New Technology and Future Developments in Biological Warfare

Mark Wheelis and Malcolm Dando

It is very hard for us today to imagine what life was like 150 ago, when there was no understanding of the causes of infectious diseases, nor any effective protection from their ravages. Then, in about a decade near the end of the nineteenth century, scientists of the stature of Koch in Germany and Pasteur in France produced a revolution in medicine by elucidating the microbial basis of infectious disease.[1] This led rapidly to genuinely effective preventive measures, and ultimately to effective remedies, for diseases such as typhoid, cholera, anthrax, plague and others. Yet it was not long — during the First World War — before this new knowledge was being used to attack military draft animal stocks (although with questionable effectiveness).[2]

This process, whereby new scientific developments in microbiology were used both for the benefit of civil society and in preparation for use in warfare, continued throughout the twentieth century. A number of European countries, as well as Japan, developed bioweapons during the 1930s and 1940s, fuelled in part by inflated intelligence estimates of the biological warfare capabilities of others.[3] Japan went on to use biological weapons extensively against China in the Second World War, causing substantial mortality.[4] In the post-war period at least three countries — the United States, the United Kingdom and the Soviet Union — are known to have had large, ambitious programmes of biological weapons development.[5] The offensive programmes of the United States and the United Kingdom were discontinued in the 1960s; that of the Soviet Union lasted at least until its break-up. More recently, Iraq is known to have had a small, but mature, biological weapons programme. The facilities and munitions were largely destroyed by UNSCOM, but concerns about its resurgence in the absence of UN monitoring remain.[6] Intelligence analysts of many countries believe that several developing countries currently have covert biological weapons programmes.[7]

In this context of past and present biological weapons programmes, it is hardly surprising that the background papers produced by States Parties to the Biological and Toxin Weapons Convention (BTWC) for the Review Conferences every five years have shown an increasing sense of concern about the potential impact of the new revolution in biology. This revolution began in the 1970s with a set of techniques known as genetic engineering, or recombinant DNA technology, and has since been expanded by the development of rapid DNA sequencing technology that has led to the field of *genomics* — the extraction of information from complete DNA sequences of organisms, and the

---

Mark Wheelis is Senior Lecturer in the Section of Microbiology at the University of California at Davis. Trained as a general microbiologist, his research interests have for more than ten years focused on the history of biological warfare, and on epidemiology as a component of biological arms control.

Malcolm Dando is Professor of International Security in the Department of Peace Studies at the University of Bradford. Professor Dando trained originally as a biologist and has worked on issues of arms control and disarmament for the last twenty years. He is presently co-director of the Bradford project on strengthening the Biological and Toxin Weapons Convention.

analysis and cataloguing of that information. A second aspect of this revolution has been the increasingly precise understanding of the physical chemistry of protein folding and of the diversity and mutual interactions of the many thousands of different proteins in the living cell, a field generally known as *proteomics*. Thus a set of immensely powerful experimental and modelling techniques have become available in the last few decades that allow an unprecedented capability to modify living organisms and their products in precise and predictable ways, and to design small molecules to interact in specific ways with proteins in living organisms to alter their functioning in predictable ways. The relevance of these technologies to biological weapons development is obvious; indeed, it has been alleged that the Soviet biological weapon programme employed genetic engineering to create novel agents.[8]

Concerns expressed at previous Review Conferences

The dangers that could arise from new scientific and technological developments in microbiology were well understood at the time that the BTWC was negotiated. As Nobel Laureate Joshua Lederberg told an informal meeting of the United Nations Conference of the Committee on Disarmament on 5 August 1970,[9] "[t]he potential undoubtedly exists for the design and development of infective agents against which no credible defence is possible, through the genetic and chemical manipulation of these agents".

As the revolution in genetic engineering got underway it is therefore not surprising that specific concerns began to be expressed at Review Conferences that the new technological developments might have applications to offensive biological weapons development. The first concern articulated was that they might allow the easier production of militarily significant quantities of toxins (by inserting the toxin gene into a bacterium that could be easily grown in industrial quantities).[10]

Thus the final declaration of the Second Review Conference in 1986 noted that in regard to Article I, on the scope of the prohibition:[11]

> "The Conference reaffirms that *the Convention unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production*. Consequently, toxins (both proteinaceous and non-proteinaceous) of a microbial, animal or vegetable nature *and their synthetically produced analogues* are covered" (emphasis added).

The Final Declaration of the Third Review Conference in 1991 was much more wide-ranging in regard to its concerns about how scientific and technological developments might impact on Article I, stating:[12]

> "The Conference, conscious of apprehensions arising from relevant scientific and technological developments, inter alia, in the fields of microbiology, biotechnology, molecular biology, genetic engineering and any application resulting from genome studies, and the possibilities of their use for purposes inconsistent with the objectives and provisions of the Convention, reaffirms that the undertakings given by the States Parties in Article I applies to all such developments. The Conference also reaffirms that *the Convention unequivocally covers all microbial or other biological agents or toxins, naturally or artificially created or altered, whatever their origin or method of production*" (emphasis added).

By the time of the Fourth Conference of the BTWC in 1996 these concerns had been clearly extended to genomics, the Final Declaration stating:[13]

> "The Conference, conscious of apprehensions arising from relevant scientific and technological developments, inter alia, in the fields of microbiology, biotechnology, molecular biology, genetic engineering, and *any application resulting from genome studies*, and the possibilities of their use for purposes inconsistent with the objectives and the provisions of the Convention, reaffirms that the undertaking given by the States Parties in *Article I applies to all such developments*" (emphasis added).

There can be no doubt that the States Parties to the BTWC see the potential impact of new scientific and technological developments as an increasingly serious problem.

Current and near-term threats

It is almost certain, as was demonstrated in Iraq's recent offensive biological weapons programme, that a proliferator nowadays is likely to attempt initially to weaponize the agents which have been weaponized previously in major offensive programmes, or other unmodified organisms. Thus the "classical" agents developed in the middle of the twentieth century by the United States — anthrax, botulinal toxin, tularemia, etc. — would likely be the first agents of choice. Such agents, having already been proven to be effective, would require limited retesting by the proliferator. However, after the development of a functional biological weapons programme along classical line, it seems probable that agents would be further developed through genetic engineering techniques.

For example, an official American study in 1997 suggested that the following novel agents might be produced:[14]

- benign micro-organisms, genetically altered to produce a toxin, venom or bioregulator;
- micro-organisms resistant to antibiotics, standard vaccines and therapies;
- micro-organisms with enhanced aerosol and environmental stability;
- immunologically altered micro-organisms able to defeat standard identification, detection and diagnostic methods; and
- combinations of the above four types with improved delivery systems.

The study then went on to suggest that it was difficult to predict what might happen as a result of further developments in biotechnology, but noted that there were clearly trends in current work which could affect biological weapon possibilities.

Before we go on to review these trends, it is necessary to consider the use of biological weapons from a wider perspective than just the use of highly lethal agents against human beings. Biological agents were used to attack draft animals in the First World War. Anthrax bacteria were also weaponized for use against the German cattle industry by the British in the Second World War, although never used. The fungal agents *Puccinia graminis tritici* (which causes stem rust of wheat) and *Pyricularia oryzae* (which causes rice blast) were weaponized in the American biological weapons programme during and after the war (also never used). Strategic application leading to considerable food shortages was the intended use of these stockpiles.[15] In the current world, use of these and other agents to attack the agricultural sector of a target country would more likely be for economic reasons, and the consequences could include international trade sanctions whose economic impact could far exceed the direct costs of disease mortality and morbidity.[16]

Agents to attack the agricultural sector of a target country would more likely be for economic reasons, and the consequences could include international trade sanctions whose economic impact could far exceed the direct costs of disease mortality and morbidity.

In regard to the use of anti-personnel biological agents, it is of course true that highly lethal weapons such as anthrax, plague and smallpox have been weaponized, and that massive strategic attacks producing enormous casualties — essentially use of biological weapons of mass destruction — would be possible. Yet lethal biological weapons could also be used on a smaller scale for tactical purposes. Non-military use of lethal agents could also be undertaken on a range of scales by terrorists. Furthermore, non-lethal biological agents could be used as incapacitants in different types of operations.

In short, when thinking about biological warfare and the potential impact of new technology, we have to keep in mind that we are not just dealing with one particular type of weapon and how it might be changed. We are dealing with many different kinds of potential weapon systems, many different ways they could be used, and, as we shall see, many different ways in which they could perhaps be modified. Biological warfare could have a multiplicity of future trajectories.

The impact of new technology

It would be a profound mistake to see genomics as simply a scientific revolution. It will open up many new civil technological possibilities and form the basis of major industrial investment and growth in the coming decades.[17] Indeed, Jeremy Rifkin has argued that the genomics revolution is at the heart of a linked set of developments which will transform human life:[18]

> "The Biotech century brings with it a new resource base, a new set of transforming technologies, new forms of commercial protection to spur commerce, a global trading market, … an emerging eugenics science, a new supporting sociology, a new communications tool … and a new cosmological narrative to accompany the journey …".

It is not necessary to accept the whole of this argument to see that massive reorganizations are taking place in the pharmaceutical and chemical industries to take advantage of the new opportunities for medical drug discovery and profit.[19] In short, the economic opportunities opened up by the new science are likely to ensure that there is ample money available for new technological innovations to be exploited and developed in civil industry. Given the dual-use (civil and military) nature of such technology, there will necessarily be many ways in which biological agents and their products, resulting from civil developments, can be manipulated for military purposes.

What many people understand by genomics at the present time is concerned with simply the structure of the human genome and that of other organisms. In reality, for the biologist, understanding the structure of the genome, though useful and interesting, is but the beginning of the story. The real aim is to have a complete understanding of how the structure works — that is, to have an understanding of *functional* genomics. As one of the scientists involved in the Human Genome Project argued "… the Human Genome Project is best understood as the twentieth century's version of the discovery and consolidation of the periodic table …".[20] (Towards the end of the nineteenth century, chemists grasped that it was possible to systematically enumerate all the elements and arrange them in an array in order to show their relationships and, more importantly, their properties and chemical behaviour.) He went on to suggest that "The Human Genome Project aims to produce biology's periodic table — not 100 elements, but 100,000 genes … a tree structure depicting ancestral and functional affinities among the human genes…".

Beyond that, he suggested, there would be a range of new goals. For example:

- systematic identification of all common variants in human genes;
- simultaneous monitoring of the expression of all genes;
- genetic tools for manipulating cell circuitry;
- monitoring the level and modification state of all proteins;
- systematic catalogues of protein interactions; and
- identification of all basic protein shapes.

Thus *functional* genomics will follow on from *structural* genomics and will have the initial aim of understanding the mechanistic details of cellular functioning and how the information encoded in the DNA determines the properties of the organism. This understanding will then allow manipulation for particular human objectives.

One aspect of this scientific and technological revolution very difficult for those of us living through it to grasp is the sheer rate of change. This results both from the opportunities that arise within genomics itself but also from its interaction in complex ways with other scientific and technological developments. Clearly, for example, the revolution in computing and information technology has provided tools essential to handle the vast amounts of information on DNA sequences and protein structures generated and used in the genomics revolution. However, genomics also affects other scientific areas. Within neuroscience, for example, over the last decade there has been an explosion of knowledge about the receptor systems on nerve cells that are of critical importance in receiving the chemical transmitter substances released by other nerve cells. One major annual review stated in 1999[21] "… Looking back, it is apparent that the past decade has brought an enormous increase in knowledge about the pharmacology and structural biology of receptors …". In the first edition of the review in 1990 there were thirty pages of data and sequence information on 25% of the receptors catalogued. Less than a decade later, "… 106 pages are required to accommodate current information on approximately 50 receptor … classes, for which structural information is present for over 90% …".

It is clear that this level of structural information has only become available because of the application of genomic techniques in neurobiology. It is also clear that "Along with the advent of cloning and expression techniques has come the ability to manipulate gene expression in vivo, which represents perhaps the most powerful method to analyse [receptor] function to date …".[22]

Once a gene has been cloned, it is thus possible to delete it from the genome, or from specific tissues, or to change the level of its expression and then study the consequences. By such means great strides are being made in our understanding, for instance, of learning and memory. But of course these same receptors are potential targets of novel bioweapons, made possible by the same technologies and knowledge that support the rapid advances in biomedical sciences.

New biological weapons

The foregoing is the context against which we have to assess the possibilities for new biological and toxin weapons. The United States report, to which reference was made earlier, suggested that the following trends could be of importance:

> "Genetically engineered vectors in the form of modified infectious organisms will be increasingly employed as tools in medicine and the techniques will become more widely available.
>
> Strides will be made in understanding of infectious disease mechanisms and in microbial genetics that are responsible for disease processes.
>
> An increased understanding of the human immune system function and disease mechanisms will shed light on the circumstances that cause individual susceptibility to infectious disease.
>
> Vaccines and antidotes will be improved over the long term, perhaps to the point where classical biological warfare agents will offer less utility as a means of causing casualties."[23]

The last point on this listing, though hopeful from the viewpoint of the potential defence, would also form part of the incentive for a proliferator to consider novel kinds of biological weaponry.

This listing suggests many ways in which new weapons might be developed. It is not difficult to imagine how, for example, as understanding of the immune system develops, and the ability to better redesign proteins comes about, highly specific weapons could become possible to attack the immune system in various ways. For instance, rather than deliberately infecting a target population with a single disease, a biological aggressor could use a toxin to cripple the immune system, and nature would insure that opportunistic infections of many different kinds ensued. Or a novel toxin agent could derange the immune system so that it becomes directly pathogenic itself, causing debility or death through its malfunctioning. Should these strategies seem fanciful, it is worth remembering that one of the classical agents, staphylococcal enterotoxin B (SEB), exerts its incapacitating effects in part via specific effects on the immune system (although this was not understood at the time this toxin was weaponized by the United States). Physiological systems other than the immune system could equally well be targets for such specific attack.

Novel toxins weapons could be normal proteins involved in immune system modulation, discovered through genomic studies, that are toxic due to their unnaturally high concentration, their presence in tissues from which they are normally absent, or the presence in adult tissues of regulatory proteins normally expressed in a specific developmental stage. Alternatively, such toxins could be genetically engineered by combining parts of different proteins, since it is now known that many proteins are composed of several functional domains. For instance, the immunomodulatory domain of a normal regulatory protein could be combined with a domain that targets the protein to a specific tissue (the brain, for example), thus leading to effects that would never be exerted by the normal protein.

Development of novel protein toxins is not the only application of bioinformatics to bioweapon development. The ability to recognize the genes for different classes of protein (e.g. ion channels, surface receptors, etc.) in genomic sequences, and to then predict their three-dimensional shape and to infer their function from comparative genomics and proteomics, will shortly lead to a massive increase in our understanding of the ways that the physiology of cells is modulated by external signals. This will in turn allow the rational design of small molecules that bind to such surface receptors and alter their function in predictable ways. Such "designer" chemical weapons could be immensely potent, easy to manufacture and stable. And perhaps most

"Designer" chemical weapons could be immensely potent, easy to manufacture and stable. And perhaps most worrisome, large numbers of such agents will be developed in the course of the peaceful study of cell functioning, and as therapeutic agents.

worrisome, large numbers of such agents will be developed in the course of the peaceful study of cell functioning, and as therapeutic agents. Thus the revolution in biology and medicine, on the brink of which we are now poised, will also open up an immense range of new technologies for novel biological, toxin and chemical weapons.

Manipulation of toxins and bioregulatory chemicals was in fact the subject of a special report produced by the Canadian government for the States Parties to the 1991 Third Review Conference of the BTWC.[24] This illustrates very clearly that even a decade ago (ancient history in the context of the pace of scientific and technological advance) there were considerable concerns about how such agents might be developed and used, particularly the possibility of new forms of non-lethal weaponry.[25]

It is also, unfortunately, possible to imagine new biological weapons with specificity for particular subpopulations of organisms. These kinds of novel bioweapon developed from the application of genomics and proteomics only affect individuals with the particular target protein or structure against which they were designed. In many cases the target would be nearly universal within the species. However, in other cases there might be alternative structures, and only individuals with a particular form of the structure would be vulnerable to the toxic effects of the new weapon. This possibility has led to speculation about "ethnic weapons"—ones that would affect one ethnic or racial group while leaving others untouched. However, among humans the amount of intragroup genetic variation is generally greater than the intergroup variation,[26] making such weapons almost certainly highly non-specific. Absent a lucky accident, it is unlikely that an appropriate target for an effective "ethnic weapon" could be found.

Especially in the developed world, but increasingly in the developing world as well, agriculture relies on the monoculture of genetically identical plants, or the intensive husbandry of highly inbred animals. This makes crop plants and domestic food animals ideal targets for such genotype-specific weapons.

Unfortunately, the same is not true for most of the staple crops and domestic animals on which humans depend for food. Especially in the developed world, but increasingly in the developing world as well, agriculture relies on the monoculture of genetically identical plants, or the intensive husbandry of highly inbred animals. This makes crop plants and domestic food animals ideal targets for such genotype-specific weapons. This vulnerability is further enhanced by the high density and huge numbers of individual plants and animals often involved—the ideal conditions for rapid and effective contagion.

The future

A recent multi-author review of such possibilities ended with the editor's opinion that:[27]

> "In the race between the defence and the offence, a race so often seen before in military history, the defence 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 into place mechanisms to meet the threat of advanced bioweaponry …".

It is essential that this opportunity be grasped and that a Protocol designed to strengthen the BTWC be completed in time for the 2001 Review Conference. To fail in that endeavour is to leave the world open to some very frightening possibilities in the early decades of this new century.

Notes

[1] R. Porter, *The Greatest Benefit to Mankind: A Medical History of Humanity from Antiquity to the Present*, London, HarperCollins, 1997.
[2] M. Wheelis, Biological Sabotage in World War I, in E. Geissler and J.E. van Courtland Moon, eds., *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945,* Stockholm, SIPRI, 1999.
[3] Geissler and van Courtland Moon, eds., ibid.
[4] S. Harris, The Japanese biological warfare programme: an overview, in Geissler and van Courtland Moon, op. cit.
[5] B. Bernstein, The birth of the US biological-warfare program, *Scientific American*, June 1987, pp. 116–21; G.B. Carter, Biological warfare and biological defence in the United Kingdom 1940–1979, *RUSI Journal,* no. 137, 1992, pp. 67–74; K. Alibek and S. Handelman, *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*, New York, Random House, 1999.
[6] R.A. Zilinskas, Iraq's biological weapons: The past as future? *JAMA,* no. 278, 1997, pp. 418–24.
[7] Canadian Security Intelligence Service, *Perspectives — Biological Weapons Proliferation*, report no. 2000/5, 2000, 4pp. Available at www. csis-scrs.gc.ca/eng/miscdocs/200005e.html
[8] Alibek and Handelman, op. cit., pp. 258–62.
[9] Quoted in L. Beaton, *The Reform of Power: A Proposal for an International Security System,* London, Chatto and Windus, 1972.
[10] M.R. Dando, *Biological Warfare in the 21st Century: Biotechnology and the Proliferation of Biological Weapon*s, London, Brassey's, 1994.
[11] Second Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, *Final Document,* BWC/CONF.II/13, Geneva, United Nations, 1986.
[12] Third Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, *Final Document,* BWC/CONF.III/23, Geneva, United Nations, 1991.
[13] Fourth Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (biological) and Toxin Weapons and on their Destruction, *Final Document,* BWC/CONF.IV/9, Geneva, United Nations, 1996.
[14] W. Cohen, *Proliferation: Threat and Response,* Washington, D.C., Department of Defence, 1997.
[15] P. Rogers, S. Whitby and M.R. Dando, Biological Warfare Against Crops, *Scientific American*, June 1999, pp. 62–67.
[16] M.L. Wheelis, *The threat of agricultural biowarfare and bioterrorism: an analytical framework*, (in preparation).
[17] M. Fransmen et al., eds., *The Biotechnology Revolution,* London, Blackwell, 1995.
[18] J. Rifkin, *The Biotech Century: The Coming Age of Genetic Commerce*, London, Victor Gollancz, 1998.
[19] J. Drews, Drug discovery: a historical perspective, *Science*, no. 287, 2000, pp. 1960–64.
[20] E.S. Lander, The new genomics: Global views of biology, *Science*, no. 274, 1996, pp. 536–39.
[21] S.P.H. Alexander and J.A. Peters, *1999 Receptor and Ion Channel Nomenclature Supplement. Trends in Pharmacological Science,* Cambridge, Elsevier Science Ltd., 1999.
[22] D.K. Rohrer and B.K. Kobilka, G Protein-coupled receptors: Functional and mechanistic insights through altered gene expression, *Physiological Reviews*, no. 78, 1998, pp. 35–52.
[23] See note 9
[24] Canada, *Novel Toxins and Bioregulators: The Emerging Scientific and Technological Issues Relating to Verification and the Biological and Toxin Weapons Convention,* Ottawa, External Affairs and International Trade Department, 1991.
[25] M.R. Dando, *A New Form of Warfare: The Rise of Non-Lethal Weapons,* London, Brassey's, 1996.
[26] K. Owens and M.-C. King, Genomic views of human history, *Science,* no. 286, 2000, pp. 451–53.
[27] R.A. Zilinskas, *Biological Warfare: Modern Offense and Defense,* Boulder, Lynne Rienner, 2000.