after the turn of the century did a series of well-publicised examples really bring the issue of possible misuse of modern biotechnology to serious public attention.

These examples are discussed here in chronological sequence. A number of less well-known examples are then reviewed before a general conclusion is drawn about the significance of the examples.

The mousepox experiment

On 13 January 2001, the London *New Scientist* carried an editorial with the title, 'The genie is out: biotech has just sprung a nasty surprise. Next time, it could be catastrophic.' The editorial discussed the main news story,[3] 'Disaster in the making: an engineered mouse virus leaves us one step away from the ultimate bioweapon.' The article gave an account of work carried out in

Australia to find an infectious contraceptive for dealing with plagues of mice. The work was later reported in an academic paper. The researchers had incorporated the gene for an antigen of fertilised mouse eggs into the genome of the virus, hoping that this would lead to infertility in the mice through antibodies being produced by the mice against their own eggs. When this did not happen, they decided to also incorporate the gene for cytokine IL-4 (interleukin-4) in an effort to boost the virulence of the virus and thereby the immune response of the mice. The researchers noted:[4]

> '...Previous studies using a variety of viral infection models have shown that overexpression or systemic administration of IL-4 impedes the development of virus-specific CTL [cytotoxic T-lymphocyte] activity, causing a delay in viral clearance although infected mice generally survive...'

The surprise was that in the mousepox study the addition of the IL-4 hugely increased the virulence of the mousepox, making the virus lethal to mice which are normally genetically resistant to it and even causing high mortality rates in such mice previously immunised against mousepox. The authors concluded, 'These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses, but also can inhibit the expression of immune memory responses.' In other words, it also overcomes previous immunisation.

This result caused the researchers to consult the Australian government before deciding to publish their results. The *New Scientist* article[5] quoted the first author of the academic paper, '[i]t would be safe to assume that if some idiot did put human IL-4 into human smallpox they'd increase the lethality dramatically.' He explained that they had eventually decided to publish in order to make it clear that dangerous organisms could be created without much difficulty. It could also be argued that once this mechanism became known, other researchers would be able to consider what kinds of therapy would be needed to deal with such an enhanced virus. So though this work caused a great deal of concern, it could be said that the authors (and

publishers) had dealt responsibly with what was an unanticipated finding. The story does not end there, however.

In October 2003 *New Scientist* reported work presented by an American scientist at a conference on 'Smallpox biosecurity: preventing the unthinkable' in Geneva.[6] The American federally-funded research had improved on the original Australian research by 'placing the IL-4 gene in a different part of the viral genome and adding a promoter sequence to maximise production of the IL-4 protein.' This created a mousepox which killed all the vaccinated mice even when they were treated with an antiviral drug. A monoclonal antibody that cleared IL-4 did save some of the mice.

Ian Ramshaw, one of the Australian research group, told *New Scientist* that they had also gone on to create more deadly forms of mousepox and had done similar experiments on rabbitpox. However, he expressed concern because the US research had gone on to construct a cowpox virus containing the mouse IL-4 gene. This was to be tested against mice at the US Army Medical Research Institute of Infectious Diseases at Fort Detrick. The problem, according to the Australian researcher, is that cowpox is not species-specific and though the mouse IL-4 should not affect humans, unexpected results with recombinant viruses cannot be ruled out.

Synthetic polio virus

Some 18 months after initial consternation over the mousepox experiment a second experiment also received a great deal of publicity. In this experiment a polio virus was synthesised chemically. The genomic sequence of polio virus is known, so the researchers from the State University of New York at Stony Brook, bought sections of DNA from companies that make such segments to order. They stitched the pieces together to obtain a full-length complementary DNA (cDNA) and then proceeded to assemble viable viruses:[7]

> '...The synthetic polio virus cDNA was transcribed by RNA polymerase into viral RNA, which translated and replicated in a

> cell-free extract, resulting in the de novo synthesis of infectious polio virus...'

Many virologists did not see this result as very surprising despite the public concern. Some reports suggested, however, that whilst the polio genome was not large and the replication mechanism rather simple, in principle the same kind of technique might be used to synthetically create something like Ebola virus.[8]

Again, that was not the end of the story. The group which synthesised the polio virus took many months to do the research. Craig Venter, the well-known leader of the human genome sequencing project in the United States, criticised the work at the time as irresponsible and a danger to US national security. However, in November 2003 it was announced that Venter and a group of colleagues had synthesised the bacteriophage phi-X174 from scratch in just two weeks.[9]

Venter's group had also bought small segments of the virus genome, but had improved on the existing DNA-linking techniques. For example, they purified the pieces to a higher degree of accuracy in order to reduce contamination with molecules of incorrect chain length. When injected into bacteria, fully-fledged viruses were produced. The work was carried out as part of a US Department of Energy project to develop new organisms that could be used to carry out specific tasks such as environmental clean-up. Venter argues that the work did not constitute a threat as the virus is harmless to people. Others naturally asked what the difference was between the synthetic polio experiment and the synthetic bacteriophage experiment.

Smallpox immune response

Perhaps less well known, but of at least equal concern is work also reported in 2002 on a comparison of the mechanism by which *Variola major* (the cause of smallpox) and vaccinia virus (which is used for vaccinations) deal with the immune response.

Mammals have two different types of immune system. The newer – in evolutionary terms – *adaptive* immune system is best known and this, through non-lethal infection or vaccination, allows us to mount specific responses to a wide range of invading organisms. The *innate* system, however, though not adaptive, is crucial in mounting responses to conserved products of microbial metabolism (that is, elements that have been preserved in many species through evolutionary time) and activating elements of the adaptive immune system.[10] An important part of the innate immune response is produced by the complement system of proteins which are involved in the recognition and destruction of foreign invaders, and important early proteins in this defence system are called C3b and C4b.

Large viruses such as smallpox and other pox viruses have evolved many different ways of disrupting both the innate and adaptive immune responses.[11] In vaccinia one such mechanism was known to be a complement control protein – specifically, vaccinia virus complement control protein (VCP) that, amongst other functions, binds and inhibits C3b and C4b. The work published in 2002 looked for the analogous protein in *Variola major* to compare it with that of vaccinia. The authors stated:[12]

> '...Because authentic variola proteins are not available for study, we molecularly engineered and characterised the smallpox inhibitor of complement enzymes (SPICE)...'

In short, published sequences of variola strains were scanned to discover whether a similar protein to VCP existed and when this was found it was then engineered. The protein was called smallpox inhibitor of complement enzymes. Crucially, the investigators then compared the effectiveness of VCP and SPICE. They found that:

> '...SPICE is nearly 100-fold more potent than VCP at inactivating human C3b and six-fold more potent at inactivating C4b...'

and they noted that the lesser activity of VCP could be one reason for its much lower lethality. Thus this is likely to be one of the reasons that vaccinia can be used for vaccination.

Again, it can be argued that this is valuable knowledge, because ways might be found to disable SPICE and used therapeutically if smallpox was ever to re-emerge. But it can also be seen that, at least theoretically, such comparisons could lead to the genetic engineering of *Variola major* back from the vaccine strain by someone with malign intent.

Genetically engineered anthrax

The three experiments just described – mousepox, synthetic polio and smallpox inhibitor of complement protein – have been much discussed in the scientific and general media, but a prior experiment, carried out in the early 1990s by Russian researchers, had previously caused consternation in the US national security community. This work first surfaced at an international conference in Winchester, England and involved the genetic engineering of anthrax.[13]

Anthrax has a long pedigree as a biological weapons agent. It is known to have been used in attempted anti-animal sabotage operations in the First World War.[14] Anthrax was the agent for the first British (anti-animal) biological weapon in the Second World War, it was weaponised by the United States in its early cold war offensive BW programme and, of course, it was the agent which caused some 70 deaths when accidentally released from a biological weapons programme facility in April 1979 at Sverdlovsk in the former Soviet Union.[15] Anthrax is therefore seen as a significant threat in any analysis of the current dangers. Furthermore, it is the subject of intensive study at present, its genome sequence, for example, being published in mid-2003.[16] In this context, any work on strains of its causative agent *Bacillus anthracis* could be of concern. The Russian researchers said their work was designed to see if there was any danger of genes being exchanged between *Bacillus anthracis* and *Bacillus cereus* in the soil (where both can be found). *Bacillus cereus* is capable of attacking blood cells, but it does not produce a lethal disease in humans, unlike *Bacillus anthracis*.

The researchers engineered genes from *Bacillus cereus* into *Bacillus anthracis* and showed that the engineered bacterium had high lethality against golden hamsters – even if they had been vaccinated with Russia's standard anti-anthrax vaccine.[17] This raised the question of whether the vaccines used in the West would be effective against the engineered bacterium. Again, that was not the end of the matter. The US Defense Intelligence Agency, in its Project Jefferson, at least considered recreating the engineered bacterium in order to check its properties,[18] an act that, if undertaken, some would certainly consider to contravene the BTWC.

Beyond bugs: bioregulators

The examples so far discussed in this chapter have involved experiments on microbial pathogens that have raised concerns about their possible misuse. However, one of the people instrumental in bringing such issues to the attention of the biomedical community, George Poste, has urged us to 'move beyond bugs' to consider what he calls 'the brain bomb.' As he explained:[19]

> '...as we begin to understand the exquisite molecular mechanisms that regulate this remarkable structure called the human body...the ability to understand those [brain] circuits means that simultaneously we gain the capacity to scramble them...'

He continued:

> '...So that means that you can engineer a series, a complete spectrum of activity from transient immobilization...to catastrophic effects which can be acute or chronic...'

All of which may have seemed far-fetched until a fentanyl derivative was used by the Russian authorities to end the Moscow theatre hostage crisis in late 2002.[20]

Opiates like fentanyl induce respiratory depression which causes

unconsciousness and starves the brain of oxygen. In the Moscow siege 600 people were saved, but 125 hostages died and an unknown number are likely to suffer from permanent disability. The use of a therapeutic agent like fentanyl in such a situation raises many difficult questions both for doctors[21] and, as we saw in chapter 2, for the national security community. Of particular interest here is what the use of fentanyl in Moscow might portend, since the authorities there and elsewhere might well judge the operation successful in view of the possibility that all the hostages could have died had the hostage-takers carried out their threat to detonate their explosives.

Fentanyl and its derivatives are well known.[22] Fentanyl was first synthesised in the 1950s and was subject to research as a potential incapacitant during the cold war era.[23] The drug acts by affecting the natural receptors for endogenous opioid peptides in the body. Our understanding of such peptides, their receptors and how drugs like fentanyl act on them has developed substantially since the 1970s, particularly as the genomics revolution has facilitated elucidation of the natural receptors.[24]

Bioregulators are defined as:[25]

> '...naturally occurring organic compounds that regulate diverse cellular processes in multiple organ systems...'

Two examples are cytokines of the immune system and neurotransmitters in the nervous system. A characteristic of these chemicals is that they are effective at very low concentrations. Furthermore, as the pharmaceutical industry has developed, it has become increasingly possible to design synthetic chemicals (drugs) to affect the natural receptors for such bioregulators. Clearly, such drugs can be used for benign purposes such as the relief of pain (morphine), or in unwelcome situations such as addiction (heroin).

In the BMA I report, it was noted that one of the worries in western military circles was that new agents might be created in which benign microorganisms had been 'genetically altered to produce a toxin, venom, or

bioregulator.' An example of an experiment in which this was done was reported in 1993 by three Russian scientists.[26] The researchers first showed that injection of the natural opioid ß-endorphin reduced the pain threshold of mice (that is, it had an analgesic effect) and also led to 'profound muscular rigidity and catatonia.' These results were to be expected from the nature of the injected material. The scientists then engineered the gene for ß-endorphin into a vaccine strain of tularemia. Though a vaccine strain was used, nevertheless tularemia is one of the traditional biological warfare agents. Injection of the genetically modified vaccine strain into mice again led to a reduction in the animal's pain threshold, but this was of longer duration and stronger effect – as might be expected since the endorphin was being produced continuously by the microorganism as well as being destroyed by proteolytic enzymes. Animals injected with the modified microorganism also exhibited 'a state of general muscular rigidity and catatonia...as in the case with [injection of] pure ß-endorphin.'

This experiment, then, was of exactly the type referred to in the BMA I report. A microorganism had been genetically engineered to carry the gene for a well-known bioregulator and this bioregulator had been effectively produced in the experimental animal. Moreover, the animal's behaviour had been profoundly affected by production of the bioregulator by the engineered microorganism, and the microorganism in question was a well-known traditional choice for a biological weapons agent.

It has to be stressed that there are many different bioregulators that could be used to deregulate human physiological functions, one recent review, for example, discussing: endogenous pyrogens to cause fever; eicosanoids to cause bronchospasm; insulin to cause hypoglycemia; and plasma proteases to cause hypotension.[27] Additionally, of course, there are many toxins that could be misused in a similar manner. Toxins are selective poisons produced by living organisms, which often have very specific effects on other organisms (for example, in snake bites or bee stings). Many natural toxins are much more lethal than chemical nerve agents. Though few were weaponised in past offensive programmes because of difficulties in production, environmental

degradation and so on, some toxins such as botulinum toxin (lethal) and staphylococcal enterotoxin B (incapacitating) certainly have been.[28] Clearly, if delivered as a gene in an infective microorganism, many more toxins could potentially be misused.

With this in mind, it is also necessary to consider genetic engineering of insect vectors. It has been argued that much genetic engineering is being used to try to make insects less dangerous as carriers of disease to humans, but:[29]

> '...While these enterprises have laudable goals, responsible regulators must anticipate that some users of the technology may, in fact, have evil designs. No other known pathogen delivery system surpasses mosquitos....experiments...could create mosquitos genetically modified to be *more*, rather than *less*, effective vectors...'

The main concern of the authors of these statements was inadvertent damage resulting from insufficiently overseen experimentation, but it is possible to find similar concerns in the national security community. One recent study pointed out that as the amount of toxin or bioregulator could be extremely low yet still suffice to produce physiological disruption, delivery by a genetically modified insect (in multiple bites) could be a way to deliver the agents:[30]

> '...By employing future discoveries related to insect ontogeny and genetic manipulation, a mosquito potentially could be genetically altered to produce and secrete a highly potent bioregulator or toxin protein in its saliva.'

The insect would then deliver the agent by inoculation as it fed on the victim's blood.

Effective aerosolisation and delivery

Ever since the UK's offensive biological warfare programme of the early Second World War years, it has been considered that the most effective way of causing mass human or animal casualties was to spread the agent as an aerosol on the wind in such a form that it was taken into, and retained, in the victims' lungs. It was also considered that one protection against mass casualty biological warfare or terrorism was the very great difficulty of producing an effective aerosol with the correct-sized (one to five microns) particles to enter, and stay in, the victims' lungs. This comforting idea was called into question by a paper published in early 2003.[31]

The authors had been involved in attempts to use the biological control agent *Bacillus thuringiensis* (which is closely related to *Bacillus anthracis*) to control populations of gypsy moths which were damaging lumber crops in British Columbia. They noted that in addition to the need to dry and formulate an agent for a really effective dose to be delivered, it was also considered that ordinary liquid crop sprayers would not produce effectively-sized aerosol droplets because of clogging of the spray nozzles, and that people indoors would be relatively unaffected by such aerial spraying.

In order to allay public concern about exposure of humans to the liquid control agent being sprayed, environmental samples were systematically collected as the spraying was done. The crop spraying resulted in 99 per cent mortality of the gypsy moth population, but it was found that a significant amount of the material was in suitably small droplets. Indeed, the authors stated:[31]

> '...Droplets of two to seven microns are formed in sufficient quantities to penetrate houses and contaminate the nasal passages of residents inside their homes. The concentration of airborne [*Bacillus*] spores indoors increased within a few hours after the spray and ultimately exceeded the outdoor concentration.'

The authors of the paper naturally concluded that their results refuted the idea that 'there are technological barriers that would prevent all but major military programs from using *B.anthracis* as an aerosol-disseminated bioweapon.' A follow-up note by different researchers analysed what the consequences would be for a large human population if the same spraying was carried out with anthrax spores. It was argued that:[32]

> '...perhaps 15 per cent of a population could receive lethal doses of *B.anthracis* under an attack carried out using similar airborne equipment...'

and, therefore, concluded that a substantial attack *could* clearly be carried out with minimal resources.

The use of such biological control measures is widespread, so it is to be expected that these disturbing results and conclusions will be quickly re-checked. It is particularly important to note, however, that our understanding of how to design extremely effective aerosols for delivering drugs[33] or vaccines[34] into the lungs is developing very rapidly for sound medical reasons. Unfortunately, this technology is also eminently applicable to the design of more effective biological warfare or terrorist attacks.[35] Clearly, also, genetic engineering techniques might be used to make the agent less susceptible to environmental degradation.[36]

A more general point that needs making is that the advances in biotechnology which are permitting the kinds of manipulation discussed in this chapter are not taking place in isolation. There are associated developments, for example, in bioinformatics,[37] combinatorial chemistry[38] and perhaps even in nanotechnology[39] which accelerate the development of new capabilities.

Drug crop control

The discussion so far has concentrated on perceived threats to humans but, historically, major offensive biological warfare programmes have also included consideration of attacks on agriculture.[40] Indeed, it can reasonably

be argued that we should be more worried about biological attacks by terrorists on our agricultural systems, because they would be technically simpler to carry out and could have quite devastating consequences.[41] For example, animal husbandry is often highly intensive and animal viruses like foot-and-mouth disease are highly contagious. This combination makes the initiation of a widespread outbreak in a vital industry very possible, with little personal risk to the perpetrators but enormous damage to the industry in dealing with the epidemic and the loss of markets.

One worrying development in recent years has been the effort to use biological agents in the war against narcotic drugs by developing fungal agents to attack the drug crops. This effort has taken place against a background of rapid developments in the use of plant inoculants and biocontrol agents and a growing industry devoted to the production of such agents.[42] The specific issue that arose in relation to drug crops was outlined in a report in early 2001 which stated:[43]

> '*Pleaspora papaveracea*, an agent to eradicate opium poppy, is currently being field tested in Central Asia and the US....Another fungus (*Fusarium oxysporum*) to eradicate coca is being developed in the US....Another type of *Fusarium oxysporum* is being developed to eradicate cannabis...'

Opponents of this strategy argue that induced epidemics might spread to other species of plant. If done without the consent of the local government it could be viewed as a violation of the BTWC, and developing the capability would inevitably produce a great deal of knowledge and practical experience that could be applied to attack other plant species.[44] The plans also appear to involve the use of strains selected for particular virulence.[45]

The scope and pace of change

It is evident from the seven examples discussed in this chapter that there are sound reasons to be concerned about the impact of advances in biotechnology on the possible means that could be used in biological warfare

or biological terrorism. However, a snapshot of cases that have come to public and expert attention cannot be considered as a systematic overview of the whole problem.

Probably the most detailed and wide-ranging overview publicly available is the 29-page document on new scientific and technological advances prepared by the United Kingdom for the Fifth Review Conference of the BTWC in 2001 and reflected in other papers by various states parties. In the main body of the UK paper a wide range of issues was discussed in some detail (see the list in box 3.1). This listing gives some idea of the *scope* of developments taking place. In regard to the *pace* of change the paper noted:[46]

> 'Thoughout the various studies and consultations carried out by the UK to inform this review, it has been clear that the rate of change in science and technology fields relevant to the BTWC has been much greater than in the previous five-year period, that is between the Third and Fourth Review Conferences...'

Thus in all the studies and contributions there was a perception of accelerated change between 1996 and 2001 as compared to 1991 through to 1996. There can be little doubt that biotechnology capabilities which could be misused are increasing and spreading, and this trend will certainly continue. What are the implications of that, and of ongoing political changes, for national and international policies to prevent the misuse of biology?

Box 3.1: Sections of the UK's background paper on scientific and technological developments

Genomics and proteomics
Bioinformatics
Human Genome Project and human diversity
Gene therapy
Virulence and pathogenicity
Vaccines and novel therapies
Recombinant protein expression
Toxins and other bioactive molecules
Human infectious disease patterns
Smallpox destruction
Drug resistance
Disease in agriculture
Pest control in agriculture
Molecular biology applications and crops
Trends in protein production technologies
Means of delivery of agents or toxins
Use of pathogens to control weeds and 'criminal' crops
Bioremediation: the destruction of material

Source: reference 46

CHAPTER 4:

OFFENCE VERSUS DEFENCE

Introduction

At the end of 2003, *Nature* in London carried an article titled 'In the shadow of war', which argued that '[i]f you look at the US federal science budget, there is little doubt that this is a country on a war footing.' The article went on to explain:[1]

> '…Since the mailed anthrax attacks of October 2001, the National Institute of Allergy and Infectious Diseases (NIAID) has distributed some $1.8 billion for projects in biodefence…'

In January 2003, the Department of Homeland Security was set up with an annual research budget of some $900 million to develop countermeasures against terrorist attacks. Privately, European officials reportedly saw the US reaction as 'over the top.'

Yet US, European Union and European national policies were changing in many areas as a result of events in 2001. Indeed, as the *Nature* report went on to suggest, the main problem for US microbiologists was how to cope with the flood of new regulations. Though Thomas Butler, a microbiologist at Texas Tech University, had been found guilty in early December of defrauding his employer, and of illegally sending plague samples to Tanzania, he had been found not guilty of most of the charges brought against him. *Nature* noted that the case was widely seen as a warning to scare biologists who might be tempted to ignore the new regulations.

It is undoubtedly true that politicians in the developed world have come under increasing pressure to act, given the growing volume of information being made available to the general public about bioweapons. In regard to state-level programmes, for example, more information has become available in mainstream press articles about the Japanese biological warfare operations in China before and during the Second World War.[2,3] Further, despite the ongoing debate about Iraqi biological weapons in 2003, it is quite clear, because of the efforts of UNSCOM chief inspectors such as David Kelly,[4] that Iraq did have an offensive biological weapons programme in the early 1990s. Similarly, the South African offensive biological weapons programme,[5] which was understood to have been dismantled, resurfaced in the media when one of the scientists involved attempted to sell a genetically engineered *E.coli* strain to the United States.[6]

Among state programmes, however, the greatest concern was about the offensive biological weapons programme of the former Soviet Union, the sheer size of which was brought more into public view through a series of books[7,8] and papers.[9,10] A further worry was whether the measures put in place during the 1990s – to help the scientists involved to move to peaceful occupations – were really effective and sufficient to deal with the problem and prevent leakage of people and information to other countries where misuse was intended.[11]

Such worries about state-level misuse of biology really only provided a backdrop to mounting media coverage and public concern about bioterrorism following the 2001 anthrax letter attacks in the United States.[12] Many experts believe that nothing significant has changed and that the likelihood of a successful mass casualty attack by a terrorist group using biological weapons remains very low.[13] Nevertheless, as an article in the 2002 *Annual Review of Microbiology*, titled 'Bioterrorism: from threat to reality' demonstrated, the anthrax letters sent in the USA so soon after the attack on the twin towers in New York transformed increasing predictions and fears about the use of bioweapons to ominous reality.[14] For such small-scale use of a biological agent to cause such large-scale disruption emphasised the need for

a careful reassessment of policy, even in a country with extensive knowledge of the issue from its own previous offensive biological weapons programme.[15] An alerted public began to learn about the wide range of viral[16] and bacterial agents[17] that could be of concern. Moreover, well publicised bioterrorism exercises[18] and ongoing analyses[19] emphasised how dire the consequences of an attack could be and how much better prepared national and local governments would have to become if they were to cope effectively with a major terrorist event.

The 2003 BTWC meeting of experts

Against this background, experts from states parties to the BTWC met to consider the first two items on their agenda (see box 2.1). Many papers were produced by the states parties, describing and analysing what had been achieved. The United States, for example, produced a working paper outlining what it had done to implement the BTWC[20] and another paper[21] gave more details on what had been done to make dangerous pathogens more secure. The topic headings in these two papers are shown in boxes 4.1 and 4.2 respectively. Evidence of similar legislation could be seen in the working papers from other states parties.

Box 4.1: National measures adopted by the United States to implement the Biological and Toxin Weapons Convention prohibitions

Background
Criminal provisions
Seizure
Security of dangerous pathogens and toxins
Export controls
Sanctions
Foreign assistance restrictions
Cooperative threat reduction
Emergency preparedness and response

Source: reference 20

Indeed, a report of a NATO advanced research workshop held in the run-up to the meeting noted:[22]

> '…that there are clearly common approaches being adopted both in the United States through its select agent programme and in several European countries to the registering/approval/licensing of facilities and of personnel working with listed/select/highly hazardous agents....A further common understanding related to the controls and approval of transfers both nationally and internationally of listed/select/highly hazardous biological agents and toxins.'

Within the overall policy responses to terrorism, there was clearly a widely perceived need to increase the controls over those biological agents and toxins that presented a particular risk because of the dangers of biowarfare and bioterrorism.

Box 4.2: Measures taken by the United States to secure dangerous pathogens and toxins

Background
Establishment of a select list of agents and toxins
Measures for enforcement of biosecurity of dangerous pathogens and toxins (DPTs)
Relevant statutes
Technical and legal advice
Emergency response
Establishment of specific guidelines for achieving adequate protection of the DPTs
Establishment of specific requirements for safe and secure transport of DPTs
Identification of national bodies to oversee biosecurity
Maintaining and monitoring national biosecurity of dangerous pathogens and toxins

Source: reference 21

The response in the European Union/United Kingdom

The European Union responded quickly to the terrorist attacks of 11 September 2001 in the United States and agreed a series of practical measures. The EU has focused on areas where it can complement what is being done by individual states, such as: police and judicial cooperation; the global fight against terrorism; air transport security; economic and financial measures; and emergency preparedness. In regard to emergency preparedness, it has focused on public health, availability of medical treatment, civil protection and research requirements.[23] Each member country, however, has had to reassess its situation carefully.

The UK is another country with considerable experience in relation to biological warfare on account of its previous offensive programme.[24] Two

working papers prepared by the UK for the 2003 BTWC Experts Group meeting set out its views on the core elements needed to effectively implement the BTWC[25] and for the security and oversight of pathogens and toxins.[26] The latter paper has an annex which lists and discusses relevant UK security and biosafety legislation (box 4.3). As the annex points out, with the exception of the 2001 Anti-Terrorism, Crime and Security Act, this legislation deals with health, safety and environmental issues.

Box 4.3: Relevant UK security and biosafety legislation

Anti-Terrorism, Crime and Security Act 2001

Control of Substances Hazardous to Health Regulations (COSHH)
- Biological Agents Directive

Genetically Modified Organisms (Contained Use) Regulations 2000

Importation of Animal Pathogens Order 1980 (IAPO)

Specified Animal Pathogens Order 1998 (SAPO)

The Plant Health (Great Britain) Order 1993 (as amended)

Source: reference 26

The Home Office is the lead department in dealing with the Anti-Terrorism, Crime and Security Act but, of course, the UK's response to the perception of a new international security situation goes much wider. In December 2003, the Foreign and Commonwealth Office published a strategy paper on *UK international priorities*. In his foreword the Foreign Secretary noted:[27]

> 'International terrorism and the spread of weapons of mass destruction have emerged as potentially the most catastrophic dangers to our national security in the early 21st century. These threats can arise across the world and are taking new forms. We need to understand them and to act to neutralise them.'

The main body of the paper elaborated:

> '…Preventing states from acquiring or spreading WMD will remain a top priority. *The highest concern of all will be to prevent international terrorist groups acquiring nuclear or biological weapons.*' (emphasis added).

Appropriately, the first of eight strategic international policy priorities for the UK is stated to be '1. a world safer from global terrorism and weapons of mass destruction.' Following up the lead role it had taken in pushing the BTWC new process forward,[28] the Foreign Office also, in order to achieve its objectives, maintained the need to:

> 'ensure that multilateral arms and export control regimes evolve to reflect technological change, agree more effective verification, and negotiate stronger compliance measures for biological arms control.'

Additionally, in December 2003 the Ministry of Defence issued a second white paper, following on from the 1998 Strategic Defence Review, setting out its analysis of the new strategic environment and the force developments needed to meet the changing threat. Again, this paper emphasised the starker threats from international terrorism and weapons of mass destruction.[29]

Nevertheless, it is the responses of the departments dealing with home affairs which are of particular interest here. As can be seen from the Home Secretary's written statement to Parliament, in relation to the Intelligence

and Security Committee's annual report, there are extensive developments with new government organisations being set up and actions being taken across a broad front.[30] Steps that might be taken can be considered in categories of: improved deterrence and detection; pre-emption and interdiction; defence and prevention; and consequence management.[31] Examples of these ongoing developments are the publication of a revised third edition of *Dealing with disaster* by the Cabinet Office[32] and publication of the draft Civil Contingencies Bill[33] at the same time in mid-2003. The introduction to *Dealing with disaster*, from the head of the Civil Contingencies Secretariat, also promised that a substantially revised fourth edition would take into account recent changes and, in particular:[34]

> '…The fourth edition will also pay more attention to topical issues (responses to Chemical Biological Radiological Nuclear (CBRN) incidents, mass evacuation, decontamination, widespread emergencies, public information and so on)…'

An opportunity to assess all this activity, from the particular scientific perspective of this report, arose in late 2003.

The House of Commons Select Committee on Science and Technology published its eighth report for the 2002-03 session, on *The scientific response to terrorism*,[35] almost a year after it announced, on 19 December 2002, that it would conduct:

> '…an inquiry to examine the extent to which the UK response was underpinned by science and technology, what contribution science and technology could make in combating terrorism and what issues needed to be faced by the research community to ensure that their activities did not unwittingly assist terrorists' activities.'

The committee certainly had differences with the government over access to information during the enquiry,[36] but its report contains praise as well as criticism.

The report is, however, very critical of the UK's efforts in several regards. In its first conclusion it argues that:

> '…It is not clear who in government is responsible for determining what threats the UK should be responding to, and with what priorities. We have not established how risk assessments are informing government policy and thus the scientific response…'

In regard to research, development and procurement, the committee goes on to state:

> 'There has been no extensive effort that we can establish to identify the research needs to develop CBRN countermeasures and as a result there has been no clear statement of what is required. Without this, the research community is in no position to respond effectively and in a coordinated manner.'

Though not seeing the need for a US-style Department of Homeland Security, the committee did recommend the creation of a Centre for Home Defence under the Home Office Minister of State for Counter-Terrorism, with a remit to 'conduct or commission research and development aimed at strengthening the UK's technical capability to prevent, respond and mitigate the effects of a terrorist attack' (box 4.4). We shall examine the need for care in taking such an approach at the end of the chapter. First, however, we must examine another positive response to the problem of preventing biological warfare and terrorism.

Box 4.4: Functions of the Centre for Home Defence

It would conduct or commission research and development aimed at strengthening the UK's technical capability to prevent, respond and mitigate the effects of a terrorist attack, in particular those using Chemical Biological Radiological Nuclear agents;

It would be under the auspices of the Home Office within the remit of the Minister of State for Counter-Terrorism...

It would have its own research budget of no less than £20 million a year and would be responsible for conducting basic research, deriving new technologies for home defence and adapting military technologies for civil use;

It would not conduct research on medical countermeasures but would have substantial input into and commission research conducted by the Department of Health (including the Health Protection Agency), the Medical Research Council and the Defence Science and Technology Laboratories;

It would have a physical presence in close proximity to a centre of academic scientific excellence;

It would identify relevant research expertise within universities and Research Council Institutes; and

It would form strong links with academic and government research laboratories overseas.

Source: reference 35

Helping to dismantle the Soviet offensive programme

One of the recommendations of the 1999 BMA I report, in regard to international action, was that support should be given to those formerly involved in the Soviet offensive biological weapons programme. The reasons for this proposal were that such support would help to ensure that the scientists would take up productive civil science and not be tempted to do weapons-related research for proliferant nations or terrorist groups.[37] Estimates are not exact but, as Smithson has noted:[38]

> 'The scale of the Soviet biological weapon program leaves even seasoned weapons experts stunned. In addition to four military facilities employing 15,000, the USSR constructed a web of about 50 nominally commercial facilities, known collectively as Biopreparat, that engaged in germ warfare research, development, testing, and production…'

She points out that further branches of the programme were hidden in other organisations such as the KGB and summarises by stating, '[t]he Soviets employed roughly 65,000 in the vast biological warfare complex, including about 40,000 in Biopreparat, of whom 9,000 were key scientists and engineers.' Finding new, long-term, productive employment for so many people in the difficult transition years of the 1990s and early 21st century was a formidable task indeed, but there can be no doubt that if this expertise had been spread around the world in states and organisations interested in developing a biological weapons capability, then the whole problem of preventing biological warfare and biological terrorism would have been far bigger.

Not surprisingly, great efforts have been made by the developed world to assist the transformation of the Soviet WMD programmes since the early 1990s. The United States, for example, has been engaged in a multibillion dollar Cooperative Threat Reduction Program. In regard to preventing the proliferation of biological weapons, it has four types of projects:[39]

> 'Collaborative research projects to prevent former BW scientists from selling their expertise to terrorist groups or proliferating states;
>
> Biosafety enhancement projects [which] are intended to make facilities safe places to work;
>
> Biosecurity projects [to] consolidate and restrict access to pathogens; and
>
> Dismantlement projects [which] target excess infrastructure and BW equipment at facilities for permanent dismantlement.'

US, EU and other government funds for such projects require long-term direction and management and the International Science and Technology Centre in Moscow and, latterly, the Science and Technology Centre in the Ukraine have played important roles in this respect.

In June 2002 the G8 group of countries meeting at Kananaskis in Canada agreed on a new global partnership to prevent the spread of weapons and materials of mass destruction. The United States, which has been spending some US $1 billion per year on threat-reduction programmes, committed to continue this for another 10 years. Other countries also made long-term commitments. The UK, for example, has committed $750 million over 10 years in a programme which has begun to add more of a focus on biological weapons problems to its traditional concern of helping to dismantle the former Soviet nuclear and chemical legacy.[40]

Despite all these worthwhile efforts, the tremendous difficulties of successfully converting a huge offensive biological weapons programme to peaceful civilian purposes can hardly be overestimated. A recent detailed study noted:[41]

> 'A major concern still is that threat reduction programmes have so far not been able to initiate a dialogue, let alone reach

> the military microbiological facilities subordinated to the Russian Ministry of Defence with support proposals…'

In general, the report points out that foreign conversion efforts have only to a small degree been directed at the huge production facilities available to the former programme. There is clearly much more for these valuable efforts to achieve over the next decade. The international cooperative efforts have also to be seen in the context of vast increases in biosecurity spending in the United States itself.

US biosecurity

The United States, because of its own offensive and biodefence programmes, had considerable experience and understanding of the problems of defence well before the current raised awareness of the dangers of bioterrorism.[42,43] As in the UK, the heightened awareness of the dangers of terrorism and WMD has led to the introduction of national strategies to combat the threat[44] and consequent developments and reorganisations of bureaucratic structures.

Of interest here are the operations of the Science and Technology Directorate of the newly created Office of Homeland Security[45] and, in particular, the work on defence against human pathogens funded through the NIAID of the National Institutes of Health (NIH) within the Department of Health and Human Services. As Anthony Fauci, Director of NIAID, stated in February 2003:[46]

> 'The US government is investing an unprecedented amount of money – $5.9 billion planned for fiscal year 2003 – to counter the threat of bioterrorism. Of that sum, *the NIH, the lead government agency in biomedical research, will receive nearly $1.75 billion, almost eight times the fiscal year 2002 budget for biodefense research, and the largest single increase in resources for any initiative in the history of the NIH…*' (emphasis added).

By the autumn of 2003 the impact of this new funding was becoming increasingly obvious with the announcement of major new grants. *Science* reported in September 2003 that:[47]

> 'The biodefense bandwagon is rolling. The US government last week awarded eight lead institutions grants totalling $350 million over the next five years to establish collaborative research centers that will focus on everything from understanding potential bioterror agents to developing new vaccines…'

and in October 2003 that:[48]

> '...the winners are…Boston and Galveston. *That's the main conclusion from the final, $373 million instalment of fiscal year 2003's biodefense bonanza*, announced on 30 September. Eagerly awaited, the series of 11 grants from the NIAID, *which will fund new lab buildings across the nation, has the potential to shape the biodefense landscape for years to come…*' (emphasis added)

It is crucial to understand how this increased funding came about and what it aims to achieve if we are to understand the future interaction of biodefence and offence. One point is obvious: injecting such large amounts of money into a system will inevitably create rapid change with, for example, industrial producers of vaccines making large fortunes[49] and universities buying up each other's high profile researchers.[50]

This is not to say that the funding was unplanned. In its summary of accomplishments in biodefence research NIAID has five headings:[51] new initiatives; ongoing initiatives; scientific accomplishments; clinical evaluations of new drugs, diagnostics, and vaccines; and strategic planning. The section on strategic planning lists seven points. For example, soon after the events of autumn 2001, in February 2002, NIAID convened:

> '...a Blue Ribbon Panel of experts to provide objective scientific advice on NIAID's biodefense research agenda by assessing current research and identifying goals for the highest priority areas. With this advice, developed and implemented the *NIAID Strategic Plan for Biodefense Research* and the NIAID *Biodefense Research Agenda for CDC Category A Agents*…'

Category A agents are those defined by the Centers for Disease Control and Prevention (CDC) as the most dangerous, such as anthrax, smallpox, plague, botulinum toxin, tularaemia and viral haemorrhagic fevers.[52] Similarly, in October 2002, another panel was convened to provide recommendations in regard to less dangerous category B and C agents (the NIAID list again closely follows that of the CDC, but highlights specific pathogens as priorities for additional research).[53] Analogous panels worked on immunology (June 2002), radiological threats (February 2003) and chemical threats (March 2003).

It is possible to gain an appreciation of the impact of NIAID's strategic plan from a progress report on the work on Category A agents published in August 2003.[54] The report's sections deal with the progress made generally (for example, in developing regional centres of excellence as described above) and then, in sequence, with the work on anthrax, smallpox, plague, botulism, tularaemia, viral haemorrhagic fevers and immunity and biodefence. Some of the areas of scientific progress for each agent are set out in box 4.5. There can be little doubt from such data that significant progress has been made in understanding how these agents cause disease and how the diseases may be prevented and treated.

Box 4.5: Scientific progress in research on Centers for Disease Control and Prevention Category A agents

ANTHRAX

- Key features in the pathogenesis of anthrax identified: research may yield an antitoxin
- Molecular mechanisms by which anthrax evades immune systems uncovered
- Researchers unravel anthrax genomes

SMALLPOX

- Understanding of pox virus pathogenesis has improved
- Immune response to vaccinia virus has been further characterised
- Existing supply of smallpox vaccine can be expanded to protect more Americans
- Pill form of cidofovir developed for treatment of smallpox

PLAGUE

- Genome sequence for the organism that causes bubonic and pneumonic plague has been completed
- Single gene change led to deadly plague organism
- Genes in the yersiniabactin iron transport system have been identified

BOTULISM

- Sequencing of the *C.botulinum* Hall strain A bacterium genome has been completed
- Research provides a better understanding of botulinum toxin entry into cells
- Animals are protected after immunisation with A and F toxins

TULAREMIA

- Host defense mechanisms revealed in mouse model
- Conjugating the O-polysaccharide of the lipopolysaccharide (LPS) of *Francisella tularensis* to bovine serum albumin (BSA) does not change the vaccine's effectiveness

VIRAL HEMORRHAGIC FEVERS

- Accelerated vaccine for Ebola protects monkeys
- Methods developed to study individual proteins from these viruses in regular, low containment laboratories
- Development of a novel assay for the detection of human antibodies to Ebola using reverse genetic systems
- Novel mechanisms of antibody-dependent enhancement discovered for Ebola

Source: reference 54

Of considerable interest also is the final section of the report on progress in understanding the immune system's responses to disease. The report points out that the more these are understood, the more routes may open up for devising protective strategies, and:

> '…Most important is the elucidation of the *innate* immune system's response to microbial invasion and its interaction with the adaptive immune system, leading to the effective development of antibodies and cellular responses that clear the infection and provide long-term protection.' (emphasis added)

The report goes on to emphasise the importance of our growing understanding of the innate system:

> '…The key to rapid innate responses is the presence of highly-specialized receptors, including the family of receptors known as the Toll-like molecules, which trigger cellular activation in response to various microbial structures. These "pattern-recognition receptors" detect and signal the presence of a broad range of microbes and viruses…'

Clearly, the investigation of this system has been an important element in the NIAID research agenda as it may provide means to more general defence mechanisms (box 4.6).

Box 4.6: Some scientific progress in research on immunity and biodefence

Protein switch for both bacterial and viral infections identified

Immune-evasion strategies determined for anthrax, smallpox, and plague

New clues discovered on how innate immune system is regulated

Prophylactic and post-exposure strategies involving innate immune stimulation can prevent or ameliorate bacterial and viral infections in animal models

Stimulation of Toll-like receptors allows immune system to overcome natural suppression

Source: reference 54

We can expect continued heavy investment in this area, the report noting that a major grant had recently been awarded for the creation of an 'encyclopaedia' of innate immunity to provide a comprehensive picture of this first line of defence. In general, there can be no doubt that the huge

increase in funding available from NIAID will massively increase our understanding of pathogens and pathogenesis. The question then is not about the consequences of this move to enhance biodefence, but the consequences of these consequences.

Implications of the enhancement of biodefence

One criticism of the rapid build-up of biodefence is that it has resulted in a rather haphazard set of outcomes. For example, a US General Accounting Office report of April 2003 noted:[55]

> 'State and local officials reported a lack of adequate guidance from the federal government on what it means to be prepared for bioterrorism. They said they need specific standards…to indicate what they should be doing to be adequately prepared…'

Much more seriously, some critics argue that even if there had been time and effort enough for biodefence to be better organised, it simply cannot be done effectively. One detailed review of the range of potential threats, including, for example, the kinds of agents being researched in the former Soviet programme, concluded:[56]

> '…The U.S. population *cannot* be "hardened" against biological attack. Emerging technologies, such as biosensor devices, are largely experimental. Vaccines will *not* be forthcoming from big pharmaceutical companies. A good defence against bioweapons has not yet been proposed…'

This is undoubtedly too negative a view. As was pointed out in the BMA I report, though it is clearly impossible to cover all possible biological weaponry attacks that might occur as the revolution in modern biology progresses, there is every reason to make sensible preparations for dealing with relatively containable attacks using known agents. If such preparations help to improve the public health system more generally for dealing with a

wider range of perhaps more frequent problems, then there is clearly a double benefit to society.

It is, however, necessary to think beyond simple failures (where the security measure is ineffective) and to consider the possibility of subtractive failure where the intended security measure actually makes people *less* secure than before.[57] It has been argued that the vast increase in spending on biodefence will suck money away from research on much more important public health threats such as AIDS and that microbiologists find the waves of new regulations being imposed threatening, which may lead to a reluctance to work on some issues. The 2001 anthrax attacks appear most likely to have been carried out by someone within the United States so there is also a concern that the vast increase in funding and resources for biodefence will simply lead to an increased risk of misuse.[58] More generally, since it can be reasonably argued that the state-level offensive biological weapons programmes of the last century fed off ongoing developments in biology,[59] it has to be accepted that any increase in our understanding of pathogens and pathogenesis could also be misused by those with malign purposes.

We surely have to consider also the situation that could arise if the norm of non-use of chemical and biological agents for hostile purposes embodied in the 1925 Geneva Protocol, the BTWC and the CWC cannot be upheld. Then, increasing defence capabilities against traditional agents such as anthrax seem likely to move those intent on evil to modify these agents in order to defeat the defence. As the defence then moves to cover such modified traditional agents, the offence can be expected to switch to a range of advanced biological agents not focused on the modification of traditional agents but on using new understanding of life processes to target specific physiological functions.[60] In short, there is the bleak prospect of an offence/defence arms race in the coming decades of this century as the revolution in the life sciences proceeds. Initially, such offensive capabilities will be in the hands of states, but progressively sub-state groups will also be capable of using modern techniques and knowledge for malign purposes.

A final concern arises from US biodefence activities prior to 2001.[61] It became known that a series of activities was carried out secretly in the late 1990s that could easily have been misperceived by other states as violating the BTWC. The CIA fabricated a biological cluster munition modelled on fragments of a Soviet munition and tested it with simulants. The Defense Threat Reduction Agency tried to discover whether terrorists could construct a sophisticated bioweapons plant from commercial materials by themselves buying the materials, constructing the plant and producing non-pathogenic bacterial spores which were then dried. Furthermore, the Defense Intelligence Agency at least planned to replicate the genetic engineering of an antibiotic-resistant anthrax strain. These activities, presumably carried out as concern about the biological weapons threat increased, were not declared in the annual Confidence Building Measures (CBMs) under the BTWC and could lead to suspicions that they were the tip of the iceberg of a range of undeclared activities and that a much greater range of projects was actually being carried out in secret.

Unless great care is taken to ensure openness about the vastly increased funding going into US and other biodefence programmes, such suspicions could easily arise and inadvertently help to fuel an arms race[62] which would be in all our worst interests. It is to the nature of the potential products of such an arms race – advanced biological agents - that we turn in the next chapter.

CHAPTER 5:

THE SPECTRE OF FUTURE MALIGN APPLICATIONS

Introduction

If the norm embodied in the 1925 Geneva Protocol, the BTWC and the CWC is seriously broken in coming decades then Meselson is surely correct in his supposition that all of life's physiological processes will increasingly be open to malign manipulation.[1] The questions are: 'What might become possible? And when?'

There have been a number of recent attempts in the open literature to suggest what we might expect. A 2001 review in *Nature*,[2] after considering modification of traditional agents through genetic engineering, went on to discuss: possible attacks on ethnic groups; directed evolution using DNA shuffling techniques to render *E.coli* thousands of times less sensitive to antibiotics; hybridisation of related viral strains to enhance virulence; misuse of gene therapy to carry harmful genes into victims; and sheer chance discoveries such as the IL-4 addition to mousepox which greatly enhanced virulence.

A review first published in the United Nations journal *Disarmament Forum* and then expanded in *Military Technology* in 2003[3] discussed the various ways in which the immune system might be attacked: from simply crippling the system by using a toxin to disable a key protein; to using a novel toxin to derange the system so that it attacked itself (as in an autoimmune disease); through to designing a protein which took an immunomodulatory part to a

quite novel target by combining it with a protein that targeted a specific tissue – say, in the brain. Though sceptical about the possibility of attacking specific groups of humans with 'ethnic' weapons, the review noted that agricultural systems were particularly susceptible to such attacks because of the use of monocultures of genetically identical plants and the intensive husbandry of highly inbred animals. The review emphasised that:

> '...We are dealing with many different kinds of potential weapons systems, many different ways they could be used, and...many different ways in which they could perhaps be modified...'

The authors therefore suggested that '[b]iological warfare could have a multiplicity of future trajectories.'

The analysis mentioned at the the end of the last chapter attempted to create a framework for thinking through the possibilities by discussing how the evolution of defence capabilities might provoke the search for enhanced offensive methods.[4] It accepted that the traditional agents pose the main threat for now, but argued convincingly that:

> '...The threat presented by traditional agents...will level off because of two major factors: (1) development of targeted medical countermeasures...and (2) the number of natural pathogens and toxins that contain properties suitable for biological warfare is finite...'

It went on to argue that:

> '...Like traditional agents, the threat posed by genetically modified traditional agents eventually will plateau partly because, ultimately, only a finite number of properties and genetic modifications can be used to enhance a traditional agent...'

It therefore saw the offence moving on and suggested that:

> '...Emerging biotechnologies will likely lead to a paradigm shift in BW agent development; *future biological agents could be rationally engineered to target specific human biological systems at the molecular level...*' (emphasis added)

Furthermore, the analysis noted that, unlike the threat from traditional agents or genetically modified traditional agents, the threat from such Advanced Biological Warfare (ABW) agents 'will continue to expand indefinitely in parallel with advances in biotechnology.' In short, if the international community goes down this road, there is no end in sight – malign applications will simply come in line with advances in biotechnology. It also argued that technology developments will assist ABW production, weaponisation, dissemination and delivery.

In specific terms the authors of this analysis suggested that advances in production of bacteria and viruses will inevitably increase the ease of obtaining:

> '...increased yield of high-quality product from decreased resources, greater consistency among product batches, and marginal requirements for "cutting-edge" expertise...'

They note that the ability to introduce foreign genes into plants could enable the easy large-scale production of bioregulatory or toxin proteins, and they even suggest that, given the small quantities required to have a malign effect, transgenic insects such as bees or mosquitoes could be used as vectors to deliver the foreign material through their bites and blood-sucking.

They also argue that ongoing studies of bacterial biofilms, in which colonies of bacteria become encased in secretions of complex sugars, might enable enhanced storage of agents and that studies of nanoparticles and microencapsulation technologies to aid delivery of pharmaceuticals could

lead to improved weaponisation systems for biological warfare agents. Given that particular physiological systems would be targeted by ABWs, there would be a much reduced requirement for quantity of agent and thus the possibility of new forms of delivery. After considering viral, lipid-based and colloidal vectors, they argue that:

> '...The ultimate expression of this technology would be development of a vector that encapsulates, protects, penetrates, and releases DNA-based BW agents into target cells but is not recognised by the immune system...'

It goes almost without saying that the ongoing development of such capabilities must open up new options for the use of ABWs. For example, the authors note that a civilian population could be covertly targeted to achieve a strategic effect with minimal risk of attribution. In short, biological warfare, on this analysis, is likely to become more rather than less attractive to those with evil intent.

Importantly, these kinds of analyses and conclusions can also be found in the openly-available publications of other governments' experts.[5] Additionally, in late 2003 the CIA issued a report titled, *The darker bioweapons future*, based on an expert panel's views, which was very strongly worded and echoed many of the same views and concerns. The report pointed out that:[6]

> 'Growing understanding of the complex biochemical pathways that underlie life processes has the potential to enable a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects...'

It also argued that the developments in biotechnology would lead to a diverse and elusive threat spectrum:

> '...The resulting diversity of new BW agents could enable such a broad range of attack scenarios that it would be virtually impossible to anticipate and defend against...'

Thus the experts suggested that in such a situation it could take a considerable time to develop effective defensive measures.

Among the possibilities suggested by the experts were 'binary' agents which become effective when the two components are mixed, for example – in an extreme case – a mild pathogen which only becomes virulent when treated with its antidote. Other examples were weaponised gene therapy vectors that made a permanent change in the victim's genetic make-up and 'stealth' viruses which lie dormant inside the victim until triggered – for example, to cripple a large proportion of an affected population with arthritis when they are in their 40s and force the targeted country to deal with a massive health and economic problem (an example of a delayed covert strategic attack on a civilian population).

Against that background what follows has to be seen as a set of illustrative examples of what might happen in future decades. It must be stressed that there are many, many possibilities if the malign application of biotechnology is allowed to proceed unchecked.

A deadly influenza: re-creation of the 1918 'Spanish' 'flu

In late 2002, cases of an atypical pneumonia began to be reported in southern China, but there was no certainty in the Chinese scientific community about the cause and the worldwide medical community was not alerted until early February 2003.[7] A medical doctor who unwittingly carried the infection stayed in a Hong Kong hotel and infected a dozen people who unknowingly carried the infection around the world. The number of cases being reported in many different countries led to a global alert being issued by the WHO on 12 March 2003 and a massive international effort eventually brought the epidemic to a close in late July. However, this was not before a total of 8,098 people became sick with what became known as Severe Acute Respiratory Syndrome (SARS) and 774 had died of the illness.[8]

SARS was found to be caused by a coronavirus (from a group of viruses which have a halo or crown-like appearance when seen under the microscope).[9]

Such viruses commonly cause a mild to moderate upper-respiratory tract illness in humans and more severe illnesses in animals such as cats, dogs, pigs and also birds. It is not clear how the virulent strain of the virus arose in southern China. After a few days' incubation period, SARS began with a high fever. Most people developed pneumonia and some developed a dry cough. The main means of viral spread was discovered to be by close person-to-person contact. The United States CDC reported:[10]

> '...Examples of close contact include kissing or hugging, sharing eating or drinking utensils, talking to someone within three feet, and touching someone directly. *Close contact does not include activities like walking by a person or sitting across a waiting room or office for a brief time.* (emphasis added)

The main means of spread is by respiratory droplets produced when an infected person coughs or sneezes. This is called 'droplet spread', but does not mean that a major source of infection is by the virus being able to infect at long distance by airborne spread.[11]

Even though the virus, therefore, was not highly infectious, the outbreak caused considerable disruption to international travel and required a major worldwide coordinated effort of case containment and contact tracing to bring it under control. It could obviously be seen as a warning to the international community of the need for the improvement of public health measures worldwide, both because such natural outbreaks are likely to recur and because someone might attempt to create such an outbreak deliberately.[12]

Part of the problem, of course, is that coronaviruses, like HIV, have an RNA genome and are therefore found to mutate more rapidly than those with DNA genomes. Although most mutations are likely to be harmful to the virus itself, it was to be expected that on entering the human population for the first time, the rate of mutation would be high and therefore a more virulent strain might evolve. In any event, given the experience of the long years to find effective anti-HIV drugs, the prospects of quickly finding an effective anti-

viral medicine for SARS looked remote during the outbreak.[13] Why, one might ask, should that be a cause for concern? Surely we shall have to deal with such natural outbreaks as they arise, and surely there is little chance of something deadly like the 1918 'Spanish' 'flu that killed 20-40 million people being created deliberately. Unfortunately, such an assumption about Spanish 'flu may not be warranted.

In 1997 researchers from the United States Armed Forces Institute of Pathology in Washington DC succeeded in isolating RNA from a formalin-fixed, paraffin-embedded lung tissue sample from a victim of the 1918 epidemic. The material was from a collection of specimens from autopsies of US servicemen of the time. As the researchers noted, large proportions of the populations of the day (28% in the US) were infected and the disease was exceptionally severe:[14]

> '...with mortality rates among the infected of over 2.5 per cent, as compared with less than 0.1 per cent in other influenza epidemics...'

Moreover, most deaths were among the young who are usually much less affected by influenza. Death rates for 15-34 year-olds from the influenza pandemic were some 20 times higher than in previous years, and average life expectancy in the US was depressed by more than 10 years. The RNA was clearly from a viral strain that was both highly infectious and lethal to this younger segment of the population.

The influenza virus has an RNA genome made up of segments. Because of the rough treatment methods used to fix the original material, the researchers in 1997 were only able to sequence nine fragments of the viral RNA, but further work has led to more of the genome being sequenced.[15] Furthermore, experiments have been carried out to determine the consequences of inserting genes from the 1918 virus into other strains of influenza. A report in 2001 concerned testing of the hypothesis that insertion of gene fragments from the virus nonstructural (NS) segment into a mouse-adapted human

influenza would play a role in virulence. Whilst the chimera virus replicated well in tissue culture, it did not replicate as well as the normal virus in mice.[16] However, a further report in 2002 showed that a more virulent strain could be developed by using two genes from the 1918 virus. From published sequences, the hemagglutinin (HA), neuraminidase (NA), and matrix genes of the 1918 virus were constructed. Then, under biosafety level three laboratory conditions, recombinant viruses were generated using these constructs. The authors stated:[17]

> '...Strikingly, recombinant viruses possessing both the 1918 HA and 1918 NA were virulent in mice. In contrast, a control virus with the HA and NA from a more recent human isolate was unable to kill mice at any dose tested...'

The effects of current anti-influenza drugs were also tested and they were shown to be effective in inhibiting the recombinant viruses in tissue culture and in mice.

The researchers who carried out these experiments were clearly well aware of the dangers, the authors of the 2002 report noting:

> 'The construction of viruses with multiple 1918 influenza virus genes makes a molecular analysis of the virulence of the 1918 pandemic influenza virus possible....the available molecular techniques could be used for the purpose of bioterrorism...'

Yet, they argue that it is necessary to continue such experiments in order to discover countermeasures in case of a natural or terrorist-produced recurrence of a 1918 influenza strain. Critics have argued that there is no need for such countermeasures to be developed unless the 1918 strain is recreated in the first place and they add that there are many available influenza strains which can be used to study influenza evolution and virulence.[18] Nevertheless, work on the 1918 virus continues and more tissue samples from diverse sources are providing further insight into the nature of the pandemic.[19]

The possible use of a genetically engineered influenza virus for malign purposes has not gone unremarked in the medical community. A review of mortality rates after influenza and after the use of influenza immunization suggests that influenza actually has a 'knock-on' effect in causing higher mortality rates through, for example, heart attacks.[20] This review also notes that aerosol transmission of influenza can take place and, in this event, far fewer virions are required than for contact infection. The authors note:

> '...Sequencing of the genome of the 1918 Spanish influenza virus is nearly complete; once it is published, unscrupulous scientists could presumably utilize...virulence sequences...'

They draw the not unreasonable conclusion that, taken together, these facts suggest 'an enormous potential for bioterrorism.' Whether it is wise for such conclusions to be drawn in the open literature is another question.

Non-lethal weapons: more realistic scenarios

Analyses of the impact of the biotechnology revolution can sometimes focus somewhat exclusively on the utility of the outcomes for the protection of friendly forces. Thus a US study of *Opportunities in biotechnology for future army operations* suggested that in 2025:[21]

> '...biosensors may be able to detect chemical, biological, and environmental threats of all kinds, bioelectronics components would enable combat systems to survive in high-radiation environments, biologically inspired materials could provide light protective armor for soldiers, and therapies for shock trauma from excessive bleeding could be developed...'

Similarly, proponents of non-lethal chemical weapons can often focus on scenarios where non-lethal chemical weapons, if effective, would be of use to friendly forces: examples are hostage rescue from terrorists or operations in built-up areas where the civilian population remains mixed with the belligerents.[22] As we shall see, it is important to keep a wider range of possible future scenarios in mind.

At the end of the cold war, in the mid-1990s, the US *Textbook of military medicine* volume on *Medical aspects of chemical and biological warfare* stated, after reviewing the many possibilities, that:[23]

> '...From this large number of possibilities, chemical compounds in a single subgroup – the "anti-cholinergics" – are regarded as most likely to be used as military incapacitating agents.'

These compounds are known to produce delirium by blocking the action of the neurotransmitter acetylcholine at its muscarinic synapses in the brain. One such compound, BZ, was weaponised by the US in the 1960s, but by the mid-1990s it was no longer in the armoury. As evidenced by the 2002 Moscow theatre siege, these cold war era incapacitants are just not specific enough in their effects. Nevertheless, enormous efforts were made, for example in the UK,[24] to develop such incapacitants for use in limited warfare.

The military researchers of the cold war era knew, of course, that they needed to be able to design chemicals that would fit the receptor structure for the natural transmitter they were trying to mimic or block. As the UK's discussion paper for the secret 1960 Fifteenth Tripartite Conference (with Canada and the United States) noted:[25]

> 'Ideally, the best possible method for preparing a new agent with a given action would be to design a molecule which would have this specific type of action...'

However, the paper went on to recognise that 'knowledge of structure-activity relationships is not sufficiently exact for this to be possible.' Of course, it is precisely the knowledge of receptor (and receptor sub-type) structures that the genomics revolution has delivered. One standard list of receptors was 30 pages long in 1990 and had structural information on a quarter of the receptors listed. By 1999 it was 106 pages long and had structural information on 99 per cent of the list.[26] Moreover, associated scientific and technological developments, for example in combinatorial chemistry, make finding specific

molecules to fit the newly described structures a much more successful operation.[27] Naturally, there is every reason for major drug companies to pursue research in this area as it appears more and more possible to discover drugs for alleviating mental illnesses that have few undesirable side-effects.[28]

It is little wonder that official documents (as the BMA I report pointed out) have reported concerns about the potential misuse of bioregulators.[29] Our growing capabilities have led some investigators to suggest that,[30] '[c]almatives and malodorants for controlling crowds and clearing facilities' were worthy of further attention. Others suggest that they have:[31]

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

This is not really surprising for the effects of dexmedetomidine on the brain noradrenaline system have been clear for some time.[32] Most of the noradrenaline-containing neurones are found in the locus coeruleus and their output appears to be linked, in general terms, to the level of arousal. One particular type of adrenoreceptor, the a_{2A}, is an inhibitory autoreceptor on the neurons of the locus coeruleus. Dexmedetomidine acts selectively at these receptors so as to *increase* the natural feedback inhibition and therefore limit the output of noradrenaline. It was originally developed as a veterinary sedative analgesic, but has recently been licensed as an anaesthetic for sedation of intensive care patients.[33] Sedation, however, is not a very sophisticated method of incapacitation. The real question that needs to be asked, if we wish to examine some alternative scenarios of malign misuse, is where this approach might take us as the technological drive and military requirements bring more and more sophisticated non-lethal systems[34] into deployment.

An example of interest here is civil work on muscarinic acetylcholine receptors, aimed at helping people with Alzheimer's disease (where there is a malfunction in acetylcholine neurotransmission). It was clear that BZ blocked

muscarinic acetylcholine transmission, but the effects were highly variable. This is not surprising since we now know that there are five muscarinic acetylcholine receptor (mAChR) sub-types (M_1-M_5).[35] Great progress has been made in elucidating the functions of these different receptors by knocking them out selectively in strains of mice through the use of gene-targeting technology. The M_2 receptor has been of interest because it functions as an inhibitory autoreceptor. Thus a selective drug that blocked such receptors, without affecting the other muscarinic sub-types, could increase the output of acetylcholine, and thus perhaps help to rectify the cognitive deficits in Alzheimer's disease. A representative of a drug company research group described:[36]

> '...the high M_2 receptor selectivity of SCH 72788 [chemical], which has a reasonable *in vivo* activity, and, in conscious rats, increases ACh [acetylcholine] concentrations in the striatum [a brain region] and shows positive effects on a rat model of passive avoidance...'

which suggests that the increased levels of acetylcholine were improving cognitive performance. However, if a selective blocking agent (antagonist) can be found, those with malign intent might be able to find an agonist that would *increase* the inhibitory feedback and decrease the output of acetylcholine. This could well lead to a more selective disruption of cognition than the cold war era agent BZ.

During the 1950s and 1960s, when BZ was being developed as an incapacitant in the United States, it was believed that an individual neuron could only produce one type of neurotransmitter and that this would be a small molecule (classical neurotransmitter) like acetylcholine. Since then we have learned that both of these ideas are false. There appear to be many different types of peptide used as neurotransmitters and these can be produced in a neuron which also produces a small molecule (classical) neurotransmitter. We are also beginning to unravel the functions of these neuropeptides.

With the increasing importance of stress-related disorders like depression and anxiety, a great deal of medical effort is naturally being devoted to finding more effective drug treatments for these conditions. It would appear from preclinical studies that a number of neuropeptides could be implicated. Furthermore:[37]

> '...Clinical assessment of several compounds is currently under way, with antidepressant efficacy confirmed in double-blind, placebo-controlled trials of tachykinin NK_1 (Substance P) receptor antagonists...'

Again, if selective antagonists can be found by those who wish to alleviate suffering, it has to be accepted that those with malign intentions might well be able to find enhanced means of inducing depression and other unpleasant states such as panic attacks.[38]

For these reasons it is not satisfactory to discuss only hostage rescue scenarios when looking to the future implications of current interest in incapacitants. We have to consider not just the friendly forces being equipped with non-lethal options, but also the future interrogator and the future torturer able to induce depression or euphoria or enhance pain by the use of drugs discovered in the future. We also have to remember that any capabilities which evolve may also become available to a future dictator or terrorist.[39] Indeed, there is every reason to note the introduction to a recent editorial in the specialist *CBW Conventions Bulletin* which states:[40]

> 'It is hard to think of any issue having as much potential for jeopardizing the long-term future of the Chemical and Biological Weapons Conventions as does the interest in creating special exemptions for so-called "non-lethal" chemical weapons...'

If we permit the growth and influence of institutions within military or police forces in major states which are dependent on the development and use of new chemical agents, it is difficult indeed to see where the process will end.

Ethnic weapons: a more likely possibility?

A central concern that led to the first (BMA I) report on *Biotechnology, weapons and humanity* was the suggestion that had been made regarding the possibility that the genomics revolution could allow the targeting of specific ethnic groups with biological weapons. At that time, in 1999, the report concluded by agreeing with the official position expressed by the UK at the 1996 Fourth Review Conference of the BTWC, that although such ethnic-specific weapons were not then possible:[41]

> '...it cannot be ruled out that information from such genetic research could be considered for the design of weapons targeted against specific ethnic or racial groups...'

The BMA I report took this position because it argued that, to produce an ethnic-specific weapon, there would be at least three specific requirements: there would have to be major genetic differences between groups; there would have to be a mechanism that could be used to disrupt the operation of the genome; and there would have to be effective vectors to get material into the intended victims in such a way that harm could be done. Whilst the report argued that population-specific differences might exist, and that gene therapy might eventually allow the vectoring in of means to cure or cause disease, it did not appear that the required criteria could then be met.

A recent report argued that these conclusions are no longer tenable. It noted:[42]

> '...Practically, many consider it impossibly difficult to use genetic variability to kill or otherwise affect populations. Others, including geneticists, argue that no suitable ethnic specific genes exist in the first place. *Both notions are wrong*...' (emphasis added)

and continued:

> '...New technologies are indeed available to translate specific genetic sequences into markers or triggers for biological activity. And a recent analysis of human genome data in public databases revealed that hundreds, possibly thousands, of target sequences for ethnic specific weapons do exist...'

The authors therefore concluded that '*ethnic specific weapons may indeed become possible in the near future*' (emphasis added). The meaning of 'near future' is not elaborated, but the conclusion is clearly at variance with that of the BMA I report. The data on which this new conclusion were reached were set out by the authors of the report. They argued that while they knew of no means by which a genomic marker could be used as a trigger for an activity (that is not related to the position of the marker), techniques now exist for the inhibition of genes with a specific sequence. As they pointed out:

> '...One of these techniques, called RNA interference (RNAi), uses a mechanism by which a specific RNA sequence is degraded by the cell if an externally applied RNA molecule of the same sequence is entering the cell...'

They suggested that if the sequence of the target gene varies between two different populations, this technique could, in principle, be used to interrupt the sequence in one population and not the other.

The discovery of RNAi came as a considerable surprise,[43] but it is now becoming increasingly obvious that the RNA mechanisms involved in the control of genome function are both varied and complex.[44] It seems entirely possible that a range of potential means of interference with the genome could soon be discovered, just in relation to the functions of RNA. Beyond that, there also appears to be a vast layer of control systems located in the chromosomes outside the DNA.[45]

In regard to population differences, the report authors argued:[46]

> '...From a military perspective, population specificity would mean that these genetic sequences are not or only to a very limited extent present in one (the aggressor's) population while the same sequences are present in a significant percentage of an opposing population.'

They further argued that a 20 per cent occurrence in the target population would be sufficient to be of military significance. An effect on 20 per cent of a military unit, as they noted, 'would wreak havoc among enemy soldiers on a battlefield or on an enemy society as a whole.' They went on to analyse a total of almost 300 single nucleotide polymorphisms (SNPs), all in coding regions or genes, from two public databases and stated that:

> '...An unexpectedly high number of SNPs are indeed population specific: 6.7 per cent of SNPs in one database...and 1.6 per cent of SNPs in the other include one allele that is not present at all in one population while it has a significant frequency of more than 20 per cent in another population.'

Whilst cautioning that because the data sets are based on a limited number of individuals and thus low frequency alleles could be missed, they noted that this finding is in line with other recent analyses and concluded that 'a considerable number of ethnic specific SNPs do exist.' Certainly, we can expect more data on this issue to become available as drug companies pursue genetic markers associated with differential responses to medication.[47]

Though the report does not discuss gene therapy for vectoring in material, and while challenges remain for the beneficial use of gene therapy technology,[48] there is no doubt that some military analysts are beginning to raise concerns about the potential for its misuse.[49]

Conclusion

The major threat from biological weapons at present is the use of well-known agents such as anthrax by the armed forces of states. The use of such agents by sub-state terrorist groups to cause mass human casualties probably remains low today, but it will increase in the future. States are likely to concentrate protective measures for their armed forces and civilians on such traditional agents. In the unfortunate event that the hostile use of biological agents cannot be prevented, it is to be expected that states, and eventually sub-state groups, will resort to the modification of traditional agents in order to subvert these defensive preparations. Then again, defensive measures will probably be able to catch up with such malign manipulations.

However, conclusions of this nature do not seem warranted should this action/reaction interaction of offensive manoeuvres and defensive countermeasures proceed beyond that point. As the examples discussed in this chapter so clearly demonstrate, there is an endless variety of physiological processes that could be attacked with advanced biological warfare agents – and an enormous choice of means for each process to do so. In these circumstances, devising an adequate defence would be very difficult indeed. It is, therefore, vital that we prevent such misuse of modern biology and medicine *now*, and it is to the question of what might best be done to achieve that objective that we turn in chapter 6.

CHAPTER 6:

A CALL TO ACTION

Introduction

At the end of his career, the British biologist and Second World War operational researcher, CH Waddington, wrote two books, *Tools for thought*[1] and *The man-made future*,[2] in which he tried to devise means whereby we can think systematically about the future impact of our actions. One of the ideas he discussed in *Tools for thought* was what he called 'epigenetic landscapes.' The idea, developed from his background in embryology, concerned the way that a social system might develop in the future modelled as a stream flowing down a valley:

> 'In such an epigenetic landscape, there are branching points at which a valley splits up into two or possibly more branches…'

He then considered various issues with respect to such branching points and societal behaviour. He noted that:

> '…Many types of change going on in society have a more or less well developed…character, once they have got well started in a certain direction, it is very difficult to divert them.'

The question here is whether we have initiated, or are about to initiate, an offence/defence arms race in biological warfare and bioterrorism in responding to a threat we have inflated beyond its current reality, and thus set

out on a course it will be very difficult to change. While it might be very difficult, in Waddington's view, to divert a system once it had gone down a particular pathway:

> '…Sometimes one knows that there is a branch point ahead of the system, and that if one can give the system a push at the right time, it can be diverted into one or other of the alternatives in front of it…'

It could well be that we are at such a branch point now.

In summarising one of the most detailed and wide-ranging recent sets of essays on this subject, *Biological warfare: modern offense and defense*,[3] the editor's opinion was that:

> 'In the race between the defense and the offense, a race so often seen before in military history, the defense seems to be leading for the moment. This being the case, the international arms control community has a small window of opportunity to design and put in place mechanisms to meet the threat of advanced bioweaponry…'

Since the 1980s some scientists have raised concerns about the potential that genetic engineering might have for the development of more advanced bioweapons,[4] but as Waddington pointed out in *Tools for thought*, timing is everything, and the system has to have the 'competence' to take the 'right' course. At present, surely, enough people are aware and concerned about this problem for the biomedical community to give the political system 'a push at the right time' and for the tragic malign misapplication of the revolution in biology to be averted?

The BMA I report concluded with a set of 17 recommendations that are briefly summarised in appendix III. As can be seen by comparison with box 1.2 (and details in appendix II), some of these recommendations are very

similar to those made more recently by the ICRC (for instance, enhancement of international capabilities for monitoring outbreaks of disease). Other points, for example regarding the 1925 Geneva Protocol and the BTWC, are elaborated in more detail in one list or the other. There are some points also, for example concerning education of the armed forces (ICRC) and of medical professionals (BMA I), which reflect the particular orientations of the two organisations.

The key point made by the BMA I report was that an effective 'web of deterrence' needs all possible policies available to be put firmly in place. It argued that:[5]

> '…The aim of such a set of integrated policies is to convince a potential proliferator that a CBW (chemical and biological warfare) capability is not worthwhile.'

The ICRC has recently stressed the same point in its appeal:[6]

> 'At the core of the ICRC's appeal is a "web of prevention" that should serve to prevent advances in biotechnology being used for poisoning or the deliberate spread of disease. This web is formed by the broad and integrative approach that should be taken by all those concerned to minimise the risk.'

Appendices II and III show quite clearly that there are many actions that can be taken by individuals, organisations, nations and the international community. We certainly do not lack options.

Before examining some of these potential actions in more detail, however, we need to be quite clear about the threats we face today, and those we may face in coming decades. This will enable us to see which are the most important elements of the web of prevention needing action *now* and those which need action, but can reasonably be put in place a little later.

The threat today and tomorrow

There has certainly been heightened concern about the threat of bioterrorism since the BMA I report – and also concern about the adequacy of measures available to deal with an incident. Some examples from late 2003 show the range of such worries. In September 2003 the UK took part in a multinational command-post exercise (that is, an exercise not involving actual events on the ground) called Global Mercury. The Department of Health stated that it was run under the auspices of the Global Health Security Initiative and that it was intended to evaluate the communications between the different countries involved, in response to a disease outbreak.[7] As a result of subsequent analyses, the department reported that it was learnt, for example, that:

> 'While all participants have developed national *smallpox* plans, many of these plans could be strengthened by greater elaboration of their international components.' (emphasis added).

A report in *The Times* was blunter, arguing that the exercise had revealed serious flaws in plans to deal with an attack and these flaws had allowed the virus to spread.[8]

In the United States, where much more attention is thought to have been given to bioterrorism than in other countries, a series of reports have been critical of preparations made so far. A September 2003 report from the US Department of Agriculture (USDA) concluded that in non-Federal research institutions which received funding from USDA, many deficiencies remained in the control over biological materials and physical security of laboratories as a result of fragmented guidance.[9] A report in November 2003 from the US General Accounting Office (GAO) went much further, arguing that four of its recent reports had found gaps in controls over agriculture and the food supply, and that these gaps left the US vulnerable to terrorism.[10] The GAO pointed out that the agricultural sector accounts for some 13 per cent of the US gross domestic product and 18 per cent of domestic employment.

More generally, of course, there is no solution in sight to the problems of biodetection. An overview of November 2003 pointed out that most detectors only give warning of immediate danger rather than long-term warning.[11] Moreover, as Zilinskas stressed:[12]

> '…no application of advanced biotechnologies is likely to become available within five years that would enable analysts to detect and *identify* pathogens and toxins in real time. Now, as in the past *and for the foreseeable future*, the mainstay of clinical and public health laboratories will be classical techniques that will allow investigators to identify bacterial species in a few days and viruses in days to months…' (emphases added)

There is a real danger, however, that the present preoccupation with (bio)terrorism will blind us to the main current danger.

It would clearly be possible for a terrorist group to carry out a small to medium-scale attack against the civilian population – say by contaminating the food supply. It remains rather unlikely at present that any group lacking the resources of a state could really carry out an attack that would cause *mass* casualties. The point was driven home by a long report on the US anthrax attacks in the journal *Science* in late November 2003. A dispute had arisen over whether really 'high quality' (that is, very dangerous) anthrax powder could be prepared on a small budget and without a silica additive, so the FBI decided to carry out an experiment in December 2002. According to the report in *Science*, the job was given to army scientists at Dugway Proving Ground. The experiment was completed in February 2003 and:[13]

> '…According to military sources with firsthand knowledge of this effort, the resulting powder "flew like penguins." The experiment had failed…'

As the report notes:

> '…If the army couldn't do it in a top-notch laboratory staffed by scientists trained to make anthrax powders, skeptics ask, who could do it in a garage or basement?'

Dangerous as the bioterrorist threat may well become, we forget about the current threat from state programmes at our peril. The persisting potential for leakage from the former Soviet Union offensive programme[14] should leave us in no doubt about the danger posed by the development or continuation of state-level offensive biological weapons programmes.

As an editorial in the *CBW Conventions Bulletin* argued, in the run-up to the resumption of the BTWC Fifth Review Conference:[15]

> '…history shows that it was in the major state-level offensive biological weapons programmes of the 20th century – especially in the UK, the USA and the USSR – that there was the most technologically advanced and most massive preparation for the use of biological weapons. *Preventing such state-level programmes in the future should be a primary concern.*' (emphasis added)

The editorial supported the full range of measures to prevent the hostile use of biotechnology but concluded:

> 'So whilst we pursue other necessary avenues…we must not become distracted from the main goal. The BWC regime has to be strengthened and effectively implemented as soon as possible, whatever the prevailing winds in Washington.… *Indeed, the pursuit of other goals to the detriment of the strengthening of the BWC would be counter-productive rather than just a distraction from what is really required to prevent the hostile use of biology.*' (emphasis added)

It is clear from the text of the editorial that the authors were not referring to the kinds of strengthening of the BTWC in what has become known as the *new process* (see chapter 2), but to the regular process of multilateral negotiation and agreement through the review conferences of the BTWC. This latter process will be considered following further discussion of the danger to the CWC.

The CWC and the BTWC

On the face of it, the CWC regime seems much more secure than that of the BTWC, with a well established international organisation pushing forward an action plan to achieve universality of membership and national implementation.[16] Yet as we have seen (chapter 5), there is a severe threat to the CWC regime emanating from the developing pressure to deploy new advanced forms of 'non-lethal' chemical weapons.

In 1996 an abstract of a scientific conference paper, summarising 40 years of work on 'less-than-lethal' chemicals by the US, was quoted as follows:[17]

> '…Depending on the specific scenario, several classes of chemicals have potential use, to include: *potent analgesics/anesthetics* as rapid acting immobilisers; *sedatives* as immobilisers; and *calmatives* that leave the subject awake and mobile but without the will or ability to meet objectives…' (emphases added)

At the time it was not possible to obtain further information on these agents. However, a report on recent documents released under the Freedom of Information Act (FOIA) cast further light on the data.[18] According to the report, work on an Advanced Riot Control Agent Device (ARCAD) was cancelled by the Pentagon in 1992 because it was thought to contradict the restrictions in the CWC then being negotiated. However, a dispute arose as to the meaning of those restrictions and when the Pentagon put out a request for proposals for non-lethal systems in 1994 the chemical weaponeers seized the chance to put forward at least four proposals for ARCADs-related studies

(box 6.1). This is not purely of historical interest because the report's authors argue that these kinds of projects now continue under the Joint Non-Lethal Weapons Directorate (JNLWD) of the US Marine Corps:

> 'In the light of the newly-released document, it was in 2000 that the ARCAD program resurfaced publicly in the form of a Pentagon contract awarded to Optimetrics, Inc. *The Optimetrics studies parallel those proposed by the army…in 1994*' (emphasis added)

If this analysis is correct, we are much closer to seeing the deployment of new 'non-lethal' chemical agents than many might have imagined and there is clear evidence of high-level interest in such deployments in the USA.[19] The time is surely overdue for the medical profession to bring its expertise to bear in helping to prevent such deployments and the inevitable development of the 'more advanced' agents that will follow.

In reviewing what is necessary to begin repairing the damage done to the BTWC regime in 2001-03, historian of the regime, Nicholas Sims, has suggested that as a first step states, international organisations and NGOs should aim to have a special conference held on 26 March 2005 – the 30th anniversary of the Convention's entry into force. While not cutting across the process agreed in 2002, this approach is based firmly on the idea that:[20]

> '…[The] review process should be revived as the main vehicle (in the continued absence of a legally-binding instrument to strengthen the Convention such as the AHG was working towards from 1995-2001) for steering the constructive evolution of the BWC as a working multilateral treaty and one equipped for the great task of countering the threat of weaponised disease in all its forms.'

The matters that Sims argues should be completed by March 2005 can be seen in box 6.2.

Box 6.1: Proposals put forward by Edgewood Research, Development and Engineering Center, 27 April 1994

Demonstration of chemical immobilizers

'…The objective of this analysis will be to select candidates with the highest probability of success versus the most likely scenarios of use…'

Antipersonnel chemical immobilizers: synthetic opioids

'...Previous studies at Edgewood…led to materials with dramatically improved safety ratios. This was achieved by mixing a fentanyl agonist with an antagonist that blocks the respiratory depression.…In the early 1990s Glaxo Pharmaceuticals patented some ultra-short acting fentanyl[s] that have half-lives of only a few minutes in man.…A class of experimental materials referred to as the 'azabicyclononones' have also been studied.…These tests also indicate that the onset times are slower than with fentanyl…'

Antipersonnel chemical immobilizers: sedatives

'…Alpha 2–adrenergic agonists that cause profound sedation without the untoward side-effect of respiratory depression exist…'

Antipersonnel calmative agents

'…This material belongs to a class generally referred to as serotonin antagonists or blockers. It is structurally related to the drug ketanserin…Dr Stanley discovered the profound calming effect that this serotonin antagonist had on the wild elk…under the influence of this drug, they remain alert and mobile but are very docile…to the point of being petted or even mounted as a rider would sit astride a horse…'

Source: reference 18

Box 6.2: Biological and Toxin Weapons Convention (BTWC) matters requiring completion by March 2005

National implementation legislation (article IV of the BTWC).

Sharing of legislative and other relevant texts through the UN for purposes of consultation (article IV of the BTWC).

For non-parties to the Geneva Protocol, ratification or accession to the Protocol (article VIII of the BTWC).

For parties to the Geneva Protocol, withdrawal of reservations on retaliation (articles I and VIII of the BTWC).

For non-parties to the Chemical Weapons Convention, ratification or accession to the Convention (article IX of the BTWC).

Confidence-Building Measures (CBMs) (articles V and X)
Here the 2005 target would be a 100 per cent response rate on each CBM...

Source: reference 20

This may seem a modest set of proposals to those not conversant with the difficult history of the BTWC, but as Sims comments:

> 'Just think how much better shape the BWC would be in if, by 26 March 2005, every state Party had completed its national implementing legislation and shared relevant texts through the UN, had made returns up to date under each CBM, and had joined the Geneva Protocol; and if no state party had any Geneva Protocol reservations on retaliation, intentionally or simply by default, still left in place.'

Yet he does not even see this as an easy task and suggests that it will require really concerted action by NGOs and a wide-ranging group of like-minded states parties. As far as NGOs are concerned, there is now more hope that a concerted effort can be made since a co-ordinated Bioweapons Prevention Project (BWPP) has been founded and is in operation. A worldwide network of NGOs working constructively together on this issue is the key objective of BWPP, in order to bring civil society monitoring effectively to bear.[21] Despite the efforts some have made to exclude the ICRC from its proper place in BTWC meetings, Sims expects it to be an important partner in achieving the goals for completion in 2005 through its appeal on 'Biotechnology, weapons and humanity.' Unfortunately, he is far less sanguine about the possibility of an effective group of like-minded states parties emerging quickly.

In order to get this platform for further advance in place, Sims proposes the conference be held in Geneva the weekend of 26-27 March 2005 (to mark the 30th anniversary of entry into force of the BTWC) where states parties could demonstrate what they have done to achieve these goals. It would obviously be best if this conference were organised by the states parties through the United Nations, but if that is not possible he argues that it should be done by NGOs. Minimally, states parties could agree to hold the 2005 meeting of experts in the new process between 14 and 25 March 2005 so that it would be convenient for many states to be represented at a completion conference over the anniversary weekend.

If progress can be made on the completion agenda by March 2005, what should we be thinking of to further strengthen the BTWC regime in the run-up to the 2006 Sixth Review Conference and beyond? This question has been considered by Jez Littlewood, who worked as a UN staffer during the latter part of the negotiations aimed at producing a legally-binding instrument to strengthen the BTWC. Littlewood takes a realistic starting position:[22]

> '…Anyone interested in the BTWC or the dangers posed by biological weapons more generally, cannot but ponder the question of whether the states parties as a collective body are

> actually up to the tasks they are legally bound to undertake: to ensure the prohibition and prevention of the development, production, stockpiling, acquisition – and ultimately use – of biological and toxin weapons…'

It follows, given the collective failure of the states parties in recent years, that a great deal more responsibility falls on civil society – including the biomedical community. Though only the states parties can act at the review conference, Littlewood argues that civil society can do much to ensure the best possible preparation for an effective meeting that will bring the BTWC back to where it should be as the *central* element in our efforts to prevent the hostile use of biotechnology. It is important to recognise that the BTWC last received an effective review at the 1991 Third Review Conference. The Fourth Review in 1996 was partial because of the ongoing AHG negotiations and the 2001-02 Fifth Review was at best a modest success which produced only the 'new process' document. What would be required in a full review in 2006 is set out in box 6.3.

Considering this agenda, there is a wide range of issues where NGOs could provide input both by advocacy of particular policies and by standing back and attempting to provide more detailed, wide-ranging and perhaps different, new perspectives. Littlewood suggested a list of possible topics for such analytical work and these are shown in box 6.4. If the standard pattern is followed, the preparatory committee for the Sixth Review Conference will meet in April 2006 to agree a provisional agenda for the meeting itself later in the year and any such NGO work should therefore be published, at the very latest, by March 2006. This does not leave a great deal of time for detailed, innovative, analytical contributions and so there is great urgency for organisations to get work under way soon.

Box 6.3: Elements of an effective Sixth Review Conference agenda

A review of the operation of the Convention itself.

The impact of any new scientific and technological developments relevant to the Convention.

The relevance, of the implementation, of the Chemical Weapons Convention on the implementation of the Biological and Toxin Weapons Convention, taking into account the degree of universality attained by the Conventions in 2006.

The effectiveness of Confidence-Building Measures as agreed at the Second and Third Review Conferences.

The requirement for, and operation of, the requested allocation of resources by the United Nations Secretary-General and other requirements to assist the effective implementation of the Convention.

The work of the annual meetings of states parties and the meetings of experts in 2003, 2004 and 2005, and any further action to be taken with regard to these meetings.

The work required between the Sixth Review Conference and Seventh Review Conference.

A decision to hold further review conferences.

Source: reference 22

Box 6.4: Possible topics for analytical studies

The impact of scientific and technological developments.
Export controls.
National implementation measures.
Confidence-Building Measures (particularly submission, processing, analysis and scope).
Societal verification at the national level.
Coordination of emergency response and assistance with international organisations, eg World Health Organisation.
The relationship to the Geneva Protocol (reservations) and the Chemical Weapons Convention.
Peaceful cooperation directly relevant to the Biological and Toxin Weapons Convention.

Source: reference 22

For the biomedical community, the first of the issues listed in box 6.4 is, perhaps, of most interest. In regard to such scientific and technological developments, Littlewood notes that the background papers prepared by states parties are not usually considered in detail at review conferences themselves. They nevertheless have a significant impact in providing input to the development of common understandings, in the final declarations, that the prohibitions set out in article I of the BTWC are comprehensive and all-embracing. Aspects of scientific and technological developments that Littlewood thinks warrant analytical attention to assist the Sixth Review Conference can be seen in box 6.5. It would clearly be of immense value if organisations of influence in the biomedical community were to address some of these issues.

Box 6.5: Aspects of science and technology of relevance to the Sixth Review Conference

A review of the submitted papers on scientific and technological developments in 1980, 1986, 1991, 1996 and 2001 to provide an overview of the scope of developments since entry into force and the methods by which states parties have adapted to such developments…

An assessment of the implications of the scientific and technological developments likely to arise in the period between 2006 and 2011.

The relationship between the Biological and Toxin Weapons Convention and the Chemical Weapons Convention and how, or if, formal coordination and liaison between the states parties and the Organisation for the Prohibition of Chemical Weapons might assist both Conventions in areas such as sub-national groups, assistance and/or emergency response.

The impact of the dissemination of certain knowledge and/or technologies, eg aerosolization and aerobiology.

The issue of biocontrol agents and genetically modified organisms.

The question of non-lethal weapons/technologies and their use in law enforcement (or other operations).

Source: reference 22

Given that a legally-binding instrument to strengthen the BTWC is unlikely to be agreed for some years to come, the annual data exchanges (or CBMs) agreed in 1986, and developed in 1991, will be of particular importance in ensuring greater transparency and trust between states parties. Littlewood argues that the CBMs could be much improved, for example by simply

moving to electronic rather than paper submissions. Other improvements could include translation of the submissions into the UN official languages and production of an annual report on submissions. Moreover, a Depositary State like the UK could follow Australia's example and put the UK CBM returns on the internet. This would encourage other states parties to do likewise and open up this data to scrutiny by civil society.

Energetic and effective input from many NGOs and international organisations such as the ICRC might help to ensure the success of the Sixth Review Conference of the BTWC and thus lay the foundations for a more substantial period of development of the regime through to 2011. However, success in 2006 will also depend, in part, on making something of the new process agreed in 2002, to which we now turn.

The new BTWC process

It is to be hoped that, despite the rather limited outcome of the new process in 2003, quiet action both nationally and internationally will lead to better national implementation of the BTWC and to effective measures on biosafety and biosecurity in states parties. Unfortunately, according to the interpretation adopted by the states parties of the mandate agreed in 2002, progress on these issues can only be considered in 2006, and the process now moves on to the issues for 2004. Both of these are of great interest to the biomedical community (see chapter 2, box 2.1):

> '*iii.* enhancing international capabilities for responding to, investigating and mitigating the effects of cases of alleged use of biological or toxin weapons or suspicious outbreaks of disease; [and]
>
> *iv.* strengthening and broadening national and international efforts and existing mechanisms for the surveillance, detection, diagnosis and combating of infectious diseases affecting humans, animals and plants.'

Given the inconclusive ending to the states parties meeting in late 2003 and the contentious nature of these two topics (particularly investigations in topic iii), it might be anticipated that little progress will be made in 2004. This would be unfortunate, both for the longer-term consequences and because there are important issues here where improvements would provide considerable benefits. The WHO's Programme for the Preparedness for Deliberate Epidemics (PDE),[23] for example, deserves greater publicity and support since it will help countries with fewer resources and technical expertise into a better position to respond – and this will help to deter use of biological agents. The programme has three aspects: international coordination and collaboration; national capacity strengthening in preparedness for and response to the deliberate use of biological (and chemical) agents; and public health preparedness for diseases associated with the deliberate use of biological agents.

In regard to disease monitoring, the BWPP of NGOs published an occasional paper on *Gaps in global surveillance* in 2003. This reported a survey carried out in September 2002, and rechecked in August 2003, of reporting of outbreaks of disease on publicly-accessible websites on the internet. The report concluded, 'it is evident that there are enormous gaps in geographical and disease coverage and in timeliness.'[24] Timeliness is crucial because, as the recent SARS outbreak demonstrated, timely reporting gives warning so that an effective response can be mounted. The report argued that:

> '…A comprehensive ability to watch for and report new outbreaks around the world, based on rapid clinical detection and laboratory diagnosis, would not only provide substantial public health benefits everywhere but would minimise the impact of a bioweapons accident or attack, should one occur…'

This can only be done by nations cooperating together and again it is to be hoped that the 2004 experts and states parties meetings provide a forum where a basis for such cooperation can be achieved. It is likely, however, that a great deal of work, particularly by the medical profession, will be required to achieve such objectives.

Meanwhile, of course, the movement of modern biology towards becoming a predictive rather than a descriptive science continues inexorably. This movement is epitomised by the growth of a new 'systems biology' which draws in physical scientists, mathematicians and computer scientists. A report in *Science* noted in December 2003:[25]

> 'In September, Harvard University opened its medical school's first new department in 20 years. Its focus: systems biology….The nearby Massachusetts Institute of Technology (MIT) had already started a Computational and Systems Biology Initiative with 80 faculty members…'

The development of this new systems biology and its modelling, prediction and testing seem set to increase and lead to novel discoveries. The importance of the discipline for the new process in 2005, which is:

> '*v.* the content, promulgation, and adoption of codes of conduct for scientists'

will clearly also increase steadily.

Codes of conduct come in many different forms and there is a world of difference between a simple statement of principles and an operational code such as a code of practice which gives rules and guidance to scientists in the conduct of their work. In the United States the issue was taken up by a National Academies study into *Biotechnology research in an age of terrorism: confronting the dual use dilemma*.[26] The committee which undertook the study concluded that domestic and international guidelines and regulations for the conduct of genetic engineering research:

> '…do not currently address the potential for misuse of the tools, technology, or knowledge base of this research enterprise for offensive military or terrorist purposes…'

They therefore proposed a voluntary self-regulatory system which:

> '…would establish a number of stages at which experiments and eventually their results could be reviewed to provide reassurance that advances in biotechnology with potential applications for bioterrorism or biological weapons receive responsible oversight…'

The committee then identified seven classes of experiment that it believed illustrate the kinds of research that would require such review. These are listed in box 6.6. However, the committee was clear that this was an initial set that it expected to see expand as the biotechnology revolution continued.

Box 6.6: Experiments of concern

1. Would demonstrate how to render a vaccine ineffective.
2. Would confer resistance to therapeutically useful antibiotics or antiviral agents.
3. Would enhance the virulence of a pathogen or render a nonpathogen virulent.
4. Would increase transmissibility of a pathogen.
5. Would alter the host range of a pathogen.
6. Would enable the evasion of diagnostic/detection modalities.
7. Would enable the weaponization of a biological agent or toxin.

Source: reference 26

The review process envisaged by the committee would be similar to those already used in regard to biosafety for genetic engineering in institutions receiving funding from US national sources, and would involve local institutional review first, supplemented if concerns required it by national-level review. They also believed that a system of prepublication review

would have to be developed. Additionally, in order to oversee the whole system, they suggested the creation of a National Science Advisory Board for Biodefence. In early March 2004, it was announced that such a high-level advisory body would indeed be set up, in the US Department of Health. This National Science Advisory Board for Biosecurity will begin work in the autumn to provide guidelines for scientists whose work might be used by terrorists. The guidelines are likely to involve procedures for the approval of research projects, the handling of papers for publication and what may be said at open meetings. However, none of the recommendations made by the board will be mandatory.[27] A voluntary self-regulation approach has received support in the UK from the powerful Wellcome Trust.[28]

The difficulties with this approach should not be underestimated. Rappert has argued that it may not be a simple matter to get scientists to agree on what research is actually dangerous.[29] If scientists believe that the experiments designated in the system are not dangerous, then the guidelines are likely to fall into disrepute and disuse. A group at the University of Maryland, which has given considerable attention to such a tiered review system,[30] has highlighted the need for the system to cover all institutions (including industry and biodefence), to have rules based in law and not guidelines, and to be international, not just national. Following the announcement of the work on pox viruses (see chapter 3), they pointed out that the development of the modified virus infringed three of the rules suggested by the National Academies committee and that publication control was sidestepped by announcing the work at a conference. Their article ended by arguing for a much tougher approach:[31]

> 'Under a global oversight system, participating governments would be required to establish review bodies to oversee and review relevant research activities…'

Moreover:

> '…No institutions – whether academic, corporate or government – would be exempt from these oversight requirements. Participating countries would also be required to submit especially dangerous research activities to an international review body for approval.'

The media are well aware of the issue of 'dangerous' biotechnology research and this issue will continue to surface in the public debate.[32] There is an urgent need for scientists to ensure that what comes about is a sensible compromise between the need to avoid inadvertent or malign misuse of biology and the safeguarding of beneficial research programmes. Of course, regulation of experimentation will take place within a much wider developing biosecurity legislative framework, and it is that framework we must now consider.

Biosecurity and biodefence

As we have seen, the threat of terrorism has led to huge new legislative and organisational changes in the United States and to a lesser extent elsewhere, but these responses to terrorism have to be balanced against other requirements, for example, the maintenance of civil rights in democracies.[33] There is every reason to support increased legislation to improve biosecurity (measures that guard against the deliberate release of pathogens for malicious purposes) by:[34]

> '…(1) mechanisms to account for pathogens that are being stored, used during experiments, or transferred or exported; (2) the registration and licensing of facilities that work with dangerous pathogens; (3) physical security at these facilities; and (4) procedures for screening laboratory personnel…'

and, of course, it would be best if such measures were implemented according to agreed international standards. But as we proceed to tighten up such legislation, there is again a need for balance.

Firstly, it has to be remembered that the revolution in biotechnology, if properly handled, could deliver enormous benefits for public health in both the developed and the developing worlds.[35] That possibility has to be safeguarded. Then the regulations being developed for biosecurity have to be seen in the context of the many other national and international legislative developments occurring in relation to the performance and impact of biotechnology.[36] This is particularly important because an integrated understanding of all the relevant regulations covering health, disease and development; trade and environment; and protection against misuse, is not easily obtained.[37] If a broader view is not taken, a headlong rush to improve biosecurity as part of the drive to deal with terrorism could lead to perhaps more important contributions to the web of prevention, such as the prohibition of biological and chemical weapons under international criminal law,[38] being ignored.

Though the process of improving biosecurity could 'backfire' in a variety of ways,[39] a particular problem would appear to come from the parallel process of increasing biodefence expenditure. Here there is an obvious tension between the need for secrecy, and the need for transparency so that suspicions are not aroused. It has to be accepted that some countries may not view the West as benign in general[40] and some biotechnology work being carried out in the West as necessarily above suspicion.[41] Distinguishing between offensive and defensive biological weapons work is far from easy so the dangers of misperceptions of increasing biodefence work have to be taken into account. Perhaps, as Milton Leitenberg was told when investigating this issue, by individuals with long experience in biodefence:[42]

> '…*transparency* was the key factor in removing questions about whether a BW program was offensive or defensive: the ability to display the site to any international visitor and to say "Here is the site and here is what we are doing"…'

As biodefence expenditure increases, it will be ever more important for everyone involved to keep this point in mind. There will also be a key role for civil society in ensuring that what is done in one country does not foster

distrust abroad.[43] The foregoing obviously reinforces the need for protection of whistleblowers in any code of conduct and particularly for those employed in defence facilities.[44]

The responsibility of the biomedical community

The biomedical community has to accept its share of the blame for the failure to strengthen the BTWC. Between 1991 and 2001 most of the community was either unaware of, or not interested in, the efforts being made by states parties in Geneva.[45] When important elements of the community did take part, they were often startlingly ignorant of what the professional negotiators and their advisers had achieved or amazingly myopic about what was really at stake.

The arguments presented here point to the fact that if the biomedical community so decides there is much they can do to push the political system along the road that will lead to a more benign future,[46] but this will necessarily also involve an increase in regulation of the community. There are people who disagree with increased regulation and argue instead for an all-out unregulated research effort, one recent article, for example, arguing that:[47]

> '…The common response to a perceived threat is to reduce the likelihood of it coming to fruition, an effort that often takes the form of regulation. However, the argument for strict regulation of biological technologies is misleading and therefore dangerous…'

The author also wrote:

> 'We could err disastrously in the short term by restricting the development of science and technology, thereby stunting our ability to respond to natural or artificial threats…'

We may indeed be at an 'Asilomar' moment (similar to that when the scientific community took important initial precautionary decisions on genetic

engineering in the 1970s),[48] when widespread support for the ICRC appeal from the biomedical community will be of critical importance for the outcome.

Conclusion

The threat from state-level offensive biological weapons programmes continues and as the biotechnology revolution accelerates, the threat of hostile use of biological agents by sub-state groups or even individuals is bound to increase. There is much that responsible biomedical organisations like the BMA could and should do to help deal with these threats.

Such responsible actions could include working with the ICRC and the British Red Cross to gain the support of the British government for the high-level political declaration on *Biotechnology, weapons and humanity* set out in the ICRC appeal. On a shorter time-scale, the BMA should ensure that it has a positive input to the BTWC states parties discussions in 2004 on strengthening existing mechanisms for disease surveillance and combating infectious diseases.

In the medium term, the BMA should consider how it can work with other like-minded groups to make the 30th anniversary of the entry-into-force of the BTWC, in March 2005, a success, with many more states parties confirming that they are living up to their obligations in regard to national legislation, CBMs and the Geneva Protocol. Centrally, of course, given its long experience of ethical issues, the BMA should contribute to national and international discussions of a code of conduct for scientists and do what it can to ensure a successful outcome to the 2005 meetings in the new BTWC process, which are to be chaired by the United Kingdom. Moreover, medical and scientific organisations have a responsibility to ensure that the scope of the problem we face is considered to go way beyond pathogens. Nowhere is the need for cautionary scientific input more necessary at present than with respect to so-called 'non-lethal' chemical weapons.

In the longer term, the BMA should consider whether the problems of bioterrorism and biowarfare (involving as they do deliberate attacks using

disease) and the regulation of the biomedical community warrant a much more systematic oversight from its organisation. There are many ways to minimise such misuse where the BMA could use its expertise to help the states parties achieve a productive and progressive outcome to the 2006 Sixth Review Conference and beyond (appendix I). In particular, in order that adequate political attention is given to this issue over the longer term, the medical profession, in its national and international organisations, may have to ensure that its activities too are subject to regular review and analysis. To do that effectively, the organisation will have to be certain that its structures and functions are set up appropriately for such reviews and analyses to be carried out as a matter of routine.

CHAPTER 7:

RECOMMENDATIONS

The recommendations that follow are targeted at different groups. The formal process of ensuring the development of international standards and norms in weapons control falls into the remit of the International Community of Nations, often through UN procedures, or under the guidance of the ICRC and the various Geneva Conventions, additional conventions and protocols. In addition, it is essential that individual national governments pass and enforce domestic legislation that ensures their own compliance. Below that citizens and those with special expertise have a responsibility to contribute to the debate. The BMA itself has some specific expertise and can help to develop activities within the medical community, at home and abroad, which can act at various levels.

International community of states

An effective and well-supported BTWC is, in our view, essential to protecting the world from the threat of use of biological weapons. Such developments in the BTWC can only be achieved by states working together through formal inter-governmental processes. To that end we make the following recommendations:

- states should take every possible step to find ways of restarting the process of agreeing a means of strengthening the BTWC through negotiation of a legally-binding instrument after 2006
- states should implement the common understanding that was agreed in the 2003-2005 rounds of discussions in the new process

- states should agree to hold a conference on the 30th anniversary of the entry-into-force of the BTWC (26 March 2005) and demonstrate at that conference that they have met all their obligations under the BTWC.

National governments

To make sure that the BTWC is safe, effective and secure each national government needs to take individual domestic measures as well as participating in inter-governmental actions.

- Governments must pass legislation to implement fully the requirements of the BTWC.
- Governments must share information on implementation of legislation and other relevant materials, through the UN.
- Governments must commit to developing national strategies to ensure compliance with the legal and ethical norms of non-use of biological and toxin weapons.
- Governments should commit to supporting the appeal of the ICRC on biological weapons.
- Governments must engage in debate with scientists, other experts and journal editors about the control of biological experimentation and the dissemination of the results of such research where that might enable others to develop weapons.
- Governments should consider whether the 'Fink Process' should be used domestically to limit the development of potentially dangerous research.

Scientists and the medical profession

While the development of scientific knowledge is important it is also one of the risk factors increasing the likelihood of the development of bio-weapons. Scientists enjoy many freedoms in deciding the course of their research. With those freedoms come responsibilities to use that knowledge wisely.

- Scientists must be aware of how their work might impact on legal and ethical norms that prohibit the development and use of biological weapons.

- Scientists should be aware of the risks associated with the rapid advances in biotechnology.
- Scientists should engage in a worldwide debate about how they police their own areas of expertise.
- Scientists should engage in discussion with scientific publishers/editors on how they make decisions on whether to publish the results of potentially 'dangerous' research.
- Scientists should engage in discussion with funders on whether, and if so how, research into some areas should be prohibited because of the danger of its results being used in the development of prohibited weapons.
- Scientists should work with governments, the ICRC and others to develop model legislation to clearly criminalise bioweapons development work.

The BMA

It is not always clear what the BMA can do itself to limit the likelihood of biological weapons development. As a group representing doctors, and with a long history of actions supporting public health, we should build upon our strengths in this area. The following recommendations are designed to build upon the BMA's strengths and recognise its areas of expertise.

- The BMA will engage with other medical bodies, especially within the world medical community, in an attempt to engage doctors worldwide in pressing government and inter-governmental organisations for action in this field.
- The BMA will continue to monitor developments in International Humanitarian Law (IHL), in negotiations around the BTWC and in biotechnology and alert interested parties to new, emerging and increasing risks in this area.
- The BMA will work with others to develop the voluntary self-policing policies that will contribute to reducing the scientific risk.

GLOSSARY

Adaptive immune system the newer arm – in evolutionary terms – of the immune system which gives us the ability to develop specific responses to foreign substances and organisms. Responses can be mediated by cellular or hormonal mechanisms and can be induced by immunization.

Ad Hoc Group (AHG) the group of state parties to the BTWC which endeavoured to develop and negotiate a verification protocol to the BTWC during the 1990s and first years of the 21st century.

Advanced biological warfare agents agents that may arise in the future when the aim is not to modify a traditional agent but to design specific attacks on particular physiological processes.

Advanced Riot Control Agent Device (ARCAD) a device designed to use a newer form of non-lethal chemical agent.

Aerosolization a process by which a colloidal dispersion of solid or liquid particles is produced in a gas.

Agonist a chemical (drug) which has the same effect at a cellular receptor as the natural signalling chemical.

Alpha$_2$-adrenoreceptor a particular type of adrenoreceptor which when located on the pre-synaptic neurone can provide negative feedback to the neurone producing the natural neurotransmitter noradrenaline.

Alzheimer's disease a neurodegenerative disease of the elderly which involves a malfunction of the acetylcholine neurotransmitter system.

Analgesic a chemical which causes a loss of pain sensitivity.

Anaesthetic a chemical which acts on neuronal conduction and synaptic transmission so as to cause loss of feeling in a specific region of the body or a general loss of consciousness, as desired.

Antagonist a chemical (drug) which interacts with a receptor to block the action of the natural neurotransmitter.

Autoimmune disease a disease caused by the reaction of the immune system to the body's own molecules.

Bacterial biofilms large collections of bacteria which are resistant to attack because of surrounding slime.

Bacteriophage a virus which is parasitic on bacteria.

ß-endorphin a natural peptide neurotransmitter which has an effect like morphine in suppressing pain.

Biocontrol agent an organism (or product of an organism) used in the artificial control of pests.

Bioinformatics the organisation and use of biological information. Usually this involves the use of modern information technology to handle the vast amounts of information generated by the genomics revolution.

Biopreparat the commercial 'front' organisation set up to conceal the Soviet offensive biological weapons programme after the negotiation of the BTWC.

Bioregulator a chemical signalling molecule which functions in the nervous, endocrine or immune system.

Biosafety an older approach (see biosecurity below) which focused on the safe use of biological materials and equipment, for example, in the designation of different levels of laboratory design required to perform certain experiments and the official control of certain types of genetic engineering.

Biosecurity the newer approach (see biosafety above) which builds on traditional biosafety in an attempt to ensure the security of biological materials and equipment, for example, by limiting access and applying controls to transportation. A current concern is whether greater control is required over experimentation and publication of data.

Bioweapons Prevention Project (BWPP) a joint project involving a number of NGOs with experience in the CBW field which attempts to form a broader international network and to bring greater civil society monitoring of potentially dangerous science and technology.

Biological and Toxin Weapons Convention (BTWC) signed in Washington, London and Moscow 10 April 1972; entered into force 26 March 1975; now has over 140 member countries. The convention prohibits the development, production, stockpiling, acquisition, retention or transfer of bacteriological (biological) and toxin weapons. At present, the Convention lacks any effective verification provisions to ensure that states are living up to their undertakings and also a permanent organisation to take care of and develop the Convention and its implementation between its five-yearly review conferences.

BTWC 'New Process' the process agreed at the broken 2001-02 BTWC Review Conference whereby there would be experts meetings and states parties meetings on set topics for the years 2003, 2004 and 2005, prior to the 2006 BTWC Sixth Review Conference where the results of the yearly meetings would be considered.

BTWC Depositary State one of the three states - the United States, the United Kingdom and the Russian Federation - designated in article XIV of the BTWC as having special responsibilities for the Convention.

BTWC Sixth Review Conference the next in the series of five-yearly review conferences of the BTWC which is to take place in 2006. The Review Conference will probably take place late in the year and be preceded by a preparatory meeting in the spring.

BTWC verification protocol an additional legally-binding instrument added to the BTWC which would greatly increase confidence over time that states parties were living up to their obligations. Negotiations aimed at achieving an agreement on such a legally-binding instrument broke down in July 2001.

BZ or 3-quinuclidinyl benzilate a non-lethal agent weaponised by the United States during the cold war period of the last century.

Calmative a non-lethal chemical agent designed to quieten the intended victim so that safe counteraction can be undertaken.

Category A agents biological agents considered by CDC to be of greatest concern in regard to misuse for hostile purposes. Includes *Bacillus anthracis* (anthrax), *Variola major* (smallpox) and viral haemorrhagic fever causing agents such as the filoviruses Ebola and Marburg.

Category B and C agents agents considered by CDC to be presently of lesser concern than Category A agents but still requiring consideration as possible threats. The NIAID lists include, for example, *Coxiella burnetii* (Q fever), *Brucella* species (brucellosis), and Yellow Fever and are very similar to those of the CDC.

Centers for Disease Control and Prevention (CDC) the leading US federal agency for protecting the health and safety of people, located in Atlanta, Georgia. One aspect of CDC's work is the protection of individuals against emerging infectious diseases - this includes bioterrorism.

Chemical and biological weapons spectrum the whole range of agents from classical lethal chemical agents, poisonous industrial chemicals, mid-spectrum agents such as toxins and bioregulators through to traditional and genetically modified biological agents.

Chemical weapons are defined, in part, in article II (Definition and Criteria) of the CWC as: (a) Toxic chemicals and their precursors, except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes. Toxic chemicals are further defined as: any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals.

Chemical Weapons Convention (CWC) the modern arms control agreement which entered into force in 1997 and in which states parties agree in article I never under any circumstances:

(a) to develop, produce, otherwise acquire, stockpile or retain chemical weapons, or transfer directly or indirectly, chemical weapons to anyone;
(b) to use chemical weapons;
(c) to engage in any military preparations to use chemical weapons;
(d) to assist, encourage or induce, in any way, anyone to engage in any activity prohibited to a state party under this Convention.

Code of conduct a statement of principles and/or practice by which a professional group goes about its activities. Codes of conduct for scientists are the subject for the 2005 meetings in the BTWC new process.

Combinatorial chemistry a modern technique which has been developed to allow the generation of many new chemicals in small amounts at the same

time. The aim is to start with a core chemical and then add a range of side or functional groups to that core, thus generating a series of different, but related, new chemicals. The technique is widely used in the pharmaceutical industry as a means of identifying new leads and optimising the potency of drug candidate chemicals.

Complement a series of serum proteins activated early within the innate immune system which attack invading microorganisms and initiate further actions by the immune system.

Completion Conference 2005 the suggestion that in March 2005 there should be a conference of states parties to the BTWC at which they could demonstrate that they have carried out the actions previously agreed to strengthen the BTWC prohibition regime.

Confidence Building Measures (CBMs) annual data returns agreed in 1986 and developed in 1991 under the BTWC whereby states parties should share significant categories of information in order to increase confidence in compliance. These measures have not been successful because of the inadequate numbers and frequently poor quality of the returns.

Cooperative threat reduction program a US programme designed to help reduce the threat from former Soviet offensive activities after the end of the cold war.

Coronavirus an enveloped virus with a single-stranded RNA genome and large particles of glycoprotein projecting from the virion surface which give the appearance of a crown when viewed through a microscope. Such viruses usually cause commons colds, avian infectious bronchitis etc, but were found to be the cause of the recent SARS outbreak.

Cytokines a range of signalling molecules which on binding to the appropriate receptor bring about changes related, for example, to cell growth, differentiation and apoptosis.

Defence Science and Technology Laboratories (Dstl) UK government laboratories designed to provide science and technology for the government and armed forces.

DNA deoxyribonucleic acid, the chemical which forms the genetic material of cells, some organelles and many viruses.

DNA shuffling new methods for creating and combining genes; for example, a single gene can be subjected to error-prone polymerase chain reaction and then the mutations are shuffled and a selection process is used to gather favourable mutations together.

Dugway Proving Ground the US testing ground for chemical and biological defence, located in Utah.

Eicosanoids derivates of fatty acids such as leukotrienes which are involved in inflammation processes.

Endogenous pyrogens chemicals generated in the body in response to infection which have the effect of raising body temperature.

Ethnic group a social group or category of the population that, in wider society, is set apart and bound together by common ties of race, language, nationality or culture. The group may also have shared genetic characteristics.

Fentanyl a synthetic chemical first produced in the second half of the last century which has effects similar to, but much more powerful than, morphine.

Foot-and-mouth disease (FMD) a viral disease of animals such as pigs, cows and sheep. The highly virulent causal organism can be the source of devastating disease outbreaks such as that in the UK recently.

Gene therapy the attempt to use gene transfer techniques to deal with human diseases caused by gene defects.

Genetic engineering techniques by which functional genes are artificially moved even between different species, for example, the use of recombinant DNA technology to put the genes for insulin into a bacterium in order to grow large quantities of the hormone artificially.

Geneva Protocol 1925 an international agreement, now considered to be part of customary law binding all states, which bans the use of chemical and biological weapons.

Global Mercury a command post exercise carried out by governments to test international communications and responses to a bioterrorist attack.

Human immunodeficiency virus (HIV) the cause of AIDS (acquired immune deficiency syndrome) in human beings.

Human Genome Project an international scientific project that recently completely sequenced the 3,000 million DNA bases in human DNA.

Incapacitating chemical agents non-lethal chemicals designed to temporarily incapacitate the victim, for example through unconsciousness.

Influenza a respiratory disease caused by an enveloped virus with an eight-section single-stranded RNA genome. The disease often causes pandemics because the virus genome mutates frequently; it is highly infectious as transmission is possible through aerosols caused by coughing and sneezing.

Innate immune system the ancient part of the immune system which provides the first lines of defence against infection. Involves the non-specific activation of defences against conserved elements of invading organisms, but is also involved in activation of the adaptive arm of the immune response.

Interference RNA (RNAi) post-transcriptional gene silencing which can be induced by the direct introduction of double-stranded RNA as a means to knock out expression of specific genes.

Interleukin-4 (IL-4) one of the soluble factors involved in the communication between elements of the immune system. The gene for IL-4 was used to produce it in the important mousepox experiment.

International Committee of the Red Cross (ICRC) the international representative organisation of national Red Cross and Red Crescent movements, located in Geneva, Switzerland.

International Union of Pure and Applied Chemistry (IUPAC) the international representative of many national chemical associations.

Locus coeruleus a small part of the brain where there is a major collection of the cell bodies of neurones which use noradrenaline as the natural synaptic transmitter. Axons from these cells ramify widely throughout the brain.

Malodorant agent a chemical with a particularly unpleasant smell that might function as a non-lethal agent by, for example, causing victims to disperse.

Microbial spore a body formed by some micro-organisms – such as anthrax – which is highly resistant to environmental degradation.

Micro-encapsulation in biological warfare – the protective coating of fragile agents to allow them to be more effectively delivered by conventional means.

Mid-spectrum agents agents such as toxins and bioregulators which are in the middle of the CBW spectrum, halfway between classical lethal chemical and traditional biological warfare agents.

Mousepox experiment the experiment carried out in Australia in which a much more lethal virus than intended was accidentally created. This raised concerns that a similar experiment could create a much deadlier version of smallpox.

Muscarinic acetylcholine receptor (mAchR) a receptor for the natural neurotransmitter acetylcholine of the sub-type that also responds to muscarine – an extract from a mushroom.

Nanoparticles particles of nanometer size range.

Nanotechnology the potential production of machines of nanometer-sized components.

Non-lethal chemical weapons chemical agents which are designed to incapacitate the victim with minimal possibility of death – a very difficult balance to achieve.

Non-governmental organisation (NGO) a voluntary civil society organisation not connected to government.

Offence/defence arms race a phenomenon often seen when a new technology is introduced by military forces in which steps taken by the defence to deal with the new offensive means provoke further offensive technological developments. Clearly seen, for example, in the development of chemical weapons and chemical defence systems during the 20th century.

Opiates naturally occurring basic alkaloid molecules with a complex fused ring structure, having high morphine-like pharmacological activity.

Opioid originally a term denoting synthetic narcotics resembling opiates but increasingly used to refer to both opiates and synthetic narcotics.

Organisation for the Prohibition of Chemical Weapons (OPCW) the organisation set up to oversee and operate the Chemical Weapons Convention. The organisation is based in The Hague, the Netherlands.

Plant inoculant a formulation containing pure or predetermined mixtures of living micro-organisms for the treatment of seedlings or other plant propagation material with the purpose of enhancing the growth capabilities or disease resistance of the eventual plants or crops.

Programme for the Preparedness for Deliberate Epidemics (PDE) a WHO programme designed to help countries lacking resources to be better able to respond to the deliberate use of disease.

RNA Messenger RNA carries its genetic information (coded in DNA) out of the cell nucleus. Transfer RNA decodes this information. Ribosomal RNA constitutes 50 per cent of the ribosome which is a molecular assembly involved in protein synthesis.

Sedative a chemical agent having a calming or sedative effect.

Severe Acute Respiratory Syndrome (SARS) the syndrome caused by a coronavirus which provoked great concern when a disease outbreak spread rapidly around the world and required drastic coordinated international measures to bring it under control.

Smallpox inhibitor of complement enymes (SPICE) the molecule which the smallpox virus produces to inhibit the protective complement enzymes of the immune system.

'Spanish' 'flu 1918 the influenza outbreak that spread worldwide at the end of the First World War causing many millions of deaths.

Staphylococcal enterotoxin B (SEB) the toxin produced by staphylococcal bacteria that was weaponised as a non-lethal biological agent in the US offensive biological weapons programme of the early years of the 20th century cold war.

Substance P a neuropeptide neurotransmitter of the tachykinin peptide family.

Sverdlovsk the city in Soviet Russia where the accidental release of anthrax caused the deaths of more than 60 people in 1979.

Synthetic polio virus experiment the experiment in which viable polio virus was created synthetically from material bought over the internet, thus raising concerns that more complex viruses could be produced by similar means.

Systems biology a new field in biology that aims at systems-level understanding of the organisation and function of the cellular components revealed by molecular biology.

Toll-like receptors transmembrane protein receptors with common structural features that can function to activate the innate immune system through recognition of conserved molecular patterns carried by micro-organisms.

Tularaemia a disease of wild animals caused by the bacterium *Francisella tularensis*. Can also cause disease in humans, particularly those in contact with affected wild animals. The bacterium was weaponised as a biological weapons agent in the last century.

UK House of Commons Select Committee on Science and Technology the committee which produced the report, 'The scientific response to terrorism,' in late 2003.

US Central Intelligence Agency (CIA) coordinates US intelligence activities and evaluates and disseminates intelligence which affects national security.

US Freedom of Information Act (FOIA) the act which allows requests to be made for the release of government information in the United States.

US Department of Homeland Security the new government department set up in the United States in response to the increasing perception of a major terrorist threat.

US National Institute of Allergy and Infectious Diseases (NIAID) is a component of the US National Institutes of Health. It conducts and supports research on infectious, immunological and allergic diseases.

US National Science Advisory Board for Biosecurity the advisory board recently set up in the Unites States in response to the suggestion by the National Academies (Fink) Report that greater oversight of biotechnology was required to prevent the inadvertent production and/or publication of dangerous information that might be misused.

Web of deterrence the original idea (see web of prevention below) that a broad range of policies encompassing, for example, both tight export controls and better protection, but centred on the norm embodied in the 1925 Geneva Protocol, the BTWC, and the CWC would, if properly implemented around the world, lead those considering the development of offensive biological weapons capabilities to decide that such capabilities were not worth having.

Web of prevention a recent formulation by the ICRC of the idea of a web of policies centred on the prohibitionary norm to dissuade people considering the development of biological weapons capabilities.

Vaccinia complement control protein (VCP) the protein found in vaccinia which interferes with the operation of the complement part of the immune system response – but not as strongly as the analogous SPICE protein in smallpox virus.

Weapons of mass destruction (WMD) nuclear, chemical and biological weapons considered to be in a separate very dangerous category because of the very large-scale impact that could result from their use.

APPENDIX I:

SIGNIFICANT DATES FOR A DECADE OF PROGRESS

2004

July BTWC Inter Review Conference New Process, second round of experts meetings

December BTWC Inter Review Conference New Process, second round of state parties meetings

2005

March 30th Anniversary of BTWC entry-into-force

Later months third round of experts and state parties meetings

2006

Sixth Review Conference of the BTWC

2008

Second Review Conference of the CWC

2011

Seventh Review Conference of the BTWC

2013

Third Review Conference of the CWC

APPENDIX II:

APPEAL OF THE INTERNATIONAL COMMITTEE OF THE RED CROSS ON BIOTECHNOLOGY, WEAPONS AND HUMANITY (FULL TEXT)

The ICRC appeals in particular:

TO ALL POLITICAL AND MILITARY AUTHORITIES

- to become parties to the 1925 Geneva Protocol and the 1972 Biological Weapons Convention, if they have not already done so, to encourage states which are not parties to become parties, and to lift reservations on use to the 1925 Geneva Protocol

- to resume with determination efforts to ensure faithful implementation of these treaties and develop appropriate mechanisms to maintain their relevance in the face of scientific developments

- to adopt stringent national legislation, where it does not yet exist, for implementation of the 1925 Geneva Protocol and the 1972 Biological Weapons Convention, and to enact effective control on biological agents with potential for abuse

- to ensure that any person who commits acts prohibited by the above instruments is prosecuted

- to undertake actions to ensure that the legal norms prohibiting biological warfare are known and respected by members of armed forces

- to encourage the development of effective codes of conduct by scientific and medical associations and by industry to govern activities and biological agents with potential for abuse; and

- to enhance international cooperation, including through the development of greater international capacity to monitor and respond to outbreaks of infectious disease.

TO THE SCIENTIFIC AND MEDICAL COMMUNITIES AND TO THE BIOTECHNOLOGY AND PHARMACEUTICAL INDUSTRIES

- to scrutinize all research with potentially dangerous consequences and to ensure it is submitted to rigorous and independent peer review

- to adopt professional and industrial codes of conduct aimed at preventing the abuse of biological agents

- to ensure effective regulation of research programs, facilities and biological agents which may lend themselves to misuse, and supervision of individuals with access to sensitive technologies; and

- to support enhanced national and international programs to prevent and respond to the spread of infectious disease.

The ICRC calls on all those addressed here to assume their responsibilities as members of a species whose future may be gravely threatened by abuse of biological knowledge. The ICRC appeals to you to make your contribution to the age-old effort to protect humanity from disease. We urge you to consider the threshold at which we all stand and to remember our common humanity.

The ICRC urges states to adopt at a high political level an international declaration on *Biotechnology, weapons and humanity* containing a renewed commitment to existing norms and specific commitments to future preventive action.

Source: International Committee of the Red Cross (2002) *Biotechnology, weapons and humanity: summary report of an informal meeting of government and independent experts, Montreux, Switzerland, 23-24 September*. Geneva: ICRC.

APPENDIX III:

THE RECOMMENDATIONS OF BMA I (SUMMARY)

The scientific and medical community

1. Ethical responsibility for this issue should be accepted and explicitly stated in codes of conduct.
2. Developments in biotechnology should be monitored and debated.
3. WHO disease reporting network should be expanded, particularly for unexpected outbreaks.
4. Medical education should include biological warfare.
5. Public education campaigns should stress ethical arms policies.

International action

6. The norm embedded in the 1925 Geneva Protocol and BTWC should be strengthened.
7. The verification protocol should be added to the BTWC.
8. The former employees of offensive programmes should be helped to find civil employment.
9. Information relevant to biological weapons should be kept off the internet.
10. The developing world should be assisted by the developed world to avoid the extremes of hostility that could lead to bioterrorism.

National government agencies

11. Governments should monitor activities in which doctors might be pressurised into taking part in biological weapons programmes.

12. A 'web of deterrence' should be constructed to prevent bioterrorism.
13. Governments should assist the build up of a consensus in civil society against biological weapons: religious and cultural leaders should be involved.
14. Civil defence preparations for dealing with, at least, smaller attacks with known agents should be supported.
15. Disease control and surveillance measures, and better detection methods would be useful.
16. National inspectorates should monitor the nature of research carried out in the biotechnology/pharmaceutical industry.
17. A warning list of dual-use materials and equipment should be available to industry and regulatory bodies in order to assist ethical export decisions around the world.

REFERENCES

Chapter 1

1. Nathanson V, Darvell M & Dando MR (1999) *Biotechnology, weapons and humanity*. London: Harwood Academic.
2. Nowak R (2001) Disaster in the making: an engineered mouse virus leaves us one step away from the ultimate bioweapon. *New Scientist* 13 January: 4-5.
3. Cello J, Paul AV & Wimmer E (2002) Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* **297**: 1016-8.
4. Rosengard AM, Liu Y & Nie Y et al (2002) Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. *Proc Natl Acad Sci* **99**: 8808-13.
5. Rhodes K (2002) *Diffuse security threats: information on U.S. domestic anthrax attacks*. Testimony before the Select Committee on Intelligence, US Senate and the Permanent Select Committee on Intelligence, House of Representatives. Washington: General Accounting Office.
6. International Committee of the Red Cross (1996) *The medical profession and the effects of weapons: report of the symposium, Montreux*. Geneva: ICRC.
7. Zanders JP, Hart J & Kuhlau F (2002) Chemical and biological weapon developments and arms control. In: *SIPRI Yearbook 2002: armaments, disarmament and international security*. Oxford: Oxford University Press.
8. Hart J, Kuhlau F & Simon J (2003) Chemical and biological weapon developments and arms control. In: *SIPRI Yearbook 2003: armaments, disarmament and international security*. Oxford: Oxford University Press.

9. Dando MR (1994) *Biological warfare in the 21st century: biotechnology and the proliferation of biological weapons*. London: Brassey's.
10. Ministry of Defence (1999) *Defending against the threat from biological and chemical weapons*. London: Ministry of Defence.
11. Royal Society (2000) *Measures for controlling the threat from biological weapons*. London: Royal Society.
12. Hawley RJ & Eitzen EM (2001) Biological weapons – a primer for microbiologists. *Annu Rev Microbiol* **55**: 235-53.
13. Wayt Gibbs W (2002) Innocence lost: is enough being done to keep biotechnology out of the wrong hands? *Scientific American* January: 12-13.
14. World Health Organization (2003) *Health aspects of chemical and biological weapons* (2e). Geneva: World Health Organization. Available at <www.who.int/csr/delikepidemics/sac/en/print.html>
15. Inglesby TV, O'Toole T & Henderson DA et al (2002) Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* **287**: 2236-52.
16. Clavijo A & Kitching P (2003) Foot-and-mouth disease: epidemiology and current situation. *Biologist* **50**: 208-12.
17. Prescott EM (2003) SARS: a warning. *Survival* **45**: 207-26.
18. Finlay T & Mines B (2003) Iraq's weapons: the US fails to best UNMOVIC. *Trust & Verify* May-June: 1-3.
19. Kwik G, Fitzgerald J & Inglesby TV et al (2003) Biosecurity: responsible stewardship of bioscience in an age of catastrophic terrorism. *Biosecurity and Bioterrorism* **1**: 1-9.
20. Directorate of Intelligence (2003) *The darker bioweapons future*. Washington DC: Central Intelligence Agency.
21. General Assembly Proceedings (2002) *Scientific session program: responding to the growing threat of terrorism and biological weapons*. Proceedings of World Medical Association General Assembly, 3-4 October, Washington DC.
22. World Medical Association (2002) *The WMA declaration of Washington on biological weapons*. Document 17.400 initiated September 2001 and adopted by the WMA General Assembly, Washington 2002. Available at <www.wma.net/e/policy/b1.htm>

23. International Committee of the Red Cross (2002) *Biotechnology, weapons and humanity: summary report of an informal meeting of government and independent experts.* ICRC, 23-24 September: Geneva.
24. Round Table of Government and Independent Experts (2003) *International Humanitarian Law and disarmament: recent developments and prospects for the future*. Canadian Red Cross, 17-18 March: Ottawa.
25. International Committee of the Red Cross (2003) *Agenda for humanitarian action.* Proceedings of 28th International Conference of the Red Cross and Red Crescent Movement, December: Geneva.
26. Stern J (2003) Dreaded risks and the control of biological weapons. *International Security* **27**: 89-123.
27. Rindskopf Parker E & Jacobs LG (2003) Government controls of information and scientific inquiry. *Biosecurity and Bioterrorism* **1**: 83-95.
28. Rappert B (2003) Coding ethical behaviour: the challenge of biological weapons. *Science and Engineering Ethics* **9**: 453-70.
29. Meselson M (1999) *The problem of biological weapons*. Presentation given at the 1818th Stated Meeting of the American Academy of Arts and Sciences, 13 January: Cambridge, Mass.

CHAPTER 2

1. Sims NA (1998) *The diplomacy of biological disarmament: vicissitudes of a treaty in force 1975-85.* New York: St. Martin's Press.
2. British Medical Association (1999) *Biotechnology, weapons and humanity*. London: Harwood Academic.
3. Pearson GS & Dando MR (1999) *The emerging protocol: an integrated reliable and effective regime*. Briefing Paper No. 25, University of Bradford. Available at<www.brad.ac.uk/acad/sbtwc>
4. Dando MR (2002) *Preventing biological warfare: the failure of American leadership.* Basingstoke: Palgrave.
5. Pearson GS, Dando MR & Sims NA (2001) *The composite protocol text: an evaluation of the costs and benefits to states parties*. Evaluation Paper No. 21, University of Bradford. Available at<www.brad.ac.uk/acad/sbtwc>

6. Pearson GS, Dando MR & Sims NA (2001) *The US rejection of the composite protocol: a huge mistake based on illogical assessments*. Evaluation Paper No. 22, University of Bradford. Available at<www.brad.ac.uk/acad/sbtwc>
7. Reference 4, Appendix 2, *Statement by the United States to the Ad Hoc Group of Biological Weapons Convention states parties*. 25 July, 2001: Geneva.
8. Deller N & Burroughs J (2003) Arms control abandoned: the case of biological weapons. *World Policy Journal* Summer: 37-42.
9. Rosenberg B (2001) US policy and the BWC Protocol. *The CBW Conventions Bulletin* **52**: 1-3.
10. See reference 8 above.
11. Rhodes E (2003) The imperial logic of Bush's liberal agenda. *Survival* **45**: 131-54.
12. Pearson GS, Dando MR & Sims NA (Eds) (2001) *Strengthening the Biological Weapons Convention: key points for the Fifth Review Conference.* University of Bradford. Available at<www.brad.ac.uk/acad/sbtwc>
13. United Kingdom (2001) *Background paper on new scientific and technological developments relevant to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*. United Nations: Geneva.
14. Rissanen J (2002) Continued turbulence over BWC verification. In Finlay T & Meier O (eds) *Verification Yearbook 2002*. London: VERTIC.
15. Pearson GS (2002) Report from Geneva: the Biological and Toxin Weapons Review Conference. *The CBW Conventions Bulletin* **58**: 19-26.
16. See reference 14 above.
17. United Kingdom (2002) *Strengthening the Biological and Toxin Weapons Convention: countering the threat from biological weapons.* London: HM Stationery Office.
18. Pearson GS (2002) *Return to Geneva: a comprehensive list of measures*. Review Conference Paper No. 7, University of Bradford. Available at<www.brad.ac.uk/acad/sbtwc>

19. Editorial (2002) Preventing the hostile use of biotechnology: the way forward now. *The CBW Conventions Bulletin* **57**: 1-2.
20. Sims NA (2002) *Return to Geneva: the next stage of the BTWC Fifth Review Conference.* Review Conference Paper No. 5, University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
21. Pearson GS & Sims NA (2002) *The resumed Fifth Review Conference: maximising the benefits from the final declaration.* Review Conference Paper No. 9, University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
22. Bolton JR (2002) *Beyond the axis of evil: additional threats from weapons of mass destruction*. Heritage Lecture No. 743. Washington DC: Heritage Foundation.
23. Financial Times (3.12.03) *Arms warning by US to 'rogue' nations*.
24. Pearson GS & Sims NA (2002) *Return to Geneva: uncertainties and options.* Review Conference Paper No. 8, University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
25. Chevrier MI (2002) Waiting for Godot or saving the show? The BWC Review Conference reaches modest agreement. *Disarmament Diplomacy*, December: 11-16.
26. See reference 15 above.
27. Sims NA (2003) Biological disarmament diplomacy in the doldrums: reflections after the BWC Fifth Review Conference. *Disarmament Diplomacy* April/May: 11-18.
28. United Nations (2002) *Draft decision of the Fifth Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*. Geneva: United Nations.
29. Anton PS, Silberglitt R & Schneider J (2001) *The global technology revolution: bio/nano/materials trends and their synergies with information technology by 2015*. Santa Monica: Rand.
30. Sims NA (2003) *The new multilateral approach for the BTWC: ambiguities and opportunities*. Briefing Paper No. 2 (Second Series), University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>

31. Pearson GS & Sims NA (2003) *Preparing for the first meeting of states parties: I. national implementing legislation.* Briefing Paper No. 8 (Second Series), University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
32. Pearson GS (2003) *Preparing for the first meeting of states parties: II. security and oversight of pathogenic microorganisms and toxins.* Briefing Paper No. 9 (Second Series), University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
33. Woodward A (2003) *Time to lay down the law: national legislation to enforce the BWC*. London: VERTIC.
34. United States (2003) *US strategy for achieving meaningful progress through annual meetings of BWC states parties, 2003-2005*. Geneva: United Nations.
35. Brazil (2003) *Brazilian views on the way forward*. Geneva: United Nations.
36. United Nations (2003) *Report of the meeting of experts (part II) annex II: statements, presentations and contributions made available to the chairman*. Geneva: United Nations.
37. Littlewood J (2003) Substance hidden under a mountain of paper: the BWC experts meeting in 2003. *Disarmament Diplomacy*, October/November: 63-6.
38. United Nations (2003) *Collation of contributions: 10 November: agenda item 4 - general debate/discussion.* BWC/Information Paper No. 2. Geneva: United Nations.
39. Pearson GS (2003) The Biological Weapons Convention new process. *The CBW Conventions Bulletin* **62**:19-28.
40. Kelle A (2003) Strengthening the effectiveness of the BTW control regime: feasibility and options. *Contemporary Security Policy* **24**: 95-132.
41. Kenyon IR (2000) Chemical weapons in the twentieth century: their use and their control. *The CBW Conventions Bulletin* **48**:1-15.
42. Borman S (2003) The many faces of combinatorial chemistry. *C & EN* 27 October: 45-56.
43. Mathews RJ (2002) The OPCW at five: balancing verification in evolving circumstances. In Finlay T & Meier O (eds) *Verification Yearbook 2002*. London: VERTIC.

44. Kelle A (2002) The first CWC Review Conference: challenges and opportunities. *Disarmament Diplomacy* January/February: 13-18.
45. IUPAC (2002) Impact of scientific developments on the Chemical Weapons Convention. *Pure and Applied Chemistry* **74**: 2229-352.
46. Director General (2003) *Report of the Scientific Advisory Board on developments in science and technology*. First Review Conference. The Hague: OPCW.
47. Kelle A (2003) The CWC after its First Review Conference: is the glass half-full or half-empty? *Disarmament Diplomacy* June: 1-9.
48. Editorial (2003) Where to from here? The first CWC Review Conference and the next five years. *The CBW Conventions Bulletin* **60**:1-5.
49. Feakes D (2002) Evaluating the CWC verification system. *Disarmament Forum* **4**: 11-22.
50. See reference 47 above.
51. Dando MR (2003) *The danger to the Chemical Weapons Convention from incapacitating chemicals*. First CWC Review Conference Paper No. 4, University of Bradford. Available at <www.brad.ac.uk/acad/scwc>
52. Gordon A (1997) Implications of the US Resolution of Ratification. *The CBW Conventions Bulletin* **38**:1-6.
53. Editorial (1994) New technologies and the loophole in the Convention. *Chemical Weapons Convention Bulletin* **23**: 1-2.
54. Ministry of Defence (1998) *Iraq CW capabilities in the Gulf War: Agent 15*. London: Ministry of Defence.
55. Dando MR (1996) *A new form of warfare: the rise of non-lethal weapons*. London: Brassey's.
56. Dando MR (2002) Scientific and technological change and the future of the CWC: the problem of non-lethal weapons. *Disarmament Forum* **4**: 33-45.
57. See reference 47 above.
58. Editorial (2003) 'Non-lethal' weapons, the CWC and the BWC. *The CBW Conventions Bulletin* **61**: 1-2.

CHAPTER 3

1. Cohen W (1997) *Proliferation: Threat and response*. Washington DC: Department of Defense.
2. Nixdorff K, Brauburger J & Hahlbohm D (1997) The biotechnology revolution: the science and applications. In Dando MR, Pearson GS & Tóth T (eds) *Verification of the Biological and Toxin Weapons Convention*. Dordrecht: Kluwer Academic.
3. Nowak R (2001) Disaster in the making: an engineered mouse virus leaves us one step away from the ultimate bioweapon. *New Scientist* 13 January: 4-5.
4. Jackson RJ, Ramsay AJ & Christensen CD et al (2001) Expession of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J Virol* **75**: 1205-10.
5. See reference 3 above.
6. Mackenzie D (2003) US develops lethal new viruses. *New Scientist* 29 October. Available at <www.newscientist.com/news/news.jsp?id=ns99994318>
7. Cello J, Paul AV & Wimmer E (2002) Chemical syntheis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* **297**: 1016-18.
8. Westphal SP (2002) Ebola virus could be synthesised. *New Scientist* 17 July. Available at <www.newscientist.com/news/print.jsp?id=ns99992555>
9. Smith HO, Hutchinson CA & Pfannkoch C et al (2003) Generating a synthetic genome by whole genome assembly: ØX174 bacteriophage from synthetic oligonucleotides. Available at <www.pnas.org/cgi/doi/10.1073/pnas.2237126100>. *Washington Post* (14.11.03) *Researchers create virus in record time: organism not dangerous to humans*.
10. Janeway CA & Medzhitov R (2002) Innate immune recognition. *Ann Rev Immunol* **20**: 197-216.
11. Seet BT, Johnston JB & Brunetti CR et al (2003) Poxviruses and immune evasion. *Ann Rev Immunol* **21**: 377-423.

12. Rosengard AM, Yu L & Nie Z et al (2002) Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. *Proc Natl Acad Sci* **99**: 8808-13.
13. Miller J, Engelberg S & Broad W (2001) *Germs: biological weapons and America's secret war*. New York: Simon & Schuster.
14. Bisher J (2003) During World War I, terrorists schemed to use anthrax in the cause of Finnish independence. *Military History* August: 18-22.
15. Jackson PJ, Hugh-Jones ME & Adair DM et al (1998) PCR analysis of tissue samples from the 1979 Sverdlovsk anthrax victims: the presence of multiple *Bacillus anthracis* strains in different victims. *Proc Natl Acad Sci* **95**: 1224-9.
16. Pilcher, HR (2003) Anthrax genome unveiled: DNA sequence may help stop killer in its tracks. *Nature* 1 May. Available at <www.nature.com/nsu/030428/030428-14.html>
17. Pomerantsev AP, Staritsin NA & Mockov YU et al (1997) Expression of cereolysine AB genes in *Bacillus anthracis* vaccine strain ensures protection against experimental hemolytic anthrax infection. *Vaccine* **15**: 1846-50.
18. See reference 13 above.
19. Poste G (2002) *Advances in biotechnology: promise or peril*. Available at <www.hopkins-defense.org/sympcast/transcripts/trans_post.html>
20. Wheelis M (2003) 'Nonlethal' chemical weapons: a faustian bargain. *Issues in Science and Society* Spring: 74-8.
21. Coupland RM (2003) Incapacitating chemical weapons: a year after the Moscow theatre siege. *The Lancet* **362**: 1346.
22. Streetdrugs (2003) *Fentanyl*. Available at <www.streetdrugs.org/fentanyl.htm>
23. Dando MR (1996) *A new form of warfare: the rise of non-lethal weapons*. London: Brassey's.
24. Snyder SH & Pasternak GW (2003) Historical review: opioid receptors. *Trends in Pharmacological Sciences* **24**: 198-205.
25. Kagan E (2001) Bioregulators as instruments of terror. *Clinics in Laboratory Medicine* **21**: 607-18.

26. Borzenkov VM, Pomerantsev AP & Ashmain IP (1993) Additive synthesis of regulator peptide *in vivo*: the introduction of the vaccine strain of *Francisella tularensis* producing ß-endorphin. *Bulletin of Experimental Biology and Medicine* **116**: 942-5.
27. See reference 25 above.
28. Croatia (1999) *Evaluation of biological agents and toxins.* Geneva: United Nations.
29. Center for Food Safety and the International Center for Technology Assessment (2001) *Petition on genetically engineered arthropod vectors of human diseases*. Available at <www.centerforfoodsafety.org/li/petition-secdshs.htm>
30. Petro JB, Plasse TR & McNulty JA (2003) Biotechnology: impact on biological warfare and biodefence. *Biosecurity and Bioterrorism* **1**: 161-8.
31. Levin DB & De Amorim GV (2003) Potential for aerosol dissemination of biological weapons: lessons from biological control of insects. *Biosecurity and Bioterrorism* **1**: 37-42.
32. Hartley DM & Peters CJ (2003) Aerosols from insect control measures show dangers of bioterrorism. *Biosecurity and Bioterrorism* **1**: 221.
33. Edwards DA (2002) Delivery of biological agents by aerosols. *AIChE Journal* **48**: 2-6.
34. Bennett JV, de Castro JF & Valdespino-Gomez JL et al (2002) Aerosolised measles and measles-rubella vaccines induce better measles antibody booster responses than injected vaccines: randomised trials in Mexican schoolchildren. *Bulletin of the World Health Organization* **80**: 806-7.
35. Dando MR (2001) *The new biological weapons: threat, proliferation and control*. Boulder: Lynne Rienner.
36. Menasherob R, Ben-Dov E & Xiaoqiong W et al (2002) Protection from UV-B damage of mosquito larvicidal toxins from *Bacillus thuringiensis* subsp *israelensis* expressed in *Anabaena* PCC 7120. *Current Microbiology* **45**: 217-20.
37. Whittaker PA (2003) What is the relevance of bioinformatics to pharmacology? *Trends in the Pharmacological Sciences* **24**: 434-9.
38. Plunkett MJ & Ellman JA (1997) Combinatorial chemistry and new drugs. *Scientific American* April: 54-9.

39. Howard S (2002) Nanotechnology and mass destruction: the need for an inner space treaty. *Disarmament Diplomacy* July/August: 3-16.
40. Whitby SM (2002) *Biological warfare against crops*. Basingstoke: Palgrave.
41. Wheelis M, Casagrande R & Madden LV (2002) Biological attack on agriculture: low-tech, high impact bioterrorism. *Bio-Science* **52**: 569-76.
42. South Africa (2001) *Background paper on new scientific and technological developments relevant to the convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction*. Geneva: United Nations.
43. Anon (2001) *Risks of using biological agents in drug eradication*. Backgrounder Series No. 4, February, Sunshine Project. Available at <www.sunshine-project.org>
44. Rogers P, Whitby SM & Dando MR (1999) Biological warfare against crops. *Scientific American* June: 62-7.
45. Sunshine Project (5.6.01) *Who's in charge of agent green in Asia?* Available at <www.sunshine-project.org>
46. United Kingdom (2001) *Background paper on new scientific and technological developments relevant to the convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction*. Geneva: United Nations.

CHAPTER 4

1. Brumfiel G & Knight J (2003) In the shadow of war. *Nature* **426**: 748-9.
2. The Times (1.2.02) *Sorry is not enough*.
3. Hill A (2003) The day the earth died. *Observer Magazine* 2 March: 24-30.
4. Stone R (2003) Bioweapons: British expert leaves impressive arms control legacy. *Science* **301**: 445-6.
5. Gould C & Folb P (2002) *Project Coast: apartheid's chemical and biological warfare programme*. Geneva: United Nations.
6. Washington Post (20.4.03) *Lethal legacy: bioweapons for sale*.

7. Alibek K & Handelman S (1999) *Biohazard: the chilling true story of the largest covert biological weapons program in the world – told from the inside by the man who ran it*. London: Hutchinson.
8. Miller J, Engleberg S & Broad W (2002) *Germs: biological weapons and America's secret war*. New York: Simon & Schuster.
9. Domaradskij IV & Orent W (2001) The memoirs of an inconvenient man: revelations about biological weapons research in the Soviet Union. *Critical Reviews in Microbiology* **27**: 239-66.
10. Williams M (2003) The coming threat: bioweapons are much more prevalent and virulent than most of us realise. And we have little defense. *Acumen* **1**: 40-50.
11. Smithson AE (1999) *Toxic archipelago: preventing proliferation from the former Soviet chemical and biological weapons complexes*. Report No 32, December. Washington DC: Henry L Stimson Center.
12. Rhodes K (2002) *Diffuse security threats: information on US domestic anthrax attacks*. Statement for the record before the Select Committee on Intelligence, US Senate, and Permanent Select Committee on Intelligence, House of Representatives. Washington DC: General Accounting Office.
13. Leitenberg M (2002) Biological weapons and 'bioterrorism' in the first years of the 21st century. In: Rippandelli D & Martinelli, M (eds) *The possible use of biological weapons by terrorist groups: scientific, legal and international implications*. Como: ICGEB and Landau Network.
14. Atlas RM (2002) Bioterrorism: from threat to reality. *Ann Rev Microbiol* **56**: 167-85.
15. Patrick W (2001) Biological warfare scenarios. In: Lyne S, Beugelsdijk T & Patel K (eds) *Firepower in the lab: automation in the fight against infectious diseases and bioterrorism*. Washington DC: Joseph Henry.
16. Peters CJ (2002) Many viruses are potential agents of bioterrorism. *ASM News* **68**: 168-73.
17. Madariaga MG, Rezai K & Trenholme M et al (2003) Q fever: a biological weapon in your backyard. *The Lancet Infectious Diseases* **3**: 709-20.
18. O'Toole T, Mair M & Inglesby TV (2002) Shining light on 'Dark Winter.' *Clinical Infectious Diseases* **34**: 972-83.

19. Danzig R (2003) *Catastrophic bioterrorism – what is to be done?* Center for Technology and National Security Policy. Washington DC: National Defense University.
20. United States (2003) *National measures adopted by the United States to implement the prohibitions set forth in the Biological Weapons Convention*. Geneva: United Nations.
21. United States (2003) *Specific measures taken by the United States relevant to security of dangerous pathogens and toxins*. Geneva: United Nations.
22. Pearson GS (2003) *Maximising the security and improving oversight of pathogenic microorganisms and toxins*. Briefing Paper No. 5 (Second Series). University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
23. Europa (2002) *EU action in response to 11th September 2001: one year after*. Available at <www.europa.eu.int/comm/110901/>
24. Carter GB (1992) Biological warfare and biological defence in the United Kingdom 1940-1979. *RUSI Journal*, December: 67-74.
25. United Kingdom (2003) *BTWC implementing and penal legislation: core elements*. Geneva: United Nations.
26. United Kingdom (2003) *The design of national measures to maintain the security and oversight of pathogenic microorganisms and toxins*. Geneva: United Nations.
27. Foreign and Commonwealth Office (2003) *UK international priorities: a strategy for the FCO*. London: HMSO.
28. Foreign and Commonwealth Office (2003) *Strengthening the Biological and Toxin Weapons Convention: countering the threat from biological weapons*. London: HMSO.
29. Ministry of Defence (2003) *Delivering security in a changing world: defence white paper*. London: HMSO.
30. Written Statement (2003) *An update on domestic counter-terrorism, security and resilience issues.* (Home Secretary's statement to Parliament). Available at <www.ukresilience.info/terrorism.htm>
31. Simpson J & Littlewood J (2003) *A framework for assessing UK responses to CBRN terrorism*. Paper presented at the British International Studies Association, 28th Annual Conference, 15-17 December University of Birmingham.

32. Cabinet Office (2003) *Dealing with disaster*. Revised 3rd edition. London: Cabinet Office.
33. Cabinet Office (2003) *The draft Civil Contingencies Bill, explanatory notes, regulatory impact assessment (local responders), and regulatory impact assessment (emergency powers)*. London: Cabinet Office.
34. Scholefield S (2003) *Introductory note to the revised 3rd edition*. In: Cabinet Office (eds) *Dealing with disaster: revised 3rd edition*. London: Cabinet Office. Available at <www.ukresilience.info/contingencies/dwd/index.htm>
35. Science and Technology Committee (2003) *The scientific response to terrorism*. Eighth Report of Session 2002-03, HC 415-1. London: House of Commons.
36. Home Office (2003) *Response to STC report: the scientific response to terrorism*. Press Release, 23 November. Available at <www.homeoffice.gov.uk/n_story.asp?item_id=672>
37. Nathanson V, Darvell M & Dando MR (1999) *Biotechnology, weapons and humanity*. London: Harwood Academic (for the British Medical Association).
38. See reference 11 above.
39. Roffey R, Unge W & Clevström J et al (2003) *Support to threat reduction of the Russian biological weapons legacy: conversion, biodefence and the role of Biopreparat*. Umeå: Swedish Defence Research Agency.
40. FCO, DTI, MOD (2003) *The G8 global partnership: first annual report*. London: Department of Trade and Industry.
41. See reference 39 above.
42. Wiener Col. SL (1987) Strategies of biowarfare defense. *Military Medicine* **152**: 25-8.
43. Wiener Col. SL (1996) Strategies for the prevention of a successful biological warfare aerosol attack. *Military Medicine* **161**: 251-6.
44. General Accounting Office (2003) *Combating terrorism: observations on national strategies related to terrorism*. Statement by the Director, Defense Capabilities and Management, before the Subcommittee on National Security, Emerging Threats, and International Relations, Committee on Government Reform, House of Representatives. Washington DC: GAO.

45. Ember LR (2003) Championing technology to thwart terrorism. *Chemical and Engineering News* 29 September: 19-23.
46. Fauci AS (2003) Biodefence on the research agenda. *Nature* **421**: 787.
47. Malakoff D (2003) Research funding: US biodefense boom: eight new study centers. *Science* **301**: 1450-1.
48. Enserink M (2003) Infectious diseases: new biodefense splurge creates hotbeds, shatters dreams. *Science* **302**: 206-7.
49. Enserink M (2003) Riding the biodefense wave. *Science* **301**: 912-3.
50. Enserink M (2003) Scientific community: Johns Hopkins biodefence pioneers depart en masse. *Science* **301**: 1824-5.
51. National Institute of Allergy and Infectious Diseases (2003) *Summary of NIAID accomplishments in biodefense research*. Washington DC: NIAID. Available at <www.niaid.nih.gov/newsroom/biodresaccomp.htm>
52. National Institute of Allergy and Infectious Diseases (2002) *NIAID biodefense research agenda for CDC category A agents*. Washington DC: National Institutes of Health.
53. National Institute of Allergy and Infectious Diseases (2003) *NIAID biodefense reseach agenda for category B and C priority pathogens*. Washington DC: National Institutes of Health.
54. National Institute of Allergy and Infectious Diseases (2003) *NIAID biodefense research agenda for CDC category A agents: progress report*. NIH Publication 03-5432, August. Washington DC: National Institutes of Health.
55. General Accounting Office (2003) *Bioterrorism: preparedness varied across state and local jurisdictions*. Washington DC: GAO.
56. See reference 10 above.
57. Mann CC (2002) Homeland insecurity. *The Atlantic Monthly* **290**: 1-16. Available at <www.theatlantic.com>
58. Check E (2003) Boom, or bust? *Nature* **426**: 598-601.
59. Dando MR (1999) The impact of the development of modern biology and medicine on the evolution of offensive biological warfare programs in the twentieth century. *Defense Analysis* **15**: 43-62.
60. Petro JB, Plasse TR & McNulty JA (2003) Biotechnology: impact on biological warfare and biodefense. *Biosecurity and bioterrorism* **1**: 161-8.

61. Wheelis M & Dando MR (2003) On the brink: biotechnology and the future of weapons control. *Chemical and Biological Weapons Conventions Bulletin* **58**: 3-7.
62. Rosenberg BH (2003) Defending against biodefense: the need for limits. *Disarmament Diplomacy* February/March: 1-6.

CHAPTER 5

1. Meselson M (1999) *The problem of biological weapons*. Presentation given at the 1818th Stated Meeting of the American Academy of Arts and Sciences. 13 January, Cambridge, Mass.
2. Dennis C (2001) The bugs of war. *Nature* **411**: 232-5.
3. Wheelis M & Dando MR (2003) New technology and future developments in biological warfare. *Military Technology* **27**: 52-6.
4. Petro JB, Plasse TR & McNulty JA (2003) Biotechnology: impact on biological warfare and biodefense. *Biosecurity and Bioterrorism* **1**: 161-8.
5. Beck V (2003) Advances in life sciences and bioterorrism. *EMBO Reports* **4**: 553-6.
6. Office of Transnational Issues (2003) *The darker bioweapons future.* Washington DC: Central Intelligence Agency.
7. Enserink M (2003) China's missed chance. *Science* **301**: 294-6.
8. Centers for Disease Control and Prevention (2003) *Basic information about SARS*. Atlanta: CDC. Available at <www.cdc.gov/ncidod/sars/factsheet.htm>
9. Centers for Disease Control and Prevention (2003) *Frequently asked questions about SARS*. Atlanta: CDC. Available at <www.cdc.gov/ncidod/sars/faq.htm>
10. See reference 8 above.
11. Anon (2003) An appropriate response to SARS. *The Lancet*, *Infectious Diseases* **3**: 259.
12. Prescott EM (2003) SARS: A warning. *Survival* **45**: 207-26.
13. Financial Times (26.4.03) *Vaccine or cure for disease likely to take years*. Available at <www.FT.com>

14. Taubenberger JK, Reid AH & Krafft AE et al (1997) Initial genetic characterization of the 1918 'Spanish' Influenza virus. *Science* **275**: 1793-6.
15. Reid AH, Fanning TG & Janczewski TA et al (2002) Characterization of the 1918 'Spanish' Influenza virus matrix gene segment. *J Virol* **76**: 10717-23.
16. Basler CF, Reid AH & Dybing JK et al (2001) Sequence of the 1918 pandemic influenza virus nonstructural gene (NS) segment and characterization of recombinant viruses bearing the 1918 NS genes. *Proc Natl Acad Sci* **98**: 2746-51.
17. Tumpey TM, Gracia-Sastre A & Mikulasova A et al (2002) Existing anti-virals are effective against influenza with genes from the 1918 pandemic virus. *Proc Natl Acad Sci* **99**: 13849-54.
18. Sunshine Project (9.10.03) *Lethal virus from 1918 genetically reconstructed*. The Sunshine Project, 9 October. Available at <www.sunshine-project.org/publications/pr/pr091003.html>
19. Reid AH, Janczewski TA & Lourens RM et al (2003) 1918 Influenza pandemic caused by highly conserved viruses with two receptor-binding variants. *Emerging Infectious Diseases* **9**: 1249-53.
20. Madjid M, Lillibridge S & Mirhaji P et al (2003) Influenza as a bioweapon. *J Roy Soc Med* **96**: 345-6.
21. Committee on Opportunities in Biotechnology for Future Army Applications (2001) *Opportunities in biotechnology for future army applications*. Washington DC: National Academy Press.
22. Alexander JB (2001) An overview of the future of non-lethal weapons. *Medicine, Conflict and Survival* **17**: 180-93.
23. Ketchum JS & Sidell FR (1997) Incapacitating agents. In: Sidell FR, Takafuji ET & Franz DR (eds) *Medical aspects of chemical and biological warfare*. Washington DC: Office of the Surgeon General.
24. DERA (1999) *An overview of research carried out on glycollates and related compounds at CBD Porton Down*. London: Ministry of Defence.
25. Biology Committee (1960) *The UK approach to new agents*. London: Public Record Office.

26. Dando MR (2002) Scientific and technological change and the future of the CWC: the problem of non-lethal weapons. *Disarmament Forum* **4**: 33-44.
27. Wheelis M (2002) Biotechnology and biochemical weapons. *The Nonproliferation Review* Spring: 48-53.
28. Williams M, Coyle JT & Shaikh S et al (2001) Same brain, new decade: challenges in CNS drug discovery in the postgenomic, proteomic era. *Annual Reports in Medicinal Chemistry* **36**: 1-10.
29. Dando MR (2001) *The new biological weapons: threat, proliferation and control*. Boulder: Lynne Rienner.
30. Committee for an Assessment of Non-lethal Weapons Science and Technology (2002) *An assessment of non-lethal weapons science and technology*. Washington DC: National Academies Press.
31. Lakoski JM, Bosseau MW & Renny JM (2000) *The advantages and limitations of calmatives as a non-lethal technique*. Pennsylvania State University: Applied Research Laboratory, College of Medicine.
32. Dando MR (1996) *A new form of warfare: the rise of non-lethal weapons*. London: Brassey's.
33. Dando MR (2003) *The danger to the Chemical Weapons Convention from incapacitating chemicals*. First CWC Review Conference Paper No. 4. University of Bradford. Available at <www.brad.ac.uk/acad/scwc>
34. Davison N & Lewer N (2003) *Non-Lethal Weapons Research Project, Report No. 4*. University of Bradford: Bradford Non-lethal Weapons Research Project. Available at <www.brad.ac.uk/acad/nlw>
35. Wess J (2003) Novel insights into muscarinic acetylcholine receptor function using gene targeting technology. *Trends in the Pharmacological Sciences* **24**: 414-20.
36. Lachowicz JE (2002) *Selective M2 antagonists facilitate acetylcholine release and improve performance in behaviour models of cognition*. Presentation 116.2 at the symposium on 'Muscarinic Receptor Research' at the International Congress of Pharmacology, 7-12 July, San Francisco,.
37. Holmes A, Heilig M & Rupniak NMJ et al (2003) Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends in the Pharmacological Sciences* **24**: 580-8.

38. Nobell F & Roques BP (1999) CCK-B receptor: chemistry, molecular biology, biochemistry and pharmacology. *Progress in Neurobiology* **58**: 349-79.
39. Wheelis M & Dando MR (2003) *Consequences of the militarisation of biology*. Paper presented at the Pugwash CBW Study Group Meeting December, Geneva.
40. Editorial (2003) 'Non-lethal' weapons, the CWC and the BWC. *CBW Conventions Bulletin* **61**: 1-2.
41. Nathanson V, Darvell M & Dando MR (1999) *Biotechnology, weapons and humanity*. London: Harwood Academic.
42. Sunshine Project (2003) *Emerging technologies: genetic engineering and biological weapons*. Background Paper No. 12. Available at <www.sunshine-project.org>
43. Lau NC & Bartel DP (20030 Censors of the genome. *Scientific American*, August: 27-33.
44. Gibbs WW (2003) The unseen genome: gems among the junk. *Scientific American* November: 46-53.
45. Gibbs WW (2003) The unseen genome: beyond DNA. *Scientific American* December: 78-85.
46. See reference 42 above.
47. Thayer AM (2003) Biomarkers emerge; pharmacogenomic indicators of disease and drug activity may promise success for R&D programs. *C & EN*, 28 July: 33-7.
48. Williams DA & Baum C (2003) Gene therapy - new challenges ahead. *Science* **302**: 400-1.
49. Black Col. JL (2003) Genome projects and gene therapy: gateways to next generation biological weapons. *Military Medicine* **168**: 864-70.
50. Pearson GS (2001) *New scientific and technological developments of relevance to the Fifth Review Conference*. Review Conference Paper No. 3, University of Bradford. Available at <www.brad.ac.uk/acad/sbtwc>
51. Bacher JM, Reiss BD & Ellington AD (2002) Anticipating evolution and DNA shuffling. *Genome Biology* **3**: 1021-4.

CHAPTER 6

1. Waddington CH (1977) *Tools for thought*. London: Jonathan Cape.
2. Waddington CH (1978) *The man-made future*. London: Croom Helm.
3. Zilinskas RA (ed) (2000) *Biological warfare: modern offense and defense*. Boulder: Lynne Rienner.
4. Geissler E (1986) A new generation of biological weapons. In: Geissler E (ed) *Biological and toxin weapons today*. Oxford: Oxford University Press (for SIPRI).
5. Nathanson V, Darvell M & Dando MR (1999) *Biotechnology, weapons and humanity*. London: Harwood Academic (for the BMA).
6. Anon (2003) *Biotechnology, weapons and humanity*. Geneva: International Committee of the Red Cross.
7. Department of Health (2003) *Exercise Global Mercury*. Available at <www.doh.gov.uk/cmo/exerciseglobalmercury/index.htm>
8. BASIC (2004) *Biological weapons update*. British American Security Information Council: London. Available at <www.basicint.org/update/BWU040108-PF.htm>
9. USDA (2003) *Audit report: controls over biological, chemical and radioactive materials at institutions funded by the US Department of Agriculture*. Washington DC: Department of Agriculture.
10. GAO (2003) *Bioterrorism: a threat to agriculture and the food supply*. Testimony before the Committee on Government Affairs, US Senate. Washington DC: General Accounting Office.
11. Kosal ME (2003) *The basics of chemical and biological weapons detectors*. CNS, Monterey Institute of International Studies. Available at <www.cns.miis.edu/pubs/week/031124.htm>
12. See reference 3 above.
13. Matsumoto G (2003) Anthrax powder: state of the art? *Science* **302**: 1492-7.
14. Ouagrham SB (2003) *Biological weapons threats from the former Soviet Union.* CIAO working papers, August. Available at <www.cianet.org/wps/ous02/index.html>

15. Editorial (2002) Preventing the hostile use of biotechnology: the way forward now. *CBW Conventions Bulletin* **57**: 1-2.
16. Anon (2003) National implementation. *Chemical Disarmament* **1** (4): 16-8.
17. Dando MR (1996) *A new form of warfare: the rise of non-lethal weapons*. London: Brassey's.
18. Anon (2004) *The return of ARCAD (Advanced Riot Control Agent)*. The Sunshine Project. Available at <www.sunshine-project.org/publications/pr/pr060104.html>
19. Los Angeles Times (4.1.04) *Pulling punches: big plans for futuristic, non-lethal weapons are afoot, but their use would raise troubling questions*.
20. Sims NA (2003) A proposal for putting the 26th March 2005 anniversary to best use for the BWC. *CBW Conventions Bulletin* **62**: 1-6.
21. Zanders JP (2003) Civil society monitoring: the BW case. *Trust & Verify* July-August: 1-2.
22. Littlewood J (2003) *Preparing for a successful outcome to the BWC Sixth Review Conference in 2006*. Briefing Paper No. 11 (Second Series), University of Bradford, December. Available at <www.brad.ac.uk/acad/sbtwc>
23. World Health Organisation (2003) *Final report: preparedness for deliberate epidemics (PDE) activities 2002-2003*. Available at <www.who.int/csr/delibepidemics/en/>
24. Woodall J & Aldis R (2003) *Gaps in global surveillance*. Occasional Paper No. 1, Bioweapons Prevention Project. Geneva: BWPP.
25. Pennisi E (2003) Tracing life's circuitry. *Science* **302**: 1646-9.
26. Committee on Research Standards and Practices to Prevent the Destructive Application of Biology (2003) *Biotechnology research in an age of terrorism: confronting the dual use dilemma*. Washington DC: The National Academies Press.
27. Check E (2004) Terror watchdog set up for 'dual-use' biology. *Nature* **428**: 109.
28. Wellcome Trust (2003) *Wellcome Trust position statement on bioterrorism and biomedical research*. Available at <www.wellcome.ac.uk/en/1/awtvispolter.html>

29. Rappert B (2003) Coding ethical behaviour: the challenge of biological weapons. *Science and Engineering Ethics* **9**: 453-70.
30. Steinbruner JD & Harris ED (2003) Controlling dangerous pathogens. *Issues in science and technology online*. Spring. Available at <www.nap.edu/issues/19.3/steinbruner.htm>
31. International Herald Tribune (3.12.03) *When science breeds nightmares*.
32. The Times (27.12.03) *Scientists' bid to combat TB made it more virulent*. Available at <www.timesonline.co.uk>
33. The Guardian (8.1.04) *Civil contingencies: ministers are listening*.
34. Tucker JB (2003) *Biosecurity: limiting terrorist access to deadly pathogens*. Peaceworks No. 52. Washington DC: United States Institute of Peace.
35. WHO (2002) *Genomics and world health: report of the Advisory Committee on Health Research*. Geneva: World Health Organisation. Available at <www.who.int/genomics>
36. Anon (2003) *Biosafety, biosecurity, and biological weapons*. The Sunshine Project. Available at <www.sunshine-project.org>
37. Rhodes C (2003) *Facilitating research on international biotechnology regulations through the development of a gateway site.* MRes, University of Bradford.
38. Meselson M & Robinson J (1998) A draft convention to prohibit biological and chemical weapons under international criminal law. *CBW Conventions Bulletin* **42**: 1-5.
39. Mackenzie D (2003) How the US crackdown on bioterror is backfiring. New Scientist 8 November: 6-8.
40. Rogers P (2004) The US military posture: a uniquely benign imperium? In: El Panitch and C Leys (eds) *The new Imperial challenge.* London: Merlin Press. pp146-65.
41. Scheer C (2003) *A plague of bioweapons.* Available at <www.alternet.org/story.html?StoryID=17319>
42. Leitenberg M (2003) Distinguishing offensive from defensive biological weapons research. *Critical Reviews in Microbiology* **29**: 223-57.
43. Malakoff D (2003) Biodefense facilities: suit targets two DOE labs. *Science* **301**: 1168-9.
44. The Financial Times (3.10.03) *Defence scientists must take ethical stance.* p6.

45. Dando MR (2002) *Preventing biological warfare: the failure of American leadership.* Basingstoke: Palgrave.
46. Fraser CM & Dando MR (2001) Genomics and future biological weapons: the need for preventive action by the biomedical community. *Nature Genetics* **29**: 1-4.
47. Carlson R (2003) The pace and proliferation of biological technologies. *Biosecurity and Bioterrorism* **1**: 203-14.
48. Petsko GA (2002) An Asilomar moment. *Genome Biology* **3**: 1014.1-1014.3.

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