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REVIEW PAPER

Challenge of Biotechnology

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ABSTRACT

The unravelling of the human genetic code whose first draft was announced in June 2000 has rightly been hailed as a momentous achievement, opening the book of life, certain to be the dominant technology of the 21st century, which will inform all about medicine and biology, and lead us to a total understanding of life. Simultaneously, concerns have been expressed about the implications of this work. In the past, major new technologies have been used intensively for hostile purposes. What is the challenge that biotechnology poses in this regard?

This review paper looks at the enormous changes in civil society that the genomics revolution could bring. Against this background, the growing concerns about its potential misuses have been reviewed. The strengths and weaknesses of the Biological and Toxin Weapons Convention (BTWC) are then touched upon. The BTWC presently lacks an adequate verification mechanism. Although biotechnology has been used by human beings since prehistoric times (eg, making of bread, cheese, wines), its scientific understanding came only in the latter part of the 19th century. The decisive turning point in the field came in the 1970s with the advent of genetic engineering. In the military context, the classical agents like anthrax and *botulinum* toxin remain the threat today. Although the current level of sophistication for many biological agents is low, there is enormous potential for making more sophisticated weapons. It might be possible to specifically target the genetic makeup of different ethnic groups. The limited varieties of staple crops and the limited strains of modern animals make agriculture particularly open to attack. Another serious possibility is the impact of genomics in neuroscience. With a better understanding of cellular receptor systems and bioregulators, it is not inconceivable that new means would be evolved for disturbing the functions of the nervous system. The genomics revolution can be used for peaceful purposes. However, a key requirement is the political will to bring into force a Protocol to strengthen the BTWC.

Keywords: Human genome code, biotechnology, genetic engineering, biological and toxin weapons convention

1. INTRODUCTION

On 27th June 2000, the world's media struggled to find words adequate to the momentous announcement of the first draft of the human genetic code. *The Times*[1] in London, for example, carried the headline 'Opening the book of life'. As one of the scientists involved in the work was quoted as saying[2] "Over the decades and centuries to come, this sequence will inform all of medicine, all of biology, and will lead us to a total understanding of not only human beings but all of life".

Whilst almost all of the commentary was favourable, there were concerns expressed about the implications of this work. The *International Herald Tribune*, for example, noted that[3] '...but the question of how to regulate this powerful information is likely to challenge society for years to come, scientists and politicians said....'. The concerns expressed were clearly with regard to the regulation of the efforts that would be made in civil society to provide tangible–even if sometimes problematic–benefits to society.

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A different, darker concern had been expressed by Prof Mathew Meselson of Harvard in the June 2000 edition of the *Chemical and Biological Weapons Convention Bulletin*[4]. He argued that in the past major new technologies had been used intensively for hostile as well as peaceful purposes. He then asked "must this also happen with biotechnology, certain to be a dominant technology of the twenty-first century". This then is the challenge of biotechnology today. Can we ensure that the new revolution in genomics is applied for the benefit of human beings around the world in medicine and agriculture, whilst ensuring that it is also not used to open up new avenues of exploitation in offensive biological weapons programme?

The paper first describes the enormous changes in civil society that the genomics revolution could bring. Against that background, the growing concerns that have been expressed about the potential malign misuses of biotechnology at successive five-year review conferences of the BTWC in 1986, 1991 and 1996 are reviewed . This is followed by a brief consideration of what States Parties to the BTWC at the next review conference in 2001 could consider in relation to the latest advances in genomics.

The progress made to strengthen the BTWC, which presently lacks an adequate verification mechanism, in the negotiations of the ad hoc group under the chairmanship of Ambassador Tibor Toth (of Hungary) in Geneva since 1995 is examined. It is finally argued that it is possible to achieve early agreement on an effective Protocol to the BTWC which has efficient compliance measures and that also satisfies the requirements of State Parties that it makes a contribution to improved international cooperation in biotechnology. With the malign misuse of biotechnology clearly prohibited through the Convention and its Protocol, one looks forward to an era of cooperation and development across a wide range of biotechnology, but in particular, to the defeat of the emerging and re-emerging diseases that are causing so much misery today.

2. CIVIL BIOTECHNOLOGY

Biotechnology has been used by human beings since prehistoric times in the making of bread, cheese, alcoholic beverages and so on[5]. However, such applications were not based upon a scientific understanding of the technology until the latter part of the 19th century and the advent of microbiology. Specific manipulation of microorganisms then became increasingly possible, first under non-sterile conditions, and then during the 1940s, under sterile conditions. The decisive breakthrough, however, can now be seen to have taken place in the 1970s with the advent of genetic engineering–the ability to move genes between different species and to have these transferred genes function to produce their proteins in the new organism. Since the early 1980s, there have been a series of therapeutic proteins, such as human growth hormone releasing factor, which after being successfully produced by bacteria has come in the market.

The modern world has been shaped by a series of scientific revolutions which have been applied in industrial technologies. The obvious ongoing example of such a revolution is information technology and computing. Well before the production of the draft human genetic sequence, it had been argued that the new advances in biotechnology, opened up by genetic engineering, would be at the core of the industrial and economic activity in the early decades of the 21st century. Moreover, whilst the initial impact was thought to be in health care, its applications in agriculture and other economic sectors were also predicted[6]. The potential impact of the revolution was, perhaps, most eloquently and dramatically set out by Jeremy Rifkin. In his view, we are, in 2000, in the biotechnology century and this brings with it[7] "... a new resource base, a new set of transforming technologies, new forms of commercial protection to spur commerce, a global trading market to reseed the earth with an artificial second genesis...". Moreover, in line with the impact of previous revolutions, he could foresee widespread social consequences when he continued predicting it as "...an emerging eugenic science, a new supporting sociology, a new communications tool to organise and manage economic activity at the genetic level, and a new cosmological narrative to accompany the journey...". It is not necessary to agree *in toto* with Rifkin's analysis to see that there will be major consequences.

The 27th June 2000 *Financial Times* carried a long article by its pharmaceutical industry correspondent titled 'Standby for a gene–rush', and, in part, discussed the merger of Glaxo Wellcome and Smithkline Beecham. The summary concluded: 'In other words, the biggest pharmaceutical merger of all time was the direct result of the genetic Klondike. Glaxo Smithkline is now preparing to throw a staggering $4 bn a year at pricing golden nuggets from the genome'.

The cost of effective research and development is forcing a wave of mergers in this high-tech industry and such levels of investment in research and development cannot fail to produce significant results and subsequent consequences for our societies. Thus there can be no doubt that there will be beneficial outcomes of various kinds–perhaps cures for Parkinsons and Alzheimer's diseases in older people, for inborn-errors of metabolism in children, and cancer in the middle-aged. But there will also be enormous ethical questions brought about by increasing powers to interfere with nature.

3. MILITARY ISSUES

The BTWC entered into force in 1975. A positive result from the Convention is that it has been subject to review of its effectiveness by the State Parties (now numbering over 140) at five-year intervals. Prior to such reviews some State Parties have contributed to background documents on scientific and technical developments which inform the review process, and some of the developments identified in these documents are incorporated into the final consensus declarations at the end of the reviews. The background documents and final declaration at the first review conference of the BTWC in 1980 were relatively sanguine about the nature and impact of the new developments in biology. By the time of the second review conference in 1986, and particularly in the third review conference in 1991, following the Gulf war, opinions had altered sharply. UK's view[9] in 1991 was, 'The 1986 paper felt there was by then an increased potential for the large-scale production of biological warfare agents with enhanced military utility. The current UK's view is that worldwide the increase in knowledge of many of the pathogenic species of microorganisms, and knowledge of toxins and other biological agents, and the continuing pace of development in civil biotechnology areas, have further increased the possibilities for production and hostile use of biological agents, whether naturally occurring or not'.

This was reflected into the final declaration of the third review conference[9] which stated, 'The Conference, conscious of apprehensions arising from relevant scientific and technological developments, *inter alia*, in fields of microbiology, genetic engineering, and biotechnology, and the possibilities of their use for purposes inconsistent with the objectives and the provisions of the Convention, reaffirms that the undertaking given by the State Parties in article I applies to all such developments'.

A broader identification of the relevant scientific and technological developments was made in the final declaration of the fourth review conference[10] in 1996 which stated, 'The Conference, conscious of apprehensions arising from relevant scientific and technological developments, *inter alia*, in fields of microbiology, biotechnology, molecular biology, genetic engineering, and any applications 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 State Parties in article I applies to all such developments'.

Article I sets out the complete prohibition of biological agents in the BTWC and the extension of the final declaration to include molecular biology and to applications resulting from genome studies clearly was a recognition of the dangers that could arise as the revolution in biology gathers pace.

The 'classical' agents, like anthrax and *botulinum* toxin, which were thoroughly tested in major state programme in the last century remain the main threat today[11]. A technical annexure to the US Department of Defence 1997 report, 'Counterproliferation: Threat and response' gives an idea of the range of novel biological warfare

threats that might now be encountered... . The report[12] suggested that in general terms: '...The current level of sophistication for many biological agents is low, but there is enormous potential–based on advances in modern molecular biology, fermentation and drug delivery technology–for making more sophisticated weapons....'.

Specifically, it suggested the following potential types of novel biological agents that could be produced:

(a) Benign microorganisms, genetically altered to produce a toxin, venom, or bioregulator

(b) Microorganisms resistant to antibodies, standard vaccines and therapeutics

(c) Microorganisms with enhanced aerosol and environmental stability

(d) Immunologically altered microorganisms able to defeat standard identification, detection and diagnostic methods.

The report also pointed to the possibility that combinations of the above types with improved delivery systems might also be possible.

It is important to recognise that as the genomics revolution proceeds, there may be many more ways–some dramatically different–in which malign misuse might take place. It has been suggested, for example, that it might be possible to target the genetic makeup of different ethnic groups. Given the prevalence in the last century of genocidal wars, that would indeed be a terrifying prospect. The suggestion that such weapons might be possible is based on the view that progress in understanding the structure and function of the human genome, the different genetics of various human groups and in gene therapy could provide the necessary means. Examination (in detail) of work in these areas does not lead to the conclusion that such ethnic weapons would be impossible[13].

Whatever the possibility of such ethnic attacks on human beings, it is quite clear that the limited number of varieties of staple crops and the limited strains and intensity of modern animal husbandry lays agriculture particularly open to attack. Fungal pathogens of crops and viral pathogens of animals could be used to inflict massive economic damage even against developed countries, and effective use of such pathogens could well be within the competence of terrorist groups[14].

Another possible new means of misuse arises from the impact of genomics on neuroscience. The key to understanding how neurotransmitters, bioregulators and hormones work is to understand the cellular receptor systems which are specifically designed to detect such critical signal substances in low concentrations. These receptors are proteins rather directly specified by different genes[15]. Instead of going through the laborious process of trying to find which receptor might be affected by a particular signal chemical, it is now possible to look for new receptors by examining computer databases of DNA sequences to discover any that looks close to those specifying known receptors. The new approach has brought a vast increase in our knowledge of the human nervous system over the last decade and this could obviously lead to, for example, major advances in the treatment of mental illness. However, it could also allow for the design of new means of distorting the functions of the nervous system, particularly because of the developing understanding of how to design proteins and small inorganic mimics of peptide (small chains of amino acids not large enough to be classified as proteins) bioregulators[16]. As is well known, small changes in the structure of such bioregulators can cause large changes in their specificity and effects.

3.1 Preventing Misuse of the New Biology

The use of biological weapons was banned by the 1925 Geneva Protocol and this prohibition was reinforced by the 1975 BTWC in article I which stated, in part: 'Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

(i) Microbial or other biological agents, or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes...'.

Unfortunately, this all-embracing prohibition is not yet backed up by the same kind of effective verification system agreed in the later Chemical Weapons Convention (CWC) and which is now being so successfully implemented by the international community.

Attempts have been made in successive review conferences of the BTWC both to strengthen the weak verification provisions originally agreed in articles V and VI through the elaboration of consultation procedures and the addition of a series of confidence building measures (CBMs–annual data exchanges), but neither of these routes have been successful in improving transparency and trust. A process was begun after the third review conference in 1991 which has led to the production of a practically complete text of a Protocol to the BTWC[17]. Whilst differences remain to be resolved on some key issues, there is a good chance that the negotiations will be completed prior to the fifth review conference of the BTWC in 2001.

The mandate given to the ad hoc group negotiating the BTWC Protocol in Geneva was 'to consider appropriate measures, including possible verification measures, and draft proposals to strengthen the Convention, to be included, as appropriate, in a legally binding instrument'. This, unlike the previous agreements of politically binding CBMs, requires negotiation of an instrument which is legally binding like the BTWC itself and the CWC. As the BTWC Protocol has as its goal, like the CWC, the provision and implementation of a verification system appropriate for a worldwide industry capable of both civil and military use, the architecture of the verification system could be expected to be equally effective if it is designed in the same manner[18].

As with the CWC, each State Party will be responsible, assuming the Protocol is agreed, for ensuring that no prohibited activity takes place on its territory. Again, as with the CWC, an international verification system will be targeted at the most relevant facilities and activities to provide transparency and confidence to all State Parties. Thus in both the CWC and the BTWC Protocols, trust does not come about because everything is verified. Given the range of chemicals and microorganisms that could be misused, such complete coverage is impossible, but that does not mean that an effective and adequate verification cannot be achieved.

The regime that would be necessary for an effective BTWC Protocol would not need to include the provisions within the CWC relating to the declaration and destruction of the huge stocks of dangerous chemical weapons and agents accumulated during the last century or of chemical weapon production facilities. The BTWC Protocol would have provisions, similar to those in the CWC, relating to the monitoring of chemical industry[18] involving

(a) Mandatory declarations of the most relevant facilities and activities

(b) A system of visits to ensure the consistency of these declarations (so that they would not be just equivalent to the failed CBMs)

(c) The possibility of challenge investigations of well-founded concerns over non-compliance.

All of this regime would be implemented by a professional international organisation. Most analyses suggest that such an organisation would only be about half-of-the-size of the OPCW because there is no comparable requirement to monitor the destruction of chemical weapons and chemical weapon production facilities in the BTWC. Objections to the visits incorporated into this system have been raised by the Trade Association for Pharmaceutical Industry in the US (and other countries' pharmaceutical industry trade associations have taken to echoing such objections)[19]. However, many State Parties have added to their experience of CWC visits by carrying out numerous practice BTWC Protocol visits and have argued that the pharmaceutical industry's concern over the possible loss of commercial proprietary information is misplaced. The number of visits that any one company will receive will be very small, the mandate for the visit will be tightly

drawn and managed across techniques that can be applied as necessary and when required.

Whilst negotiation of an effective BTWC Protocol is not yet complete, a successful outcome is looking increasingly probable after five years of complex negotiation. Entry into force of the BTWC Protocol alone cannot guarantee that the misuse of the new biotechnology will be prevented, but it is an essential centrepiece for an effective international response to this very dangerous threat. The potential ready availability, at a time of rapid technological change of a weapon known to have an equivalent lethality to nuclear weapons, cannot be conducive to international peace and security. Yet it can be reasonably argued that a strengthened BTWC and Protocol backed up by a range of other measures could largely remove this problem from the international agenda[20].

3.2 International Cooperation for Development

The BTWC is not solely concerned with the prohibition of misuse of biology. Article X of the Convention states, in part, that the State Parties: '...undertake to facilitate, and have the right to participate, in the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. Parties to the Convention in a position to do so shall also cooperate in contributing individually or together with other states or international organisations to the further development and application of scientific discoveries in the field of bacteriology (biology) for prevention of disease, or for other peaceful purposes'.

The Protocol mandate to strengthen the effectiveness and improve the implementation of the Convention also has specific language that requires the ad hoc group to consider *inter alia* specific measures designed to ensure effective and full implementation of article X. Such specific measures to ensure full and effective implementation of article X of the Convention are addressed in the Protocol article VII 'Scientific and technological exchange for peaceful purposes and technical cooperation'. The current text is largely free of square brackets indicating that there is now widespread agreement on this part of the Protocol. Necessarily, there are provisions in the article for assistance with the implementation of the Protocol, for example, with regard to the establishment of national authorities and the preparation of the declarations required under the Protocol. Other aspects of the article deal with subjects in which there might be scientific and technological exchanges. Of particular interest here is section F 'Scientific and technological exchange for Protocol purposes and technical cooperation', where a number of areas are identified in which the future BTWC organisation might be involved in cooperative relationships in order to

- 'Derive the greatest possible synergy, and benefits from: (i) The collection and dissemination of information on the peaceful uses of biological agents and toxins, (ii) sharing information on environmental release of genetically modified organisms, (iii) current good manufacturing produce (GMP), good laboratory produce (GLP), biological containment and other biosafety regulations and produces, (iv) facilitation of access to databases containing information on the peaceful uses of bacteriological agents and toxins, biosafety, and results of scientific research in the life sciences in areas of particular relevance to the Convention, (v) collection of information on diagnosis, surveillance, detection, treatment and prevention of diseases caused by biological agents or toxins, in particular, infectious diseases, and (vi) regulations governing the handling, transportation, use and release of bacteriological (biological) agents and toxins...'.

Clearly, cooperation in these areas brings benefits, both nationally and internationally, to States Parties to the Protocol. For example, the introduction of GMP and GLP brings national benefits in the assurance of safety and reproducibility of pharmaceuticals, facilitates the opening of international markets for such pharmaceuticals, and also brings international assurance that production establishments are producing licensed products and are being

regularly inspected. Similarly, effective regulations on handling, storage, use and release of biological agents and toxins bring assurance, nationally and internationally, to neighbouring states that dangerous pathogens are being handled and used safely, and also bring assurance internationally that dangerous pathogens are being controlled within the particular State[21]. Likewise, international cooperation with regard to the diagnosis, surveillance, detection, treatment and prevention of diseases caused by biological agents and, in particular, infectious diseases, brings confidence, both nationally and internationally, that outbreaks of disease will be recognised, reported and steps taken to counter the outbreak, bringing significant benefits, both nationally and internationally, to adjacent states. After all, it is widely recognised that infectious diseases–and biological agents–know no frontiers. In this way, the Protocol to strengthen the BTWC can make a significant contribution to the wider cooperation on biotechnology which will be required for this technology to make a major contribution to the wellbeing of all of the world's population within a peacefully orientated economy[22].

4. CONCLUSION

It is clear that the challenge of this newest and most profound of the series of scientific revolutions which have shaped, and are shaping, the modern world, can be met. The genomics revolution can be used for peaceful purposes. However, a key requirement is that the political will to complete and bring into force soon a Protocol to strengthen the BTWC must be generated through a much wider appreciation of the potential dangers from the use of the advances in biotechnology fueling a new biological arms race, and of the benefits to be derived from a Protocol with universal adherence. The clear prohibition of the malign misuse of biotechnology through the Convention and its Protocol will mean that States Parties to the Convention and the Protocol can look forward to an era of cooperation and development across a very wide range of biotechnology, enabling its benefits to be harnessed in the defeat of the emerging and re-emerging diseases that are causing so much misery today.

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