Chemical and Biological Warfare: Some Ethical Dilemmas

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> *The physician must be able to tell the antecedents, know the present, and foretell the future, must mediate these things, and have two special objects in view with regard to diseases, namely to do good or to do no harm.*
> *Hippocrates of Cos, Of the Epidemics*, Book 1

When Hippocrates (or perhaps a contemporary) wrote these words, some time after 430 BC, he and his colleagues could do little for either good or harm to sufferers from infectious disease. Indeed, they themselves were at particular risk. Thucydides, describing the so-called plague of Athens of 430 BC (probably not bubonic plague, but unidentified) in his *History of the Peloponnesian War*, writes that "mortality among the doctors was the highest of all, since they came more frequently in contact with the sick."

With the advent of microbiology, antimicrobial chemotherapy, genetics, and modern molecular biology, our understanding of infectious disease has increased exponentially and led to an understanding of the epidemiology, treatment and prevention of many infectious diseases. But at the same time it has become possible to progress from the crude attempts at biological warfare of past centuries[1] to threaten major epidemics. Knowledge of physiology and pharmacology, particularly of the nervous system, has led to far more lethal chemical weapons than the chlorine and phosgene of World War I. Moreover, research into fields such as microbiology, molecular biology, and neurobiology with the entirely laudable object of preventing and treating major epidemics and serious diseases can be misapplied with the opposite intent. Yet a recent *Nature* editorial[2] quotes discussions by Brian Rappert of Exeter University with 600 biologists in the United Kingdom, which showed that most were unaware of the possibility for "dual use" for good or ill of the knowledge in such fields.

Not many doctors take the Hippocratic oath today, but his exhortation to "do no harm" must still be quoted to the majority of medical students and must always be kept in mind in practice. Doing harm to patients through carelessness can lead to at least a reprimand and perhaps being sued for negligence. Very few doctors do deliberate harm—cases such as that of Dr. Shipman in the United Kingdom are rare. But past efforts in chemical and biological warfare, some of which are briefly considered below, involved the active participation of some of the doctors of their time. The Hippocratic code concerns a doctor's relationship with his or her own patients, and it is no defense of their actions to claim that the victims were not their patients; such actions would be regarded as war crimes today. But with the global spread of information, worldwide travel facilitating the dissemination of infectious disease, and the

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continued existence of organizations—and nation states—wishing harm to others, researchers into microbiology and clinical pharmacology, whether medically qualified or not, are faced with a whole new set of ethical dilemmas. This paper reviews the background to these problems and tries to define them more clearly.

As already noted, and discussed in more detail later, entirely legitimate medical research can be misused as well as used to help the sick. Difficulty arises when the potential for misuse can be linked to matters of state security. Scientists and engineers from Archimedes onward have been involved in weapons research, most notably recently in the design of nuclear weapons; Miller[3] discusses the attitudes of scientists both in 20th century Germany and in the Manhattan Project on nuclear weapons research. Chemical and biological weapons are classified along with nuclear weapons as weapons of mass destruction; a key issue for medically trained scientists is whether their national or other group loyalties, especially if their group feels under threat, should take precedence over their ethical position as doctors.

The Past

Crude attempts at biological warfare, as by poisoning wells, may have implied a vague understanding of contagious disease. The best known of these attempts is at the siege of Kaffa (now Feodosiya) in the Crimea by the Mongols in 1346 AD. Bubonic plague broke out among the besiegers, who abandoned the siege after catapulting some of their dead into the city. The disease developed among its inhabitants and some Genoese merchants sheltering there, who took it home with them—the origin of the Black Death. It is unlikely that the Mongols had any ethical concern about their actions, but as the fleas that transmit the disease soon leave a dead body, it is in fact more likely that it entered the city with rats under the gates or through crevices in the walls.[4]

Connivance of medical staff is perhaps more likely in the use of blankets from smallpox victims to infect American Indians during the English/French war in America in the 1750s. When the Germans used anthrax against animals being exported to the Allies in World War I, and chlorine as a chemical weapon, it is hard to imagine that medical as well as scientific advice was not obtained. Ishii Shiro, who headed the Japanese biological weapons program involving atrocities in China and against prisoners of war in World War II, and Wouter Basson, who led the chemical and biological warfare program of the apartheid regime in South Africa, were both medical doctors.

Many countries, including the United Kingdom, the United States, and the former Soviet Union, had active biological warfare (BW) programs during World War II and the subsequent Cold War, with various claims and counterclaims about possible use that are difficult to assess.[5] The 1925 Geneva protocol banned first use of biological and chemical weapons, but not research, stockpiling, or "testing." The 1972 Biological and Toxin Weapons Convention (BTWC) outlaws stockpiling as well as use, but allows research for "prophylactic, protective, and other peaceful purposes" and has no verification protocol. The Soviet Union, although a party to the BTWC, continued research and development on biological weapons until the 1990s. The accidental release of anthrax spores led to an outbreak of the disease with over 60 deaths around Sverdlovsk in 1979, and strains of antibiotic-resistant bacteria were developed.

Health-trained professionals were involved in all these programs. They presumably justified their activities variously on the programs being primarily defensive, that they were not involved in doing harm to their own patients, or that the interests of the state overrode other ethical considerations. The Aum Shinrikyo cult in Japan, which used the nerve gas sarin in the Tokyo subway in 1995, is believed to have attempted to develop biological weapons, including Ebola virus. Its members included graduate scientists and a surgeon, for whom once again group loyalty presumably came above any ethical concerns.[6]

The Present: Three Case Studies

As noted above, a major problem for medical scientists is that the results of their research, no matter how potentially beneficial, can be made use of in work on biological and chemical weapons.[7] Moreover, many biologists are apparently unaware of this possibility, perhaps in part at least because of the variety of guises in which the dilemma can appear. In this section and the following one, some of today's and future episodes highlighting this variety are discussed briefly and their implications considered.

Mousepox

A group of Australians attempted to find an infectious contraceptive to deal with plagues of mice using a strain of mousepox virus incorporating an antigen from fertilized mouse eggs. To increase the virulence of the virus they also incorporated the gene for the cytokine interleukin-4; unexpectedly, the new strain of virus was lethal even in mice either normally resistant to mousepox or immunized against it. Realizing the implications of their work for genetically engineering possible other pathogens that might be used as bioweapons, the group consulted the Australian government before their findings were published.[8] Researchers in the United States have indeed made the mousepox virus even more virulent for mice and are experimenting with cowpox, which can affect humans.

Polio

The genome of several microorganisms, including poliomyelitis, is now known, and no doubt many more will follow. In 2002 a group in the United States was able to obtain DNA complementary to polio RNA and use it to synthesize de novo infectious poliovirus. It would presumably be possible using such technology to synthesize other viruses such as Ebola.

SARS

The SARS (Severe Adult Respiratory Syndrome) virus outbreak of late 2002 could be a warning of what might happen from an attack with a previously unknown bioweapon.[9] Cases of atypical pneumonia in southern China proved to be due to a previously unknown coronavirus, a group that usually causes a mild illness in humans but more severe effects in animals. It is still not clear whether the SARS virus was a new mutation or happened to spread because some of its victims took long air flights early in their illness. Human case-to-case transmission occurred, particularly in doctors and nurses, and over 8,000

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cases were identified with more than 750 deaths. Major efforts coordinated by the World Health Organization were needed to contain the epidemic.

Future Threats?

Medical science, particularly in the field of molecular biology, is expanding at an ever-increasing rate. The genomes of many organisms, from microbes to man, are now known and many more will follow. When there is a real threat of a major epidemic, as with influenza, such work is essential even if it might be open to misuse. When there is no threat, as in the case of smallpox, it is surely better to "let sleeping dogs lie"; the motives of those who wish to do otherwise can even be questioned. In the next few decades, neuroscience is likely to expand as rapidly as molecular biology has done. Neuroscience will lead to more understanding of the brain, but will also show ways of controlling and harming it. Understanding the human genome could also allow selective and malign manipulation of the human species.

Influenza

As I write this, there are widespread fears of a new influenza pandemic. This could match the 1918–19 "Spanish flu," which is thought to have killed from 10 to 40 million people. Further pandemics recurred in 1958 and 1968. The H5N1 "bird flu" strain is now widespread in southeast Asia, and spread to humans with a high fatality rate has occurred, but so far there have been only isolated cases of human-to-human spread. Isolated outbreaks in birds have occurred in Africa, the Middle East, and Europe. A mutation of bird flu allowing its ready spread between humans, with global travel and today's increased world population, is thought by leading virologists to be inevitable and could be disastrous. It is impossible to provide nearly enough antiviral drugs, and a vaccine cannot be designed and produced until the new epidemic strain is identified.

The RNA genome of the 1918–19 strain has been partially characterized from material from victims buried in the Arctic tundra and studies made of the factors responsible for the infectivity and virulence of the strain.[10] Given today's threat to public health, this research seems essential, even if the knowledge gained could theoretically be helpful in designing bioweapons. Even if a "rogue state" or non-state-actor gained early access to a new virulent strain of influenza virus, in the absence of an effective vaccine its own population would be as much at risk as anyone else from the resulting pandemic.

Nevertheless, the influenza threat does emphasize that knowledge is ethically neutral and the use to which it is put is what matters. Moreover, the mention of vaccination highlights a related issue. Suppose a State thought capable of biological warfare were found to be immunizing its population, or even just its military, against a microorganism capable of being used in BW but not known to be an immediate threat. The obvious inference would be that it was contemplating actual use of the organism. Even if today's supportive treatment and public health measures prevented a Spanish-flu-like pandemic, the SARS experience described above could be the outcome.

Smallpox

Smallpox as a disease was eradicated by the WHO vaccination campaign in the 1970s. The genome of the virus is known, and stocks remain in high-security laboratories in Russia and the United States. An attempt in WHO to have these stocks destroyed was defeated, but research on the virus continues.[11] A WHO advisory committee has recently agreed in principle to allow genetic modification of the virus, probably in the United States, and with the claimed objective of developing new drugs and vaccines; as part of the research, smallpox genes would be transferred to other viruses and their effects tested in animals.

This research is difficult to justify. Unless there is reasonable suspicion that smallpox virus was allowed out of the Russian laboratory during that country's economic difficulties in the 1990s, there is no risk of the disease recurring if the stocks in both countries are destroyed. The WHO committee's deliberations on smallpox are secret; presumably the putative researchers were able to convince them of the safety of their projects. Will the results of the study, if it goes ahead, be published? If they are thought unsafe for publication, as could well be the case, was it ethical to authorize the research at all?

Expertise and Biological Weapons

All experiments involving smallpox genes run a significant risk of creating what is in effect a new pathogen. The Australian experience with mousepox described above also highlights this hazard, as does the outbreak of anthrax by letter in the United States late in 2001. The anthrax spores used in this episode were clearly of BW capability, being finely powdered to make them freely dispersible, and the letters are widely believed to be the work of an insider in the U.S. research program. The anthrax letters episode highlights the importance of expertise in an attempt at a major biological weapons attack. Although anthrax is widespread and therefore readily accessible, only a specialist could put the spores into the form used in the letters, and such a person with access to smallpox virus or the facilities to create variants of other pathogens could start a devastating epidemic. However, it is unlikely that this level of expertise would exist except in a relatively small number even of developed countries. It would only be within the reach of non-state actors if they had access to laboratories in developed countries, though dissident or aggrieved staff in the laboratories could provide a link.

Chemical Weapons

The earliest chemical weapons (CW), chlorine and phosgene, were selected for their known toxicity. Even in this field there is an overlap between toxicity and benefit; mustard gas (sulphur mustard) is chemically related to nitrogen mustard (mustine) and related substances, which were the first generation cancer chemotherapy agents.

Today's most potent chemical weapons, the nerve gases, arose out of research into the role of the neurotransmitter acetylcholine in neuromuscular transmission in the 1930s. Research into the role of this and other neurotransmitters is vital for understanding the far more complex neurophysiology of the brain, which in turn is basic to understanding major disorders of the brain such as schizophrenia and Alzheimer's disease. But this field too is open to abuse.

The use of CW, like BW, was banned by the 1925 Geneva protocol, but research, such as development of nerve gases, was still permitted. The 1997 Chemical Weapons Convention also banned stockpiling and development, and unlike the BTWC has a verification system that seems to be working reasonably well. It too, however, has a loophole; the use of calmative (riot-control) agents for law enforcement is not covered. These agents are regarded as "nonlethal" but in misuse, for example, in a confined space, as in the 2002 Moscow theater siege when a fentanyl derivative was used, they are far from nonlethal. Today's agents are not highly selective in their targets in the brain. However, continuing research into the variety of receptors and neurotransmitters in the brain and ways of influencing them will inevitably open up opportunities for brain control of individuals or groups that can only be described as Orwellian.[12] Once again, then, entirely ethical research with essential medical applications is wide open to abuse.

Ethnic Weapons

Another field in which research will inevitably continue, but with a high probability that information will emerge that can be misused, is into the human genome. An aspect of this that could be applied to chemical and biological warfare is in genetic differences between human ethnic groups, which could be used to target chemical or biological weapons against a specific group.

Genetically based differences in susceptibility to therapeutic agents and infections are well known. Certain drugs, such as the antituberculous agent isoniazid, are metabolized at various rates under genetic control, which influences both their effectiveness and rate of side effects. Inherited glucose-6-phosphate dehydrogenase (G6PD) deficiency can lead to severe hemolysis from certain drugs and infections. Both G6PD deficiency and heterozygous sickle-cell disease, on the other hand, protect against malaria and are therefore more common where this disease is endemic. The issue is whether more subtle genetic differences can be utilized to target chemical or biological weapons against a particular ethnic group, while sparing the aggressor's own military or population. On the one hand, there is almost as much genetic variability within ethnic groups as between them.[13] On the other, it has been argued that a 20% susceptibility to a toxic or infectious agent in an opponent's armed forces that was not present in ones' own could be of military significance and that there are so many potential targets in the human genome that it is feasible to generate such agents as potential weapons.[14] This is not an immediate threat, and in the first instance would only be achievable by those few countries with a sophisticated biotechnology infrastructure, but its control should clearly be a key part of preventing developments in CBW in the future.

An Ethics-Based Response

The 1925 Geneva protocol banning the use of CBW translated the widespread abhorrence at the use of chemical weapons in World War I—an ethical response—into binding international law. As previously noted, prohibition on use was extended to a ban on development and stockpiling in the Biological and Toxin Weapons Convention (entered into force 1975) and the Chemical Weapons Convention (1997). The BTWC currently has 152 States Parties[15] and the CWC 162.[16] Both permit appropriate defensive measures and legitimate medical research in related fields.

As described above, concern today arises from new scientific knowledge, which although beneficial and indeed essential for modern medicine, can also be misapplied, but also from the fear after 9/11 that CBW could fall into the hands of terrorist groups such as Al Qaida.[17] If this is to be prevented, the framework of international law must be strengthened. Scientists, both medical and nonmedical, working in relevant fields will have to consider carefully what activities they are prepared to undertake within their individual ethical standpoint and an attempt made to reach agreement on what, if any, constraints should be imposed on biomedical research to avoid misuse.

The Legal Framework

The first need is for both the BTWC and the CWC to become universal. Most of the nonsignatories are small states with no intention to acquire, still less use, CBW, but there are some key nonsignatories. Israel, Egypt, and Syria have not ratified either treaty, the latter two citing Israel's presumed possession of nuclear weapons.

In the case of the BTWC, an effective verification protocol is essential. A draft was presented to the 2002 Review Conference of the convention, but was vetoed by the United States. This was on the (somewhat contradictory?) grounds that the proposed protocol would be ineffective, and that it would present unacceptable limits to the commercial confidentiality of the U.S. biotechnology industry. The Bush Administration has a blanket objection to multilateral treaties. In this instance, the failure of the United States to trace the perpetrator of the 2001 postal anthrax attacks, together with the likelihood that they were the work of an insider, raises a more serious possibility. Inspection of the U.S. biodefense program, if permitted and accepted, might well reveal that it goes beyond the legitimate defensive activities permitted under the BTWC. It is surely neither an ethical nor a practical position for the United States to expect other countries to accept constraints that it refuses to accept for itself.

Scientists and Their Research

Within this framework, individual scientists, both medically trained and others, will differ in their ethical attitude to research in relevant aspects of biotechnology and neuropharmacology. Relatively few will work directly for governments and the military except in war time; hopefully most of those that do will regard their work as purely defensive or at most intended to protect their country's soldiers and civilians should chemical and biological warfare threaten. Others will feel that such participation involves a significant likelihood that their own country could use CBW agents, regard this as unacceptable, and refuse any part in the work.

One solution to this ethical dilemma lies in going beyond verification of what goes on in relevant laboratories, whether public or private, to imposing stricter limitations. In most developed countries, before research on patients is permitted, the objectives and protocol have to be approved by national and local ethical committees. In the United Kingdom, both a former President of the Royal Society, Sir Michael Atiyah,[18] and the current President and Astronomer Royal, Lord Martin Rees,[19] have suggested that there must be limitations on what scientists should do, taking into account the possible uses to which their research might be put. I suggest that the organizations set up to administer the working of the BTWC and the CWC should include international ethical committees that should assess relevant projects. The membership of such committees should include independent scientists and jurists of high repute as well as nominated representatives of national research ethics committees if they are to be seen as trustworthy. The committees would need access to supranational authorities such as the International Court of Justice and the U.N. Security Council to ensure that their recommendations are enforceable.

The 2005 work program of the BTWC is concerned with codes of conduct for scientists. This could be a forum for the scientific community to be involved in a wider assessment and regulation of research in biotechnology, particularly but not only related to activities with CBW potential. A detailed proposal for a code of conduct has been put forward; this stresses that the value of such a code depends upon the practical commitment of organizations, including governments, to promote and implement them.[20] The idea of "codes of conduct"—which clearly implies limitations on what can be done—has been endorsed in the recent *Nature* editorial:[21] "[S]cientists would do well to engage in a constructive discussion about what role they might play." Most medical scientists would surely wish to be in the forefront of such discussions.

This idea may seem far-fetched in view of the limitations it would place on governmental secrecy in the military and security fields and on commercial confidentiality. But participation in the United Nations system and in regional organizations such as the European Union already imposes constraints on national sovereignty, and commercial confidentiality must surely take second place to global human security. This could be part of the acceptable face of globalization.

An objection to this approach is that it is only applicable to nation states and does nothing to control the activities of substate actors and, in particular, terrorist groups. Manipulation of dangerous pathogenic organisms occurs daily in every country with modern healthcare, and such organisms could come into the possession of terrorist groups. This must have happened in the little-known episode in Oregon, United States, in 1984, when the Rajneeshee sect contaminated several salad bars with the food-poisoning organism *Salmonella typhimurium* in an attempt to influence the result of a local election.[22] About 750 people were made ill, but there were no deaths, and the election was unaffected! Such an episode would be a major sensation today.

Any country with a chemical industry could manufacture chemical weapons, but today's chemical weapons, like dangerous pathogens, are not easy to handle and could be also beyond the scope of smaller independent terrorist groups acting alone. As already noted, Aum Shinrikyo in Japan with a membership including university graduates was able to achieve a very nasty attack with sarin nerve gas, but could not acquire BW capability. In passing, it could be noted that nuclear capability would be even more difficult to acquire independently for terrorist groups and small nation-states in view of the large scale of nuclear technology.

"Breakout"—and a Parallel Solution

Because many countries have a chemical industry and most have medical microbiology, some episodes of chemical or biological warfare in their widest sense will, then, be difficult to avoid. At one extreme, this could be local malevolence such as the Oregon food poisoning episode or anthrax-by-post. At the other, it could be "an instance of bio-error or bio-terror [that] will have killed a million people" by 2020, on the occurrence of which Rees has staked a thousand dollars (while hoping he will lose the bet).[23] Only time will show.

The perpetrators could be as variable, from religious fanatics (inspired by what they themselves would regard as ethical principles), through scientists, some loyal to their country, others disaffected or underpaid, to substate actors or even nation-states with genuine grievances. In response, tighter security measures will be helpful. Here too there is an ethical dilemma that has been highlighted recently in dealing with suspected terrorists: Should such measures be allowed to erode civil and human rights?

Dealing principally with the nuclear threat, but mentioning that of biological and chemical warfare in passing, the late Sir Joseph Rotblat, in his Nobel Peace Prize acceptance speech,[24] shared the call for all scientists to desist from work on weapons of mass destruction. He also called for those who become aware of possible threats to act as whistle-blowers, though admitting that the treatment of Mordechai Vanunu, who revealed Israel's nuclear weapons and as a result was kept in solitary confinement for 18 years, has shown that they could pay a heavy price.

But he accepts that this is not enough. Because the knowledge of how to make nuclear weapons—and, as has been shown above, biological and chemical weapons also—will always be with us, Rotblat concludes that the only way of preventing ultimate catastrophe is to abolish war altogether. As he notes, this implies a new loyalty—to humankind. As part of such a commitment, the economic and political injustices that underlay today's wars, both between and within nation-states, have to be resolved peacefully and equitably. Some, perhaps many, doctors as well as other scientists will always see loyalty to their nation-state as having primacy over other ethical issues.[25] It is likely that the more probable route to avoiding the use of weapons of mass destruction in the Middle East would be settlement of the various disputes there than the adoption of codes of conduct by the U.N. or the organizations administering the CWC and the BTWC. Further discussion of such issues, though relevant, is beyond the scope of this paper.

Conclusion

In a war-free world, the research and other professional activities of doctors and other biomedical researchers toward treating and preventing ill health, itself a significant factor underlying social unrest, would not need to be restricted. The fear that their work might contribute to the deliberate creation of illness would be removed. The ethical dilemmas discussed above may not be resolvable, but at least they may, with sufficient effort and goodwill, be avoidable.

Biological and chemical warfare has been called *The Eleventh Plague*. The author states that this "is entirely a human invention. . . . Its occurrence represents a moral failure. Its avoidance is a statement of human decency, an act of will born of high principle."[26]

Notes

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21. See note 2, Rules of engagement 2005:2.
22. See note 1 Dando, Nathanson, Darvell 1999:31.
23. See note 19, Rees 2003:74.
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