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Dual use issues in research – A subject of increasing concern?

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ABSTRACT

Dual use is defined as the application of materials, knowledge or technologies for military or terrorist purposes, as well as for good. In biological science, it is considered to be a growing threat as the genetics of pathogenicity traits and toxins are becoming on one hand elucidated in a detail that was not anticipated 20 years ago and on the other hand technological advances in genetic engineering and synthetic biology are continually enabling easier access to these technologies. On a theoretical and policy level, much has happened over the past decade, but translating these policies and concepts to operational level awareness and robust processes requires more attention. Where the research is conducted, scientists have to make ethical judgements and account for their data sharing and publication policies. How can we ensure the requirement for dual use review is taken on board, but is not skewing research detrimentally and imposing a disproportionate burden?

1. What is dual use?

Most scientists working in the field of biology are aware of the history of biological weapons. Their development was explored by numerous countries during the first half of the 20th Century – and they were deployed in several conflicts [1], even after they were banned under the Geneva Protocol in 1925. After World War II, much of the activity in this area continued, being led by national governments (also termed "States Parties"), in response to concerns over development by other nations, peaking during the Cold War era. A spectrum of human, animal and plant pathogens and toxins were developed, weaponised and stored ready for field deployment. The United States and the former Soviet Union were the major players in this arena, though other countries with significant programmes included the UK, France and Canada [1]. The majority of these programmes were officially terminated by the early 1970s, though work in the Soviet Union on delivery mechanisms continued up until at least 1992 [1]. Other notable exceptions to this termination included an Iraqi programme which carried on until 1991, in response to perceived threats posed by Israel and Iran. A programme in South Africa continued until 1995, which investigated the use of poisons for the assassination of "enemies of the state" [2].

The ultimate cessation of such programmes by countries can largely be credited to the establishment of the Biologic and Toxin Weapons Convention (BTWC) in 1972, which built on the earlier Geneva Convention and, when enacted in 1975, became the first multilateral disarmament treaty to ban an entire category of weapons.

Over the same time, numerous activities in biological and toxin weapons of "non-State Parties" have also been observed – individuals or groups not directly affiliated to a particular nation state. These include the release of Salmonella by the Rajneeshee cult in Oregon, US in 1984 and the release of anthrax in 2001, also in the US [3]. Up until now, these attacks have been based on naturally occurring pathogens and toxins.

The two key provisions of the BTWC concern: (a) a ban on the development, production, stockpiling or otherwise acquiring or retaining microbial or other biological agents or toxins in any quantity or for any purpose other than for prophylactic, protective or peaceful purposes, and (b) weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict. The responsibility to implement these high level overarching goals is cascaded down from governments to individual scientists.

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2. An ethical code for scientists?

The idea of an ethical Archimedian Oath for scientists and engineers, similar to the Hippocratic Oath taken by the medical profession, was established in 1990 [4] and has been adopted by a number of universities since. It can be summarised as a commitment to work for the good of mankind, for human rights and the environment; to support the development of weaker countries, to be alert to technical, social and ecological aspects of the work and to practice and communicate science with intellectual honesty, conscience and dignity. The overarching ethic of "do no harm" also includes a commitment to be mindful of any military application of the work and to be alert to any activity, information or technology we develop, which might aid others to do so.

The increasing ability of scientists to manipulate the genomes of pathogens and their hosts has led to a new wave of scrutiny over this subject, with ever-increasing requirement to fully assess what we do, why we do it and how we communicate it.

3. Why should scientists be concerned?

With the advent of ever-more-sophisticated methods for altering pathogens at the molecular level, concern is growing over the potential misuse to which these technologies might be put. This was first highlighted by the 2003 "Fink Report" [1] an accordingly, the Sixth Review of the BTWC 2006 agreed to "*the prohibition of all naturally or artificially created or altered microbial or other biological agents and toxins, as well as their components, regardless of their origin and method of production and whether they affect humans, animals or plants, of types and in quantities that have no justification for peaceful purposes*".

Given that most, if not all technologies ever developed for peaceful applications in the past have ultimately also found hostile and/or military applications, the ability to distinguish peaceful purposes from offensive ones, at concept, can be difficult. The vast majority of applications are beneficial, yet it is indisputable that the same research results can also inform malicious applications. This potential malicious use creates the "dual use dilemma" which imposes an ethical responsibility on researchers, institutes, funders and publishers to ensure misuse is avoided. Researchers are the most important part of that equation as they can assess the real potential of their technology with the greatest level of detail. The development of an original list of seven "Experiments of Concern" [1,5] has assisted in the identification of certain classes of work which would require particular scrutiny. These primarily focus on areas of R&D, which might be pursed with the laudable purpose of more informed risk assessment for pandemic potential, understanding the basis of pathogenesis, improved preparedness, better vaccines or diagnostics, but which might confer an altered capability on an agent to remain infectious longer, infect or spread differently among hosts, or evade prophylactic, therapeutic or detection methods. These experiments of concern, originally seven [1] and now nine in number [6,7] are those which would:

1. Demonstrate how to render a vaccine ineffective.
2. Confer resistance to therapeutically useful antibiotics or antiviral agents.
3. Enhance the virulence of a pathogen or render a non-pathogen virulent.
4. Increase transmissibility of a pathogen.
5. Alter the host range of a pathogen.
6. Enable evasion of diagnostic/detection modalities.
7. Enable the weaponisation of a biological agent or toxin.
8. Enhance the susceptibility of a host population to a pathogen or toxin.
9. Generate or reconstitute certain eradicated or extinct pathogens or toxins.

Of course, the two main risks are those posed by the engineered agent itself and the dissemination of the knowledge gained. The first risk may be fully mitigated by biosafety and biosecurity measures, whilst restricted or censored publication of information may mitigate the second risk, it does rather go against the principal scientific ethos of public dissemination of scientific findings.

Initially, dual use was focussed on established lists of microorganisms [8], assembled and maintained by the "Australia Group" [9] that were considered to pose a particular threat if introduced into human animal or plants, along with equipment to produce or weaponize such agents. The rapid advancement of biotechnology has enabled and continually reduced the hindrances to the artificial generation of hazardous microorganisms with artificially engineered properties. The dangers in knowledge transfer were initially seen in large scale production capability, but the technologies for synthetic biology and gene technology are so pervasive that scientists are facing a further dilemma; that is with whom they are sharing their everyday gene technology skills.

The concerns over unanticipated detrimental consequences of emerging technologies in DNA manipulation led American scientists in mid 1974 to call for a moratorium on such research [10]. This moratorium was globally adhered to until the Asilomar Conference on Recombinant DNA in 1975. A safety regime emerged, which matches categories of perceived risks to agreed safeguards. It is interesting to note that the main recommendations of this conference focussed almost exclusively on the management of potential biohazards of such work, with potential for bioweapons largely overlooked. This conference had been organised by molecular biologists who likely had little appreciation of the pathogenesis of *E. coli* and the strong attenuation of the strains they were using, as a consequence these recommendations were perhaps overly alarmist. Nevertheless, the Asilomar Conference can be credited with the establishment of the Recombinant DNA Advisory Committee within the US National Institutes for Health, with the purpose of promoting transparency and oversight of this developing technology, such that concerns are subject to considered ethical and safety consideration.

The game-changing example of unexpected outcome was the transgenic expression of mouse IL-4 in recombinant Vaccinia virus [11]. The group destroyed the materials, as the increased virulence was addressed in the local risk assessment and required additional containment under the regulations for contained use of genetically modified organisms (GMMOs) in the UK. The unintended effect was briefly mentioned in the publication, enough to warn alert readers, but without drawing any parallels to smallpox. This did not stop other groups from repeating the work and further exploring the concept in Ectromelia virus with the intent to subvert mouse fertility [12]. Despite and perhaps also because of the consequent controversy, other groups followed up on the work to explore the implications of Bembridge's work on the vaccine strain of smallpox and published more detailed studies on countermeasures [13]. This controversy exemplifies the dilemma between publishing and not publishing and the time lag for developing counter-measures. The first publication only mentioned the finding discretely, as one might expect if the intention is to only create awareness in the specialist community, which needs to know this to avoid a potentially dangerous release into wild rodent populations. This issue contributed to the post 9–11 debate and led to the term "Dual Use Research of Concern" (DURC) [5], which poses a threat to the health of humans, animals, or plants.

The dual use dilemma came again into sharp focus in 2011, when the publication of work on avian influenza H5N1 was called into question by the US National Institute for Health, who

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