Genetic engineering and biological weapons

New technologies, desires and threats from biological research

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Rapid developments in biotechnology, genetics and genomics are undoubtedly creating a variety of environmental, ethical, political and social challenges for advanced societies. But they also have severe implications for international peace and security because they open up tremendous avenues for the creation of new biological weapons. The genetically engineered 'superbug'—highly lethal and resistant to environmental influence or any medical treatment—is only a small part of this story. Much more alarming, from an arms-control perspective, are the possibilities of developing completely novel weapons on the basis of knowledge provided by biomedical research—developments that are already taking place. Such weapons, designed for new types of conflicts and warfare scenarios, secret operations or sabotage activities, are not mere science fiction, but are increasingly becoming a reality that we have to face. Here, we provide a systematic overview of the possible impact of biotechnology on the development of biological weapons.

The history of biological warfare is nearly as old as the history of warfare itself. In ancient times, warring parties poisoned wells or used arrowheads with natural toxins. Mongol invaders catapulted plague victims into besieged cities, probably causing the first great plague epidemic in Europe, and British settlers distributed smallpox-infected blankets to native Americans. Indeed, the insights into the nature of infectious diseases gained by Louis Pasteur and Robert Koch in the nineteenth century did not actually represent a great breakthrough in the use of infectious organisms as biological weapons. Similarly, the development of a bioweapon does not necessarily require genetic engineering—smallpox, plague and anthrax are deadly enough in their natural states. But the revolution in biotechnology, namely the new tools for analysing and specifically changing an organism's genetic material, has led to an increased risk of biowarfare due to several factors. First, the expansion of modern biotechnology in medical and pharmaceutical research and production has led to a worldwide availability of knowledge and facilities. Many countries and regions, where 30 years ago biotechnology merely meant brewing beer and baking bread, have established high-tech facilities for vaccine or single-cell-protein production that could be subverted for the production of biological weapons. Today, nearly all countries have the technological potential to produce large amounts of pathogenic microorganisms safely (Fig. 1). Second, classical biowarfare agents can be made much more efficiently than their natural counterparts, with even the simplest genetic techniques. Third, with modern biotechnology it becomes possible to create completely new biological weapons. And for technical and/or moral reasons, they might be more likely to be used than classical biowarfare agents. These possibilities have generated new military desires around the world, including within those countries that have publicly renounced biological weapons in the past. This paper deals predominantly with the last two factors, and with the use of real-life examples, we shall discuss the possibilities for such military abuse of biotechnology.

Fig. 1 | The US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, is the centre of the USA's defensive research on biological weapons. (© (2001) Jan van Aken/Sunshine Project.)

By using genetic engineering, biological researchers have already developed new weapons that are much more effective than their natural counterparts. Countless examples from the daily work of molecular biologists could be presented here, not least the introduction of antibiotic resistance into bacterial pathogens, which today is routine work in almost any microbiology laboratory. Indeed, many research projects in basic science show—sometimes unwillingly and unwittingly—how to overcome current scientific and technological limits in the military use of pathogenic agents. Furthermore, genetic engineering is not merely a theoretical possibility for future biowarfare: it has already been applied in past weapons programmes, particularly in the former Soviet Union. One example is the USSR's 'invisible anthrax', resulting from the introduction of an alien gene into *Bacillus anthracis* that altered its immunological properties (Pomerantsev *et al.*, 1997). Existing vaccines proved to be ineffective against this new genetically engineered strain.

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In debates about genetic engineering and biological weapons it is often stated that natural pathogens are sufficiently dangerous and deadly, and that genetic engineering is not necessary to turn them into more effective biological weapons. This is indeed true in that biological weapons can be used without genetic engineering—or, for that matter, without any scientific knowledge—as has been shown by their effective use in past centuries. In fact, genetic engineering does not necessarily have a central role in the early stages of a biowarfare programme. The development of reliable, effective biological weapons requires an intense and resource-demanding research programme that must, step by step, solve increasingly complex problems: the procurement of virulent strains of suitable agents, the mass production of the agents without loss of pathogenicity, and the development of an effective means of delivery. In particular, the third step is very demanding, and has rarely been accomplished, with the exception of the huge former biowarfare programmes in the USA (Fig. 2) and the USSR. Even Iraq, after several years of an active biowarfare programme, had developed only rudimentary methods of delivery. From this perspective, genetic engineering is a step taken relatively late in the development of biowarfare potential, which most probably will not be taken before the first, essential steps are solved. Indeed, we know only from the massive biowarfare programme in the former Soviet Union that pathogens have been genetically modified to increase their effectiveness as bioweapons, but there may have been other, so far undetected, attempts elsewhere.

By contrast, it must not be underestimated that hardly any natural pathogens are really well suited to being biowarfare agents from a military point of view. Such a bioweapon must fulfil a variety of demands: it needs to be produced in large amounts, it must act fast, it must be environmentally robust, and the disease must be treatable, or a vaccine must be available, to allow the protection of one's own soldiers. This explains why only a minority of natural pathogens are suitable for military purposes. Anthrax is of course the first choice because the causative agent, *B. anthracis*, fulfils nearly all of these specifications (Fig. 3). However, potential victims of an anthrax attack can be treated with antibiotics even several days after an infection. Therefore, only a minority of the infected persons will die from an anthrax attack in most instances, as has been shown by the anthrax attacks in 2001 in the USA. However, a very simple genetic intervention could produce much more drastic and deadly results.

In addition, another important restriction of bioweapons might be overcome by genetic engineering techniques in the future. Today, access to highly virulent agents and strains is increasingly regulated and restricted. In particular, smallpox, which was eradicated more than 20 years ago, is officially only stored at two high-security laboratories in the USA and Russia, and it is at present virtually impossible to gain access to these virus stocks. But considering the rapid development of molecular biology, it is only a question of time before the artificial synthesis of agents or new combinations of agents becomes possible. This danger was highlighted last year by a worrying article in *Science*: a research team at the State University of New York in Stony Brook chemically synthesized an artificial polio virus from scratch (Cello *et al.*, 2002). They started with the genetic sequence of the agent, which is available online, ordered small, tailor-made DNA sequences and combined them to reconstruct the complete viral genome. In a final step, the synthesized DNA was brought to life by adding a chemical cocktail that initiated the production of a living, pathogenic virus.

In principle, this method could be used to synthesize other viruses with similarly short DNA sequences. This includes at least five viruses that are considered to be potential biowarfare agents, among them Ebola virus, Marburg virus and Venezuelan equine encephalitis virus. The first two in particular are very rare viruses that might be difficult to acquire by potential bioweaponeers—according to rumours, members of the Japanese cult Aum Shinrikyo, famous for the nerve gas attack on the Tokyo subway, tried unsuccessfully to get their hands on Ebola virus during an outbreak in former Zaire in the 1990s. Using the method that has been published for polio, such a group or an interested state could theoretically construct Ebola virus in the laboratory. However, it should be noted that this method is complex, and probably only a few highly trained experts would be able to master this technique, at least for the time being.

The polio virus itself is not an effective biological weapon, but the experiment shows the tremendous potential of genetic engineering and also highlights its problems, particularly when applied to smallpox. The current risk assessments with regard to this

Fig. 2 | The so-called '8-ball', a 1 million litre steel ball built in 1949 in which the US Army tested the effectiveness of biological weapons. The ball is in Fort Detrick, Maryland, and is a 'historical monument' today. (© (2001) Jan van Aken/Sunshine Project.)

virus rate the likelihood of an attack as being rather low, because it is highly unlikely—although not completely impossible—that countries other than Russia and the USA have access to it. If it should become possible to rebuild variola major, the smallpox virus, in the laboratory from scratch—and the virus's genome sequence is available from biological databases—this risk could change greatly. Smallpox is an ideal biological weapon, particularly for terrorist groups, because it is highly infectious and lethal and there is no effective treatment available. The relative safety that can be assumed today will then be gone.

However, the method for creating polio virus artificially cannot be directly transferred to the smallpox virus. The variola genome, with more than 200,000 base pairs, is far bigger than that of polio, and even if it were possible to recreate the full smallpox sequence *in vitro*, it could not easily be transformed into a live infectious virus particle. But there might be other ways. It would, for example, be possible to start with a closely related virus, such as monkeypox or mousepox, and to alter specifically those bases and sequences that differ from human smallpox. Some months ago, researchers documented for the first time that the sequence of a pathogenicity-related gene from the vaccinia virus could be transformed through the targeted mutation of 13 base pairs into the sequence of the corresponding smallpox gene (Rosengard *et al.*, 2002). It is probably only a matter of time before this technique is applicable to full genomes, and then we shall have to reconsider our current assessment of the smallpox threat. Considering the extreme danger that smallpox poses to a now largely unvaccinated human population, it seems at least questionable to make the smallpox sequence available on the World Wide Web.

However, the genetic enhancement of classical pathogens is only a small part of the broad array of possibilities that new biomedical techniques have created. From the point of view of disarmament, another trend is much more alarming: new types of biological weapons are becoming possible that were entirely fictitious until a few years ago. This is especially true of so-called 'non-lethal' weapons that are designed for use outside classical warfare. The danger is that these new possibilities generate desires even in countries that previously renounced the use and development of classical biological weapons.

The global norm against biological weapons, laid down in the 1925 Geneva Convention and the 1972 Biological and Toxin Weapons Convention, clearly contributed to the fact that few countries have been engaged in research into offensive biowarfare during recent decades. This moral barrier seems to be lower for 'non-lethal' weapons that are targeted against materials or drug-producing plants. Indeed, today's technical possibilities are creating a new interest in this area that might be leading to a new biological arms race. In the following paragraphs, we document three real examples of biological and chemical weapons development that are now being pursued by democracies in the Western world. All three examples have been researched and extensively published by the Sunshine Project (further reading is available at www.sunshine-project.org).

The US military has repeatedly discussed possible uses of biotechnology for warfare scenarios, including the development of material-degrading microorganisms to destroy fuel, constructional material or stealth paints (Strategic Assessment Center of Science Applications International Corporation, 1995; US Army War College, 1996). This idea is based on the fact that natural microorganisms are able to degrade nearly every material and are already being used to detoxify environmental pollution. The natural organisms are rather slow-acting and unreliable, but, with the help of genetic engineering, the development of much more effective organisms might become possible—probably effective enough to be used as biological weapons (Sayler, 2000). The specific interest of military researchers in material-degrading microbes is due to the synergistic effects of two concurrent developments: first, the military, particularly in the USA, has a renewed interest in these non-lethal weapons for use in media-sensitive mili-tary operations so that visible civilian victims can be avoided; second, rapid developments in biotechnology provide the technological basis to change natural microorganisms into anti-material microbes. New technological possibilities met new military concepts in the USA and led to a renewed interest in weapons that, until recently, had been banned and rejected.

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Fig. 3 | Until 1969, the US Army produced anthrax spores for offensive warfare in this building at Fort Detrick, Maryland. (© (2001) Jan van Aken/Sunshine Project.)

In 1998, it became public that the US Naval Research Laboratory in Washington DC was developing genetically engineered fungi with offensive biowarfare potential. They isolated natural microorganisms that degrade a variety of materials, such as plastics, rubber and metals, and used genetic engineering to make them more powerful and focused—one of these genetically engineered microbes can destroy military paints in 72 hours. The principal investigator at the Naval Research Laboratory, James Campbell, described possible applications of this technology in his presentation at the 3rd Non-Lethal Defense Symposium in 1998. Among them were "microbial derived or based esterases [that] might be used to strip signature-control coatings from aircraft, thus facilitating detection and destruction of the aircraft" (www.dtic.mil/ndia/NLD3/camp.pdf). This work is purportedly defensive in nature, although no threat has been articulated, and continuing research by the US Navy and Army continues to strive towards taking

these weapons from the laboratory to the field. Just a few years later, in 2002, several research proposals by the US military that were clearly offensive in nature became public.

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About a decade ago, the USA also increased their efforts to identify microorganisms that kill drug-producing crops; by the late 1990s, this research focused largely on two fungi. The testing of one, *Pleospora papaveracea*, against opium poppy, was conducted in Tashkent, Uzbekistan, with financial and scientific support from the USA, and was completed in 2001. Pathogenic *Fusarium oxysporum* strains developed in the USA to kill coca plants were scheduled for field tests in Colombia in 2000, but international protests halted this project. These fungi provide a quintessential example of the hostile use of biological agents. In Colombia, the biggest areas of coca and opium poppy cultivation are in combat zones, and the 'War on Drugs' is part of the country's continuing armed conflict. These biological agents are lowering the political threshold for the use of biological weapons and are likely to have tremendous environmental and health impacts. The pursuit of crop-killing fungi as weapons would be a further slide down a slippery slope that, by following the same logic, could easily lead to the use of other plant pathogens, animal pathogens or even non-lethal biological weapons against humans (van Aken & Hammond, 2002).

The third example is not about biological weapons but new types of chemical, or rather biochemical, weapons. As in the other examples, the revolution in biomedicine created new desires in the East and the West, and there are already new weapons under development that violate international treaties. This area came under the spotlight of the international media after the use of psychoactive substances in the Moscow hostage crisis last year, causing the death of more than 170 people. These supposedly 'non-lethal' chemical weapons had been developed as early as the 1950s, particularly a substance called 'BZ', known in the US army as 'sleeping gas'. But BZ caused very different effects in different individuals and was considered to be unreliable, leading to its banishment from the US chemical arsenal in the late 1960s. Today, however, modern neurobiology provides comprehensive knowledge about a broad range of neuroreceptors and manifold psychoactive substances that make 'non-lethal' chemical weapons attractive for the military once more. For instance, the US Marine Corps recently investigated the potential military usefulness of calmatives such as benzodiazepines and α2-adrenoreceptor agonists. However, the identification of suitable substances is only one part of the renewed chemical weapons research in the USA. Recently published documents show that the US military forces are also developing new delivery devices for chemicals with a range of more than 2.5 km—a distance that makes sense only for warfare scenarios as opposed to police operations, in which ranges from 10 to 50 m for tear gas grenades are common. The Chemical Weapons Convention prohibits any use of chemicals, including 'non-lethal' chemicals, in warfare situations. Even the use of tear gas is prohibited because of the enormous danger of escalation. In a specific combat situation, the attacked side will be unable to identify the nature of the chemical used and might feel tempted to retaliate in kind with potentially lethal chemicals.

Molecular biology and genetic engineering are still in their infancy, and more technical possibilities will arise in the years to come—for military abuse too (Fraser & Dando, 2001). More efficient classical biowarfare agents will probably have only a marginal role, even if the genetically engineered 'superbug' is still routinely featured in newspaper reports. More likely and more alarming are weapons for new types of conflicts and warfare scenarios, namely low-intensity warfare or secret operations, for economic warfare or for sabotage activities. To prevent the hostile exploitation of biology now and forever, a bundle of measures must be taken, from strengthening the Biological and Toxin Weapons Convention to building an awareness in the scientific community about the possibilities and dangers of abuse. Any kind of biotechnological or biomedical research, development or production must be performed in an internationally transparent and controlled manner. In cases in which military abuse seems to be imminent and likely, alternative ways to pursue the same research goal have to be developed. Furthermore, as we mentioned above with regard to the smallpox genome sequence, it might also be necessary to apply restrictions to certain research and/or publications.

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