Next Generation Bioweapons: Genetic Engineering and BW

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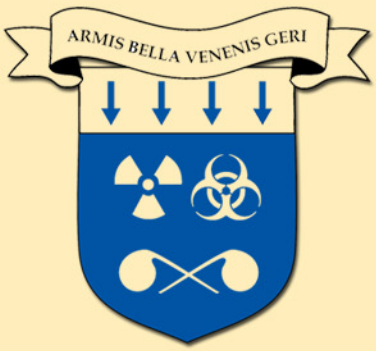

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CHAPTER 9

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Introduction

The history of warfare and the history of disease are unquestionably interwoven. Throughout the history of warfare, disease and non-battle injury have accounted for more deaths and loss of combat capability than from actual battle in war itself. The most striking example is the great influenza pandemic during World War I that killed 20 million people or more worldwide in 1918.[1] Although this was a naturally occurring event, what if a country could create a biological agent that could yield the same catastrophic loss of life on the enemy? That, in essence, is the potential effect of applying genetic engineering[2] for biological warfare (BW) or bioterrorism (BT).

Today, we face not only natural diseases (including emerging infectious diseases), but also threats of BW or BT, possibly with genetically engineered agents, that may resist known therapies. In simple terms, genetic engineering is the process of human intervention to transfer functional genes (DNA) between two biological organisms. In the BW/BT context, it is the manipulation of genes to create new pathogenic characteristics (increased survivability, infectivity, virulence, drug resistance, etc). Organisms with altered characteristics are the "next generation" biological weapons.

In this century, it is widely predicted that advances in biology and biotechnology will revolutionize society and life as we know it. At the same time, the "black biology" of biotechnology which can be used to

create biological weapons, will be one of the gravest threats we will face. In this era when cloning and "designer genes" are topics of the evening news, much has been written about biowarfare and bioterrorism resulting from genetically altered microbes, and it is often difficult to discern fact from fiction. This chapter has two purposes. The first part consolidates accounts of genetic engineering from sources close to the former Soviet Union's BW program. The remainder of the paper discusses near-term future capabilities of genetic engineering and biological warfare from an American perspective. The "next generation" of biological weapons made possible through genetic engineering will be asymmetric weapons par excellence.

The Former Soviet Union's Biological Warfare Program

Biopreparat

Despite signing the 1972 Biological and Toxin Weapons Convention (BWC), it is now certain that the former Soviet Union (FSU) continued a clandestine and illegal offensive biological weapons program until at least the early 1990s. Biopreparat (a huge military program with civilian cover) was organized to develop and weaponize biological agents for BW.[3] It employed approximately half of the Soviet Union's 60,000 workers in more than 18 BW facilities, and in the 1980s had an annual budget equivalent to tens of millions of U.S. dollars.[4] Unlike the American offensive BW program (1942-69) that worked primarily with organisms that were not contagious in humans (e.g., anthrax and tularemia), the Soviet BW research and development program also sought out the most contagious and lethal bacteria (e.g., plague) and viruses (e.g., smallpox) known to man.[5]

Because Biopreparat and other Soviet BW research facilities operated under the highest security classification of "Special Importance" (higher than Top Secret), the U.S. intelligence community did not even know it existed until 1989 when a top ranking scientist from the BW program defected to the United Kingdom.[6] From his extensive debrief, and subsequent collaboration by two other defectors from the program, we

now know detailed information on the genetic engineering successes and other advances in Russian microbiology. Obviously much of the data remains classified, but the three defectors' accounts have been documented to some extent in various unclassified books and articles. This paper discusses their open-source accounts.

Pasechnik

In October 1989, Dr. Vladimir Pasechnik, the first primary source from inside the Soviet program, defected to England.[7] A top Soviet microbiologist and Director of the Institute for Ultra Pure Biological Preparations in Biopreparat, he described the extensive organization of biological research and production facilities in the program.

In addition to confirming that the Soviet Union had an offensive BW program in violation of the 1972 BWC, he disclosed that the Soviets had an "extensive genetic engineering program aimed at developing new kinds of biological weapons against which the West would be defenseless."[8] His institute's top priority was to increase the lethality of plague and tularemia, and at the same time make them more resistant to antibiotics and temperature extremes. By introducing specially engineered plasmids[9] into successive generations of tularemia cultures, the strain became resistant to all known Western antibiotics. The dried, powdery super-plague became the Soviet weapon of choice (20 tons in stock at all times) and was loaded on various munitions. The use of BW had been integrated into Soviet special war plans for a range of tactical operations where they would have been delivered using spray tanks and cluster bombs and strategic operations where intercontinental ballistic missiles (ICBMs) and strategic bombers would have carried plague, anthrax, or smallpox.[10]

Pasechnik also detailed work on perfecting other new strains of bacteria and viruses that would aerosolize well for use in weapons.[11] After 30 years of experimentation, Soviet scientists had solved the problems of fragile microbe survival in major atmospheric pressure changes and temperature extremes during missile flight by fitting BW rockets with astronaut cabin-like protective systems. They solved the "destruction on explosion" problem by selecting the hardiest strains and calculating the required redundant quantity needed based on explosive testing done in Biopreparat and other BW research labs.

In summary, Pasechnik had disclosed that the Soviets (1) had genetically engineered bacteria and viruses, (2) weaponized the microbes in a powder form, (3) loaded them onto various munitions, and (4) integrated BW into their doctrine and had specific plans for use of BW.[12]

"Temple Fortune"

In the spring of 1992, a lower-level bench scientist who had worked on plague research in Pasechnik's lab also defected to the United Kingdom.[13] He has remained undercover and is referred to by code-name "Temple Fortune." He fully corroborated Pasechnik's previous account, and then updated the British on Soviet BW work in the 30-month interval from Pasechnik's departure to that of "Temple Fortune." President Mikhail Gorbachev had ordered the termination of biological offensive programs in 1990, and despite the fact that President Boris Yeltsen had also announced (by televised address to the Russian people and in a personal commitment to President Bush) termination of the program, research on new forms of plague had secretly continued.[14]

"Temple Fortune" stated that, in addition to being even more resistant to multiple antibiotics, the improved super-plague would be non-virulent in its stored form, but could be easily converted into a deadly antibiotic-resistant form when needed for weaponization.[15] The genes that cause plague virulence are located on a plasmid. What he was describing was a binary biological weapon, where benign bacterial plague cells would be mixed with virulence-enhancing plasmids immediately before loading on a weapon, and the transformation would take place in a small bioreactor on the weapon itself.[16]

Alibekov

In late 1992, shortly after "Temple Fortune's" defection, Dr. Kanatjan Alibekov became the third defector from the Russian BW program.[17] As the Deputy Director (number-two man) of Biopreparat and an infectious disease physician/epidemiologist, he was the highest ranking defector ever from the program. (Dr. Alibekov anglicized his name and now goes by Ken Alibek.) In 1999, Alibek published *Biohazard,* a first-hand detailed account of his experiences. Alibek disclosed a virtual encyclopedia of

intimate details on Biopreparat from the top down: personnel and facilities, history of the offensive research, medical and microbiological discoveries, special production methods, weaponization techniques, aerosol testing, Russian BW defensive innovations, prior deceptions and secret plans, and the future direction of the program.[18]

Alibek confided that Soviet biologists in the 1960s and 1970s were already interested in using genetics and gene manipulation to produce BW agents. In 1973, President Leonid Brezhnev established the "Enzyme" program to modernize the BW program and develop genetically altered pathogens.[19] Early in his career, Alibek had been in charge of developing Biopreparat's first vaccine-resistant tularemia bomblet.[20] Later, by 1986, his team had also tripled the potency of the "battle strain" of anthrax (Strain 836).[21] He was the first to weaponize glanders, and supervised the first Soviet tests with the Marburg virus (an Ebola-like virus).[22]

Alibek disclosed that by 1992 the Russians possessed a grand total of *fifty-two* different biological agents or combination of agents, including deadly Marburg, Ebola, and smallpox viruses, that could be weaponized. The most infectious and easiest to manufacture and transport microbes were labeled "battle strains."[23] The favorite "battle strains" were anthrax (Strain 836), Pasechnik's super-plague, and a special Russian strain of tularemia (Schu-4). By 1991, Alibek stated that Russian scientists had "improved" all three of these so that they could overcome all immune systems and current medical treatments.[24] In May 1998, Alibek testified before the U.S. Congress:

> It is important to note that, in the Soviet's view, the best biological agents were those for which there was no prevention and no cure. For those agents for which vaccines or treatment existed – such as plague, which can be treated with antibiotics – antibiotic-resistant or immunosuppressive variants were to be developed.[25]

Although Biopreparat had worked with a highly virulent, rapidly infectious "battle strain" of smallpox (India-1) since 1959, they began research in 1987 to develop an even more virulent smallpox weapon, and tested it in 1990.[26]

In his book *Biohazard*, Alibek wrote about using plasmids to increase virulence or antibiotic resistance in bacteria.[27] This corroborated Pasechnik's and "Temple Fortune's" prior statements. He also discussed transfer of a gene for myelin toxin to *Yersinia pestis* (plague bacteria), however this agent was reportedly not yet weaponized. He said that a new Moscow-based company named Bioeffekt Ltd. had offered, by mail order, three strains of tularemia produced by "technology unknown outside Russia" (i.e., genetically engineered strains).

Most astounding of all, Alibek revealed that genetic engineering research was underway to create entirely new life forms.[28] The goal of hybrid "chimera" viruses was to insert genes from one virus into another to create an even more lethal virus. Alibek stated that the Russians had created the first chimera virus from inserting DNA from Venezuelan equine encephalitis (VEE) virus into vaccinia virus (genetic structure almost identical to the smallpox virus).[29] Chimeras, of VEE, Ebola, and Marburg genes inserted into the actual smallpox virus, were in the research phase when he left in 1991.

Near the end of his book, Alibek talks about how biotechnical knowledge was shared with other countries.[30] For many years the Russians taught courses in "genetic engineering and molecular biology for scientists from Eastern Europe, Cuba, Libya, India, Iran, Iraq, and other countries." In fact, Cuba had set up a pharmaceutical company near Havana and was producing interferon from a genetically altered bacteria that contained an inserted plasmid.

Yeltsen and Sverdlovsk

In 1979, an accidental release of anthrax spores from the BW facility at Sverdlovsk (now Yekaterinberg, Russia) killed at least 66 people. In 1998, a DNA sequencing study done on preserved samples from eleven victims revealed the simultaneous presence of up to four distinct genetic variants of *Bacillus anthracis*. These findings indicate that at least some level of engineering of military anthrax had taken place, because only one strain would likely be found after a natural outbreak.[31] The Soviet Union at the time denied the existence of a military program and the official in charge of the province where the incident occurred was none other than Boris Yeltsen.

More than a decade later, after becoming President of Russia, Boris Yeltsen visited Britain in 1992. In a public speech, discussing biological warfare research, he stated that the Russians "had undertaken research on the influence of various substances on human genes." Yeltsen's statements substantiated the existence of a previous Soviet genetic engineering research program.[32] Yeltsen, as Russia's President, later issued a public decree outlawing the entire Russian BW research and production program.

Scientific Reports

In 1995, Russian scientists presented a study at a conference in Britain that they later published in the British medical journal *Vaccine* in December 1997.[33] They reported that they had successfully transferred genes from *Bacillus cereus* into *Bacillus anthracis* cultures, making the anthrax resistant to Russian anthrax vaccine (at least in hamsters). This raised the obvious question about effectiveness of the American anthrax vaccine. American agencies sought to obtain a sample of the more potent Russian anthrax strain.[34] Unable to do so, in early 2001 the Pentagon made plans to duplicate the Russian work and genetically engineer its own modified strain for biodefense purposes.[35]

Implications

Biological-type weapons have been used many times in history. Humanity's ancient enemies are, after all, microbes.[36] What is new today is the tailored development of more contagious and lethal pathogens and the increasing number of states and terrorist groups that may have access to the knowledge or cultures of them.[33] The above accounts from Russians knowledgeable about their BW programs indicate active research and success in genetic engineering, chimera agents, and binary biologicals. From public record accounts, we know that the former Soviet Union (FSU) used genetic engineering techniques in their massive offensive BW program.[38]

Because the FSU classified its offensive BW program as "Special Importance" (higher than Top Secret), it is clear that they considered BW missiles to be as valuable as their nuclear missiles.[39] Because of the protective military secrecy, it is plausible that even many top ranking Soviet/Russian officials did not know the full extent and details of the offensive program nor have control over it.[40] This Mafia-like secrecy may explain Gorbachev's and Yeltsen's confusions, hesitancies, and contradictions when talking to the West about treaty violations.[41] Incredibly, Pasechnik claimed that he had never been told about the existence of the Biological and Toxin Weapons Convention and learned of it first from his British debriefers.[42] Indeed, despite Yeltsen's decree to dismantle the FSU's offensive BW program, many intelligence analysts suspect that it is still viable, hidden deep in the military structure which is reluctant to surrender their BW secrets.[43]

Major General John Parker, the former Commander, U. S. Army Medical Research and Materiel Command, acknowledged that "bioterrorists could just re-engineer diseases such as anthrax to negate the effect of existing vaccines."[44] Some western intelligence experts believe a Russian genetic engineering program such as Alibek described is still in its infancy.[45] The pace of recent discoveries in molecular biology makes it imperative to contemplate new BW threats.[46] Advances in "the dark side" of biotechnology predict a future of antibiotic-resistant bacteria, vaccine-resistant viruses, and the creation of completely new pathogens (chimeras).[47] The expertise and technology to create lethal new strains of viruses and bacteria are available at most major universities around the world. Some American scientists predict that we have some 20 years before genetic engineering will effectively make current biological defenses completely ineffective and obsolete against BW attacks. Science fiction may become science fact within two decades.[48]

The threat of a war with ICBM exchange with Russia has been greatly reduced in recent years. However, as nuclear and BW missiles were decommissioned and Biopreparat and portions of the rest of the BW scientific infrastructure were dismantled, many Russian scientists were suddenly unemployed. There is concern that knowledge of genetic engineering, or even cultures of highly infectious agents (sold, stolen, or smuggled), may have been transmitted to "nations of concern" or terrorist organizations. If true, such leaks, combined with the ease of flow of

technology and information around the world, would result in a proliferation of capability that makes biological weapons use increasingly likely in major theater wars, smaller scale contingencies, and terrorist events.[49]

A biological weapon consists of both the biological agent and its means of delivery. Growing microbes is easier than their weaponization or dissemination. As Larry Johnson, former deputy director of the State Department's Office of Counter-Terrorism, said, "producing these weapons requires infrastructure and expertise more sophisticated than a lab coat and a garage."[50] However, terrorists may attempt to recruit former biological weapons researchers to obtain information on weaponization techniques. Well-funded terrorist organizations might be able to buy the Russian scientists they need. A small subset of terrorist groups is likely to possess the technical know-how needed to carry out an effective biological attack.[51] Unless they are able to buy knowledge or microbe cultures from large programs such as the former Soviet BW program, it is unlikely, though not impossible, that small terrorist units would have access to or produce genetically engineered biologicals.

Genetic Engineering, Bioterrorism and Biowarfare

Revolutions in Medicine and Military Affairs

The techniques of genetic engineering began to be developed in the 1970s.[52] In the 1980s, genetic engineering was already a global multibillion-dollar industry.[53] In the last decade of the 20th century, the knowledge of molecular biology increased exponentially. The recent revolution in molecular biology may have incidentally unleashed a new threat to mankind, in the form of genetically engineered pathogens, which could be used to develop many new offensive biological weapons. The same biotechnology that has promised to save lives by treatment of many human diseases, also has a dark side that could be misused for the development of deadly bioweapons. The future of this "black biology" is the subject of the remainder of this chapter.

The revolution in molecular biology and biotechnology can be considered as a potential Revolution in Military Affairs (RMA). Andrew F. Krepinevich noted 10 RMAs in the history of warfare.[54] Four elements

are required for a RMA: technological advancement, incorporation of this new technology into military systems, military operational innovation, and organizational adaptation in a way that fundamentally alters the character and conduct of conflict. The Gulf War has been seen as introducing the space/information warfare RMA. From the technological advances in biotechnology, biowarfare with genetically engineered pathogens may constitute a future such RMA. The Russians have integrated BW into their doctrine, but fortunately there is no present evidence that they have had any occasion to practice it in the past few decades.

Lieutenant General Paul Van Riper, USMC (Ret.), former commanding general, Marine Corps Combat Development Command, asserts that we are at the front end of strategic change and that there are currently multiple RMAs in progress.[55] It is difficult to assess their impact and meaning while they are still works in progress. Indeed, only time can prove that a technological innovation will contribute to a RMA. It may take 20 or 30 years until we fully understand their significance. It is currently believed by some that the next true major threats to our national security are in information and biological warfare.[56] We are arguably farther along in the information warfare RMA than a biowarfare RMA. Ironically, genetic engineering is becoming routine and commonplace while weaponization of biologicals is currently a less developed art. However, the recent spate of anthrax-laced letters sent through the mail communicates the message that terrorists can be very creative in their delivery methods.[57]

Whether or not biotechnology contributes to a future RMA, it certainly is revolutionizing medicine. The human genome has been sequenced. Gene therapy, which will allow the replacement or repair of faulty genes, promises to be the Holy Grail of modern medicine.[58] The techniques of molecular genetics, genome sequencing, and gene splicing therapy have dual-use potential. Paradoxically, the same biotechnology for developing a new drug or new vaccine may be used to develop more virulent bioweapons. The same science that can be used to save lives may also used to take lives. The rise of biotechnology knowledge presently parallels an increase in the willingness of terrorists to inflict mass casualties and increased devastation.[59] Following the historical pattern of interaction between warfare and disease, these two relatively new phenomena of unprecedented biotechnology and terrorists willing to inflict

mass casualties will very likely intersect in history. The anthrax attacks in the United States following the September 11, 2001 terrorist attacks on the twin towers of the World Trade Center and the Pentagon likely are previews of coming events.

Emerging Infectious Diseases

Richard Preston's 1997 novel *The Cobra Event* was a fictional scenario of bioterrorism with a genetically engineered supervirus.[60] President Clinton's reading of this novel sensitized him to the bioterrorist threat. He looked more deeply into the BW/BT threat and subsequently issued two Presidential Decision Directives to address national security deficiencies related to biological and chemical terrorism and warfare.[61] In the wake of the September 11 terrorist attacks on the World Trade Center and the Pentagon, and the multiple anthrax-tainted letters subsequently sent to national legislators, the Governor of New York, and news media offices, President Bush established the Homeland Security Council to coordinate a national effort of some 40 diverse agencies and organizations that were already involved in homeland security.

Because we do not know what new diseases will arise, we must always be prepared for the unexpected.[62] The Centers for Disease Control and Prevention (CDC) in Atlanta is the nation's lead agency for disease epidemics and tracks naturally occurring emerging infectious diseases worldwide. The CDC has traveled all over the world and investigated outbreaks of Ebola hemorrhagic fever, Marburg virus, hantavirus, and other emerging diseases.[63] These were challenging natural outbreaks of pathogens that had not been previously known to man. An outbreak of a biologically engineered pathogen might create a similar situation and may have an even greater disease potential (contagion and mortality) than recently discovered naturally emerging diseases. The epidemiological investigations of these emerging infectious diseases and other outbreaks serve as templates for responses to future biowarfare and bioterrorist events.

Natural versus Biologically Engineered Pathogens

In late 2001, anthrax spores in letters mailed through the U.S. Postal Service resulted in more terror than actual morbidity. In the three months following the anthrax letter attacks, five people died of inhalational anthrax and a total of 18 others had contracted some form of the disease.[64] Over 50,000 people took broad-spectrum antibiotics, and many more people purchased antibiotics for future prophylaxis. "Anthrax anxiety" was reported on the nightly news. Hundreds of thousands of the "worried well" deluged the medical care system.

Yet, as bad as anthrax-by-mail was, an outbreak of a biologically engineered pathogen could be potentially even more devastating. Although highly lethal, the anthrax of September 2001 was determined to be a well-known strain and it was not contagious (spread from person to person). Although anthrax spores are highly stable and can remain viable for years, compared to other pathogens a relatively large number of organisms is required to cause illness.[65] These facts may explain why investigators found traces of anthrax spores in many office buildings and post offices, but only a few people actually contracted the disease. Furthermore, if evidence of an anthrax attack is determined (as was the case just after September 11), people can be screened for exposure and/or treated with antibiotics that are highly effective if taken before symptoms begin. There is also an FDA-approved vaccine for anthrax.

Genetically engineered pathogens would likely prove to be a more difficult challenge than the 2001 anthrax attacks. Most likely they would be novel in characteristics with either higher transmissivity, communicability, or antibiotic resistance. Such "tailoring" of classical pathogens could make them harder to detect, diagnose, and treat. In effect, they would be more militarily useful.[66] Obviously, a vaccine would not be available for a novel pathogen. Biological warfare expert Steven Block outlines other qualitative differences and attributes possibly expected from genetically engineered pathogens. They could be made safer to handle, easier to distribute, capable of ethnic specificity, or be made to cause higher morbidity or mortality rates.[67]

The entire DNA sequence of the smallpox genome is known, and some scientists fear that it has already been genetically manipulated.[68] Although the only authorized laboratories in the world for smallpox are the CDC in Atlanta and the Russian State Research Center for Virology and Biotechnology in Koltsovo, it is believed that cultures may exist elsewhere in the FSU and

possibly have been transferred to other nations of concern or to non-state organizations.[69] Ken Alibek described in his book *Biohazard* that the FSU was working on genetic modifications of smallpox in 1992.[70] Because it was eradicated from the world's population in 1980, any release of even the original form of the disease would affect millions of people and constitute an epidemic of worldwide concern. Certainly, a biologically "improved" strain of smallpox would be ominous.

Offensive Biological Weapons Capabilities

The Office of the Secretary of Defense has identified countries that maintain various levels of offensive biological warfare capabilities or research facilities. This list includes Russia, China, Iraq, Iran, North Korea, Syria, Libya, India, and Pakistan. The Henry L. Stimson Center also lists Egypt, Israel, and Taiwan as countries of "proliferation concern."[71] Also, the Al Qaeda network reportedly sought to buy biological agents.

Most developed nations maintain some level of defensive capability against biological warfare and bioterrorism. This typically includes deployment military mission-oriented protective posture (MOPP) gear and civilian hazardous material (HAZMAT) responder "space suits." Also important are vaccines and antibiotics stockpiled against the BW/BT threats. The United States Department of Defense maintains a defensive capability. In 1969, President Nixon issued an executive order to unilaterally and unconditionally renounce biological weapons. Our program was terminated and stockpiles were destroyed.[72] The closure of our offensive program has had a serious and limiting effect on our ability to develop medical defensive measures, such as our capability to develop appropriate vaccines, antibiotics, and other treatments.[73]

Biowar and Bioterrorism

As our adversaries look for "asymmetric"[74] advantages, biological weapons are always a consideration. Bellicose national leaders and terrorists, allured by the potentially deadly power of biological weapons, persevere in seeking to acquire them. Yet, curiously, when biological weapons have been employed in battle, they have proven relatively ineffectual. They have been

undependable and uncontrollable.[75] Because they have been difficult to deploy reliably, their military value has been marginal.[76] Stabilizing biological agents and deploying them, either overtly with sophisticated weaponry or covertly without endangering the perpetrator or friendly forces,[77] requires expertise not widely held. Possibly, with the capabilities of biological engineering and a new generation of weapons, this may change.

Nation-state and nonstate actors obviously have differing capabilities, requirements, and expectations for biological weapons. Whereas military troops often train to operate in chemical and biological environments, vulnerable civilian populations do not have either the protective equipment or defensive training for a biological attack, and would therefore be the most likely target in a bioterrorist attack. It is increasingly likely that nonstate terrorists will use biological attacks as appears to be the case of the anthrax mail attacks following the September 11th attacks on the Pentagon and the World Trade Center towers.[78]

In the event of an attack with a genetically engineered pathogen, it would likely require some time to sort out whether we were confronting simply a naturally occurring event or one triggered by those with a sinister motive.[79] Identification of the cause may be delayed. Initially, there may not be a high index of suspicion. The disease may not be recognizable if it takes the initial form of a familiar complex of symptoms. Most physicians have never seen patients with anthrax or smallpox, and few have had training to diagnose the most likely bioterrorism pathogens. For example, one of the U.S. postal workers who died of anthrax in late 2001 was diagnosed as having a harmless viral syndrome and released from a physician's care. In the initial stages of an investigation, it might be difficult to determine if the outbreak is a naturally occurring event, an act of terrorism, or an act of war. For example, the first inhalational anthrax victim in Florida in late 2001 was initially thought to have been infected from natural exposure because he was an outdoorsman. It may be difficult for investigators to determine the source of the pathogen or the mechanism of exposure. It took some time before anthrax spores from letters were connected to the first anthrax cases. At the time of this writing, the perpetrator of the events in the United States and the source of the anthrax remain unknown.

A terrorist attack with a biologically engineered agent may unfold unlike any previous event. The pathogen may be released clandestinely so there will be a delay between exposure and onset of symptoms. Days to weeks later,

when people do develop symptoms, they could immediately start spreading contagious diseases. By that time, many people will likely be hundreds of miles away from where they were originally exposed, possibly at multiple international sites. Acutely ill victims may present themselves in large numbers to emergency rooms and other medical treatment facilities. In this scenario, medical professionals would be "on the front lines" of the attack. If the pathogen was highly contagious, medics would then become secondarily infected. Unsuspecting hospitals would become contaminated and soon overwhelmed. This would necessitate the quarantine of a large number of people, with the situation exacerbated by the declining numbers of medical care givers. The media would contribute to public anxiety. Civil disorder and chaos may ensue. We have very little experience in coping with such an epidemic. Advanced warning of an impending specific bioterrorist incident, especially with a genetically engineered BW agent, will be extremely rare—similar to an emerging disease outbreak. Unless we happen to have excellent intelligence, we can only be prepared to respond after the fact.[80]

Six Paths to Enhance Biothreats

At about the same time *The Cobra Event* became popular in 1997, the United States Department of Defense released *Proliferation: Threat and Response*, which identified trends in biological warfare capabilities. These included the increasing use of genetically engineered vectors and the growing understanding of both infectious disease mechanisms and the immune defense system.[81] An annex to *Proliferation: Threat and Response* stated "the current level of sophistication of BW is comparatively low, but there is enormous potential—based on advances in modern molecular biology, fermentation, and drug delivery technology—for making sophisticated weapons.[82] The most recent Report of the Quadrennial Defense Review (September 2001) also recognizes that "the biotechnology revolution holds the potential for increasing threats of biological warfare."[83]

Also in 1997, a group of academic scientists met to discuss "the threat posed by the development and use of biological agents." This JASON[84] Group provides technical advice to the U.S. government and "facilitates

the contributions of scientists to problems of national security and public benefit." Their meeting concentrated on the near-term future threat of biological warfare, specifically on genetically engineered pathogens and weapons.

The JASON Group that met in 1997 grouped potential genetically engineered pathogens into six broad groups of potential futuristic threats.[85]

- *Binary biological weapons*
- *Designer genes*
- *Gene therapy as a weapon*
- *Stealth viruses*
- *Host-swapping diseases*
- *Designer diseases*

The biotechnology exists today for some of these possibilities. Indeed, some genetically engineered agents may have already been produced and stockpiled.

1) <u>Binary Biological Weapons</u>:[86] Analogous to a binary chemical weapon, this is a two-component system consisting of innocuous parts that are mixed immediately prior to use to form the pathogen. This process occurs frequently in nature. Many pathogenic bacteria contain multiple plasmids (small circular extrachromosomal DNA fragments) that code for virulence or other special functions. The virulence of anthrax, plague, dysentery, and other diseases is enhanced by these plasmids. What occurs naturally in nature can be artificially conducted with basic biotechnology techniques in the laboratory. Virulent plasmids can be transferred among different kinds of bacteria and often across species barriers.

To produce a binary biological weapon, a host bacteria and a virulent plasmid could be independently isolated and produced in the required quantities. Just before the bioweapon was deployed, the two components would be mixed together. The transformation of the host organism back into a pathogen could conceivably take place after a weapon is triggered and during transport/flight. "Temple Fortune" indicated that scientists in the FSU had mastered this technique.

2) <u>Designer Genes</u>:[87] The Human Genome Project has decoded the alphabet of life and provided a human molecular blueprint.[88] Likewise, the complete genome sequences are now known for 599 viruses, 205 naturally occurring plasmids, 31 bacteria, one fungus, two animals, and one plant.[89] Many of these genomes have been published in unclassified journals and on the internet. To the bioweaponeer these are essentially blueprints that would enable him to make microorganisms more harmful.[90] Now that the codes are known, it seems only a matter of time until microbiologists develop synthetic genes, synthetic viruses, or even complete new organisms. Some of these could be specifically produced for biological warfare or terrorism purposes.

Perhaps the most obvious way to increase the effectiveness of any biological warfare pathogen is to render it resistant to antibiotics or antiviral agents. Some bacteria naturally develop resistance to antibiotics fairly quickly. Many antibiotic resistance genes have been identified. The best known of these is the gene that codes for beta-lactamase, the enzyme that defeats the action of penicillin. Such genes could be activated or introduced into other pathogens.

Entire viruses may similarly be created, analogous to the natural mutation of the influenza virus. A new strain of influenza could be created by induced hybridization of viral strains, simply swapping out variant or synthetic genes. Slightly altering a common virus like influenza to make it deadlier might be easier than manipulating more rare or biologically complicated pathogens.

For a bioweaponeer, the databases of increasing numbers of microbial genomes provide a virtual "parts list" of potentially useful genes for a genetic "erector set" to design and produce a new organism. It is possible to pick and choose the most lethal characteristics.[91] Some think it may be possible to create an entirely new organism from scratch. Some animal viruses are so small that their entire genome could be stitched together, at least in principle, from machine-synthesized fragments using current technology. Mycoplasma, an organism that causes pneumonia in humans, has the smallest known bacterial genome.[92] Genetic analyses of strains of mycoplasma indicate that only 265 to 350 genes are essential under laboratory growth conditions. Thus, it may be possible to create an entirely synthetic "minimal genome"[93] organism in the near future. If a

streamlined cell of this type were available, it would be an attractive template to build a bioweapon.[94]

As stated previously about viruses, although it may be possible to create life artificially from a set of component parts, this would probably be beyond the sophistication of most bioterrorists. It would be extremely difficult to engineer all of the desired "attributes" into a single pathogen and still have an organism that transmitted effectively and predictably. It would be much more likely that an existing pathogen would be subtly genetically modified to be more difficult to detect, more virulent, or more resistant to drugs, all within the capabilities of today's biotechnology.[95]

3) <u>Gene Therapy as a Weapon</u>:[96] Gene therapy will revolutionize the treatment of human genetic diseases. The goal is to effect a permanent change in the genetic composition of a person by repairing or replacing a faulty gene. Genes have already been spliced into bacteria to produce "human" insulin in large quantities.[97] The eventual goal is to splice a gene that codes for the production of insulin into human pancreatic tissue to cure diabetes. Similar research is progressing on adding in the missing gene to prevent the symptoms of cystic fibrosis. However, the same technology could be subverted to insert pathogenic genes.

There are two general classes of gene therapy: germ-cell line (reproductive) and somatic cell line (therapeutic). Changes in DNA in germ cells would be inherited by future generations. Changes in DNA of somatic cells would affect only the individual and could not be passed on to descendants. Manipulation of somatic cells is subject to less ethical scrutiny than manipulation of germ cells.

This concept has already been used to alter the immunity of animals. The vaccinia virus (a poxvirus used to make immunization against smallpox) has been used as a vector to insert genes in mammalian cells. This genetically engineered virus has been used successfully to produce an oral vaccine to prevent rabies in wildlife.

Research for similar gene splicing in humans continues for possible vectors to carry the replacement genes to their targets.[98] As has been done for animals, there is potential for human "vaccination" against certain diseases, or as a targeted delivery capability for therapeutic drugs or cytotoxic effects.[99]

One class of experimental vectors is the retroviruses which permanently integrate themselves into human chromosomes.[100] HIV, which causes AIDS, is a retrovirus. So it should not be hard to understand that gene therapy might have sinister capability.

A viral vector has already produced a lethal strain of mousepox virus.[101] The genetically manipulated virus completely suppressed the cell-mediated response (the arm of the immune system that combats viral infections) of the lab mice.[102] Even mice previously vaccinated against the natural mousepox virus died within days of exposure to the super virus. Mousepox (which does not infect humans) and smallpox are related viruses. If smallpox were to be similarly genetically manipulated, our current vaccine may not protect against it. These vectors are not yet very efficient in introducing genes into tissue cells. But if a medical technique is perfected, similar vectors might eventually be used to insert harmful genes into an unsuspecting population.

Techniques for cloning tissues and embryos continue to advance. Reproductive (germ-cell) cloning aims to implant a cloned embryo into a woman's uterus leading to the birth of a cloned baby. Therapeutic (somatic cell) cloning aims to use genes from a person's own cells to generate healthy tissue to treat a disease. For example, such cloning could be used to grow pancreatic cells to produce insulin to treat diabetes, or to grow nerve cells to repair damaged spinal cords.[104]

Already sheep, mice, swine, and cattle have been cloned. However, success (defined as births of live animals) rates are low.[105] Initial cloning work with human embryos to produce omnipotent stem cells has been reported.[106] Theoretically, the stem cells could in turn grow into virtually any cell type and serve as replacement tissue in diseases like diabetes.[107] Researchers have also used a virus to insert a jellyfish gene into a rhesus monkey egg and produced the first genetically altered primate.[108] The use of embryos and germ cells has raised many ethical questions.

4) <u>Stealth Viruses</u>:[109] The concept of a stealth virus is a cryptic viral infection that covertly enters human cells (genomes) and then remains dormant for an extended time. However, a signal by an external stimulus could later trigger the virus to activate and cause disease. This mechanism, in fact, occurs fairly commonly in nature. For example, many humans carry herpes virus which can activate to cause oral or

genital lesions. Similarly, varicella virus will sometimes reactivate in the form of herpes zoster (shingles) in some people who had chicken pox earlier in life. However, the vast majority of viruses do not cause disease.

As a biological weapon, a stealth virus could clandestinely infect the genome of a population. Later, the virus could be activated in the targeted population, or a threat of activation could be used as blackmail.

Oncogenes are segments of DNA that, when switched on, can initiate wild cellular growth and misbehavior—the hallmarks of cancer. Some viruses have segments of DNA that can mimic oncogenes and directly, or perhaps through bioregulators or host genes, cause cancer. These changes may take years for clinical effect, but the concept may still be considered by bioterrorists.[110]

5) <u>Host-Swapping Diseases</u>:[111] As previously stated, the vast majority of viruses do not cause disease. In nature, animal viruses tend to have narrow, well-defined host ranges. Unlike bacteria, viruses often infect only one or just a few species. When a virus has a primary reservoir in an animal species, but is transmissible to humans, it is called a zoonotic disease. Animal viruses tend to have a natural animal reservoir where they reside and cause little or no damage. Examples of reservoirs include birds for the West Nile Virus, water fowl for Eastern equine encephalitis and rodents for hantavirus. The bat is thought to be the reservoir for Ebola virus, and the chimpanzee is thought to have been the original reservoir for the HIV virus that causes AIDS. When viruses "jump species" they may occasionally cause significant disease. These examples illustrate that manageable infectious agents can be transformed naturally into organisms with markedly increased virulence.[112]

When this happens naturally, the process results in an emerging disease. If it were to be induced by man, it would be bioterrorism. In the laboratory of inspired, determined and well-funded bioterrorists, an animal virus may be genetically modified and developed specifically to infect human populations. Emerging diseases could have serious implications for biological warfare or terrorism applications.

6) Designer Diseases:[113] Our understanding of cellular and molecular biology has advanced nearly to the point where it might be possible to propose the symptoms of a hypothetical disease and then design or create the pathogen to produce the desired disease complex. Designer diseases may work by turning off the immune system, by inducing specific cells to multiply and divide rapidly (like cancer), or possibly by causing the opposite effect, such as initiating programmed cell death (apotosis). This futuristic biotechnology would clearly indicate an order-of-magnitude advancement in offensive biological warfare or terrorism capability.[114]

The concepts and mechanisms of the six classes of biological innovations that could be weaponized, as outlined by the JASON Group and discussed above, have some overlap. These classes were meant to identify a spectrum of conceivable bioterrorist threats based on current or near-future biotechnological capabilities. They were not meant to be all-inclusive or mutually exclusive of possibilities.[115]

Another authority on biological warfare, Malcolm Dando asserts that benign microorganisms might be genetically engineered to produce BW toxins, bioregulator compounds, or venoms.[116] Pathogens may also be genetically manipulated to enhance their aerosol or environmental stability, or defeat current identification, detection, and diagnostic capabilities.

Six Ways Science Can Improve Biodefense

Biological warfare and bioterrorism are multifactorial problems that will require multifactorial solutions. We need our best critical thinkers and biological researchers to solve this constantly evolving problem. Fortunately, the same advances in genomic biotechnologies that can be used to create bioweapons can also be used to set up countermeasures against them. There are six areas where biotechnology will likely make significant contributions:

- *Understanding the human genome*
- *Boosting the immune system*
- *Understanding viral and bacterial genomes*

- *Bio-agent detection and identification equipment*
- *New vaccines*
- *New antibiotics and antiviral drugs*

1) Understanding the human genome.[117] The Human Genome Project will have a profound influence on the pace of molecular biology research and help solve the most mysterious and complex of life's processes. New biotechnology should allow the analysis of the full cascade of events that occur in a human cell following the infection with a pathogen or the uptake of a toxin molecule. Circumstances that cause individual susceptibility to infectious diseases will become clear. Currently, the functions of nearly half of all human genes are unknown. Functional genomics studies should elucidate these unknowns and enable design of possible new strategies for prevention and treatment in the form of vaccines and anti-microbial drugs.

There have been reports of biological agents to target specific ethnic groups.[118] Although "biological ethnic cleansing" is a theoretical possibility, most experts are skeptical of this potential.[119] Analysis of the human genome sequence to date has failed to reveal any polymorphisms[120] that can be used to absolutely define racial groups. Several studies have shown that genetic variation in human populations is low relative to other species and most diversity exists within, rather than between, ethnic groups.

2) Boosting the immune system.[121] The complete sequencing of the human genome also provides a new starting point for better understanding of, and potential manipulation of, the human immune system. This has a tremendous potential against biological warfare.

After years of effort in the FSU to genetically engineer pathogens for biological warfare, Dr. Ken Alibek is now working to protect against the use of biological agents. He is researching mechanisms to boost the immune system to defend the body against infectious diseases. One of his initial projects is conducting cellular research that could lead to protection against anthrax. Similar immunological research in other labs has great promise to heighten the general human immune response to microbial attack in an effort to move beyond the "one bug-one drug" historical approach.

3) Understanding viral and bacterial genomes.[122] The genome projects for various microorganisms will explain why pathogens have the characteristics of virulence or drug resistance. A "minimal genome" was discussed previously in this paper. Creating a minimal genome would be an important milestone in genetic engineering as it would prove the capability to create organisms simply from the blueprint of their genomes. This research may provide insight into the very origins of life, bacterial evolution, and understanding the cellular processes of more complex life forms.

Bacteria may also be modified to produce bioregulators against pathogens. For example, *E. coli* has been genetically engineered to produce commercial quantities of interferon,[123] a natural protein that has antiviral activity against a variety of viruses. Xoma Corporation has patented a bactericidal/permeability-increasing (BPI) protein made from recombinant DNA (genes inserted into DNA sequences) technology that reverses the resistance of some bacteria to some widely used antibiotics. The search is on for other bioactive proteins that can affect the human response to infections.

4) Rapid/accurate bio-agent detection and identification techniques and equipment.[124] Biotechnologists need to continually develop more definitive, rapid, and automated detection equipment, regardless of whether or not bacteria have been genetically engineered. The capability to compare genomes using DNA assays is already possible. It is reasonable to contemplate a DNA microchip that could identify the most important human pathogens by deciphering bacterial and viral genomes. This detector could provide information on the full genetic complement of any BW agent even if it contained genes or plasmids from other species, had unusual virulence or antibiotic-resistance properties, or was a synthetic organism built from component genes. The ability to quickly identify and characterize a potential BW agent with a single test will greatly reduce the delays in current detection methods.

Geneticists deciphered the genome of the anthrax bacteria contained in the terrorist letters after September 11, 2001. DNA tests confirmed that the anthrax in every letter was the Ames strain.[125] Forensic scientists also looked for human DNA that might be inside the letters. The information was used for both the criminal investigation (gene clues that might help

track back to the perpetrator or origin of the culture) and for further medical research for diagnosis and treatment.[126] Gene sequencing techniques (molecular fingerprinting) for anthrax and other microbes will undoubtedly contribute to future forensics and diagnostics.

5) New vaccines.[127] Vaccines stimulate humoral[128] immunity, the production of specific antibodies for specific pathogens. The availability of many pathogen genome sequences has already led to development advances in new vaccines for some meningitis and pneumonia bacteria. Researchers have genetically engineered viruses in an attempt to create novel vaccines that would stimulate immunity against multiple diseases with a single treatment.[129] A California laboratory, Maxygen, is combining proteins from related pathogens in hope of developing vaccines that could provide broad protection.[130] Several other laboratories also have initiated genome-enabled efforts investigating ways to boost cell-mediated immunity against those pathogens for which it might be most effective. As yet, this approach has not been as successful as the development of vaccines but, as a result of genome sequencing, having knowledge of all available antigens has been enormously valuable.

6) New antibiotics and antiviral drugs.[131] Advances in microbial genomics hold great promise in the design of new anti-microbial drugs. Current antibiotics target three processes in bacterial cells: DNA synthesis, protein synthesis, and cell-wall synthesis. From deciphered genome information, any other protein essential for cell viability is a possible target for a new class of antibiotics. Although the first such antibiotics may be "silver bullets" for a specific infectious agent, the information gained may lead to broad-spectrum anti-microbial agents.

If the 1950s were the golden age of antibiotics, we are now in the early years of the age of antivirals.[132] With viral genomes decoded, scientists will soon decipher how viruses cause disease, and which stage of the disease-producing process might be vulnerable to interruption. Insights gleaned from the human genome and viral genomes have opened the way to development of whole new classes of antiviral drugs.

Conclusions

Genetically engineered pathogens constitute the "next generation" of biological warfare agents. Evidence indicates that the Russians have genetically engineered biological warfare agents. Ken Alibek's original debriefings were so shocking that some military and intelligence personnel preferred to believe that he was exaggerating.[133] As his statements about genetic engineering and FSU capabilities began to be substantiated, however, the reality began to sink in. Such genetic innovations obviously enhance adversarial offensive biological warfare effectiveness and complicate our defensive capability. Because we cannot know with certainty the specifics of these agents (lethality, communicability, and antibiotic resistance), it is imperative that we prepare for the unexpected. Two quotes come to mind. George Orwell said, "Life is a race between education and catastrophe." Further, Gene Kranz said, "Failure is not an option."

Although biologically engineered weapons may currently be less of a concern than their naturally occurring counterparts, the threat they pose can only increase as technology develops.[134] We are only in the initial stages of a revolution in biotechnology.[135] Historically, the available state-of-the-art biotechnology has been used in offensive BW programs (i.e., FSU applied the technology of the 1970s and '80s). Biotechnology is the ultimate double-edged sword. Once knowledge is attained, there is no going back.[136] As is the case with most powerful technologies, they can be employed for good or evil.[137] We must proceed with caution when developing new life-forms.[138] As new organisms are introduced into our delicate bio-equilibrium, we cannot fully predict all potential consequences to the biosphere. The same technology that is used to benefit mankind may paradoxically pose a threat to our military forces and civilian populations either by accident or by sinister forces. It is possible today to genetically engineer microorganisms for specific positive medical and industrial purposes. It is likewise possible to genetically engineer pathogens for biological warfare purposes. It seems likely that such weapons will be used in our lifetimes. Inevitably, sometime, somewhere, someone seems bound to try something with genetically engineered pathogens.[139] If they are ever released, they will pose an ominous challenge for medical care and governmental response.

The use of biological warfare agents on the battlefield against the United States has been restrained in recent history. There have been many declarations and conventions to attempt to define international norms and to regulate the use of biological weapons. In the end, the *law of war* is

somewhat of an oxymoron.[140] Several signatories of the 1972 BWC, including Iraq and the former Soviet Union, have participated in activities outlawed by the convention.[141] These events demonstrate the ineffectiveness of the convention as the sole means for eradicating biological weapons and preventing further proliferation. Ultimately, the most effective deterrent to their use has turned out to be fear of retaliation.[142] During the Gulf War, it is believed that Iraq was deterred from using biologicals and chemicals because Saddam Hussein feared nuclear or otherwise overwhelming retaliation.[143] We cannot be sure that future enemies will be so intimidated. Certainly, non-state terrorists actors will not be deterred as easily. Biotechnology has made it possible to inflict mass casualties using only small scale special operations that can evade detection in attempt to avoid retribution. In asymmetric warfare, biological weapons are seen as a "great equalizer."

The probability of a terrorist use of a genetically engineered biological agent on a given city is very low, but the consequence of such an event would obviously be very high.[144] With maximum casualties the likely goal, metropolitan areas are at the highest risk.[145] This dilemma is the challenge of local communities, which are sensitive to the need for preparedness, but have finite resources. Local communities must have a plan and sufficient medical and public health resources accessible to sustain a response for up to 24 hours. A robust federal assistance would be made available promptly, but it would not be immediate. Currently, dozens of federal entities fiercely compete for the missions and money associated with the unconventional terrorism response.[146] The Homeland Security Council is charged to coordinate a more efficient network of disaster response

capability.[147] At present, all military and civilian populations throughout the world are vulnerable to a BW attack.[148] We remain grossly ill-prepared to respond to an epidemic caused by a novel genetically engineered biological agent.

The 20th century was dominated by physics, but recent breakthroughs indicate that the next 100 years likely will be "the Biological Century."[149] There are those who say: "the First World War was chemical; the Second World War was nuclear; and that the Third World War – God forbid – will be biological."[150]

Notes

1. Stephen M. Block, "Living Nightmares: Biological Threats Enabled by Molecular Biology," in *The New Terror: Facing the Threat of Biological and Chemical Weapons*, eds. Sidney Drell, Abraham D. Sofaer, and George D. Wilson (Stanford, CA: Hoover Institution Press, 1999), 58; see also, Robert G. Webster, William J. Bean, Owen T. Gorman, Thomas M. Chambers, and Yoshihiro Kawaoka, "Evolution and Ecology of Influenza A Viruses," *Microbiological Reviews*, March 1992, 152-179.

2. Genetic engineering is a type of molecular biotechnology that uses laboratory techniques to isolate, manipulate, transfer, recombine, and allow expression of genes (DNA segments) between different organisms. In biological warfare or bioterrorism, adversaries might use genetically engineered agents that included both modified existing microbes and possibly novel synthetic life forms created to render them more effective as biological weapons than found in naturally occurring organisms.

3. Tom Mangold and Jeff Goldberg, *Plague Wars* (New York: St. Martin's Press, 1999), 92.

4. Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999), 43; see also, Lester C. Caudle III, "The Biological Warfare Threat," in *Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare*, eds. Frederick R. Sidell, Ernest T. Takafuji, and David R. Franz (Washington D.C.: Office of the Surgeon General, US Army, 1997), 454. Biopreparat constituted only half of the Soviet BW program. See Alibek's *Biohazard*.

5. Jonathan B. Tucker, *Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons* (Cambridge, MA: MIT Press, 2000), 4-5; and Jim A. Davis, "The Anthrax Terror," *Aerospace Power Journal*, Vol XIV, no. 4 (Winter 2000), 17.

6. Mangold and Goldberg, 182.

7. Ibid., 91-105; and Caudle, 453-4.

8. Mangold and Goldberg, 93-5.

9. Caudle, 454. Bacterial cells frequently contain extrachromosomal (located outside the cell nucleus), autonomously replicating DNA molecules known as plasmids. Some plasmids carry DNA sequences that can produce antibiotic resistance, virulence, or infectivity. Plasmids can move between bacteria.

10. Mangold and Goldberg, 94-5, 164; Col John Alexander, *Future War: Non-Lethal Weapons in the Twenty-First Century* (New York: St Martin's Press, 1999), 191.

11. Mangold and Goldberg, 93-7.

12. Ibid., 91-9.

13. Ibid., 163-5.

14. Alexander, 192; Mangold and Goldberg, 158-63.

15. Ibid., 164.

16. Block, 55-6.

17. Mangold and Goldberg, 177-95; Alibek, ix-xi.

18. Mangold and Goldberg, 178-9,182; Alibek, 3-304.

19. Alibek, 40-2, 155-6; Alexander, 191. Immediately after the 1972 Biological Weapons Convention treaty, President Brezhnev initiated the largest biological weapons program in history.

20. Mangold and Goldberg, 186.

21. Ibid., 180. 187-8.

22. Ibid.

23. Ibid., 179.

24. Ibid., 180.

25. Block, 49-50.

26. Mangold and Goldberg, 181.

27. Alibek, 160-1, 163-7, 272.

28. Ibid., 259; and Mangold and Goldberg, 181.

29. Alibek, 258-61; Mangold and Goldberg, 181.

30. Alibek, 273-5.

31. Block, 50-1, Alibek, 69-86.

32. *Plague War*, Frontline, PBS Home Video, Public Broadcasting Service, FROL-1706, 1998, 60 minutes.

33. A.P. Pomerantsev, N.A. Staritsin, Yu V. Mockov, and L.I. Marinin, "Expression of Cereolysine AB Genes in Bacillus anthracis Vaccine Strain Ensures Protection Against Experimental Hemolytic Anthrax Infection," *Vaccine*, Vol. 15, No. 17/18, 1997, 1846-1850.

34. Judith Miller, Stephen Engelberg, and William Broad, *Germs: Biological Weapons and America's Secret War* (New York, Simon and Schuster, 2001), 218-220.

35. Judith Miller, Stephen Engelberg, and William J. Broad, "U.S. Germ Warfare Research Pushes Treaty Limits," *New York Times*, 4 September 2001, A1, A6.

36. Laurie Garrett, The Coming Plague (New York: Penguin Books, 1994), 10.

37. Peter R. Lavoy, Scott D. Sagan, and James J. Wirtz, *Planning the Unthinkable: How New Powers Will Use Nuclear, Biological, and Chemical Weapons* (Ithica, NY: Cornell University Press, 2000), 5.

38. Malcolm R. Dando, *The New Biological Weapons: Threat Proliferation, and Control* (Boulder, CO: Lynne Rienner Publishers, Inc, 2001), 11.

39. Mangold and Goldberg, 182.

40. Ibid., 110,159-61, 176.

41. Ibid., 183.

42. Ibid., 98.

43. Tucker, 5.

44. *Association of Military Surgeons of the United States Newsletter*, vol. 9, issue 2, (Summer 2001), 4.

45. Mangold and Goldberg, 181; Alibek, xi.

46. Block, 41-5.

47. Lavoy et al, 4-5.

48. Mangold and Goldberg, 373.

49. Peter L. Hays, Vincent J. Jodoin, Alan R. Van Tassel, *Countering the Proliferation and Use of Weapons of Mass Destruction* (New York: The McGraw-Hill Companies, Inc., 1998), 9; Zilinskas estimates that it may only take five years for scientists working for "proliferant governments or subnational groups" to develop biological weapons from the new biotechnologies. R.A. Zilinskas (Ed.) *Biological Warfare: Modern Offense and Defense* (Boulder, CO: Lynne Rienner, 2000).

50. Tucker, 9.

51. Ibid., 8-9. Lavoy et al, 232, 257.

52. Raymond A. Zilinskas, *Biological Warfare: Modern Offense and Defense* (Boulder, CO: Lynne Rienner Publishers, 2000), 2-3.

53. Laurie Garrett, The Coming Plague: *Newly Emerging Diseases in a World of Balance* (New York: Penguin Books, 1994), 53.

54. Andrew F. Krepinevich, "Cavalry to Computer: The Pattern of Military Revolutions," *The National Interest*, No. 37, (Fall 1994), 30-42.

55. Moisés Naím, "Reinventing War," *Foreign Policy*, November/December 2001, 37.

56. Claire M. Fraser and Malcolm R. Dando, "Genomics and Future Biological Weapons: The Need for Preventive Action by the Biomedical Community," Published online: 22 October 20001 by Nature Publishing Group @ http//genetics.nature.com, 1.

57. Even crop duster aircraft and mosquito sprayer equipment are potential delivery mechanisms for bioterrorism.

58. Block, 60.

59. Ian O. Lesser, et. al, *Countering the New Terrorism* (Santa Monica, CA: RAND, 1999), 7-38. Although the total number of terrorist events worldwide has declined in the 1990s, the percentage of terrorist events resulting in fatalities (and total numbers of fatalities) increased; Ehud Sprinzak, "The Lone Gunman," *Foreign Policy*, November/December 2001, 72-3. According to Sprinzak, today's "megalomaniacal hyperterrorists" are innovators and developers. They incessantly look for original ways to surprise and devastate the enemy. They think big, seeking to go beyond "conventional" terrorism and, unlike most terrorists, could be willing to use weapons of mass destruction. If the intent of terrorists is to inflict mass casualties, then biological agents are likely to be used.

60. Richard Preston, *The Hot Zone* (New York: Anchor Books/Doubleday, 1994). Tom Clancy's *Executive Orders* and Michael Critchton's *The Andromeda Strain* were other popular books on pathogens.

61. Alexander, 215. PDD-62 contained major initiatives to combat internationalterrorism. PDD-63 addressed protection of the nation's critical infrastructure from both physical and cyber attacks.

62. *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century*, (Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, reprinted August 2000), vii.

63. Garrett, 6; Block, 59. New infectious diseases are thought to emerge due to situations where humans now live in close proximity to animals.

64. William J. Broad, "Genome Offers 'Fingerprint' for Anthrax: Analysis of Bacterium Could Help Investigators," *New York Times*, 28 November 2001, B-1-8.

65. Block, 45. The minimum lethal dose for inhalational anthrax (reported to be5,000 to 10,000 spores) is high compared to some other biological agents.

66. Fraser and Dando, 2.

67. Block, 46-7.

68. Drell, 355.

69. Ibid., 355; Sheryl Gay Stolberg with Melody Peterson, "U.S. Orders Vast Supply of Vaccine for Smallpox," *New York Times*, 29 November 2001, B-8.

70. Alibek, 258-61; Block, 49. The FSU's biological warfare program was massive, totaling over 18 complexes and 60,000 workers. Considering that this dwarfed the worldwide commitment to the Human Genome Project, there is significant concern about what the FSU bioscientists were able to accomplish. Despite President Yeltsen's order to close the Russian BW program, biological warfare research is thought to continue in the FSU.

71. Block, 51.

72. Caudle, 63-4.

73. Personal conversation with Bill Patrick, 6 September 2001.

74. Asymmetric warfare is the use of less technological, less expensive, and/or more unconventional weapons, tactics and strategies. Historically, this has taken the form of guerilla warfare, but today includes cyber war and the use of weapons of mass destruction.

75. Zilinskas, 1-2.

76. Katherine McIntire Peters, "Behind in the Biowar," *Government Executive*, December 2001, 28.

77. Ibid., 28. The potential to inflict damage on the enemy is obvious. Less clear is how to protect friendly troops from disease while spreading it among the enemy.

78. *The Worldwide Biological Warfare Weapons Threat*, 2001, 1.

79. Zilinskas, 6.

80. David Franz quoted by Peters in "Behind in the Biowar," 30.

81. Fraser and Dando, 2.

82. Dando, 58.

83. Donald Rumsfeld, *Report of the Quadrennial Defense Review*, (Washington D.C.: Department of Defense, September 2001), 7.

84. Block, 39-40.

85. Ibid., 51-70.

86. Ibid., 52-56.

87. Ibid., 56-60.

88. International Human Genome Sequencing Consortium, "Initial Sequencing and Analysis of the Human Genome," *Nature*, Vol 409, 15 February 2001, 860-921 (http://www.tigr.org/tdb/mdb/mdbcomplete.html); see also, David Baltimore, "Our Genome Unveiled," *Nature*, Vol 409, 15 February 2001, 814-816.

89. International Human Genome Sequencing Consortium, 860-921.

90. Rachel Nowak, "Disaster in the Making," *New Scientist*, 13 January 2001, 4-5.

91. Fraser and Dando, 3.

92. Clyde A. Hutchison, et al, "Global Transposon Mutagenesis and a Minimal Mycoplasma Genome," *Science*, Vol 286, 10 December 1999, 2165-2169.

93. A minimal genome can be defined as the smallest set of genes that allows forreplication of the organism in a particular environment.

94. Philip Cohen, "A Terrifying Power," *New Scientist*, 30 January 1999, 10.

95. Carina Dennis, "The Bugs of War," *Nature*, 17 May 01, 232-235.

96. Block, 60-63.

97. Zilinskas, 13. The bacteria *E. coli* have been genetically engineered to produce commercial quantities of valuable complex proteins, including insulin, human growth hormone, interferon, hepatitis B surface antigens, and angiotensin.

98. Bernard Moss, "Genetically Engineered Poxviruses for Recombinant Gene Expression, Vaccination, and Safety," *Proceedings of the National Academy of Sciences of the United States of America*, 1996, Vol. 93, 11341-11348, as abstracted in the *Journal of the American Medical Association*, 6 August 1997, Vol. 278, No.5., 350.

99. Block, 60.

100. Ibid., 62.

101. Ronald J. Jackson, et. al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology*, February 2001, 1205-1210.

102. Nowak, 4-5; see also, Stanley L. Robbins, Ramzi S. Cotran, and Vinay Kumar, *Pathologic Basis of Disease, Third Ed*. (Philadelphia: W.B. Saunders Company, 1984), 158. The immune response compromises all the phenomena that result from the specific interaction of cells of the immune system with antigens (foreign material). Entrance of an antigen into the body can have two possible outcomes: (1) a humoral immune response, involving the synthesis and release of antibody molecules within the blood and extracellular fluids; or (2) cell-mediated immunity, manifested by production of "sensitized" lymphocytes capable of interacting with antigens such as bacterial toxins and cause neutralization of the toxin, or they can coat the antigenic surfaces of microorganisms and render them susceptible to lysis by complement or to phagocytosis by macrophages. In the second type of reaction, the sensitized cells are responsible for such actions as rejection of foreign tissue grafts and resistance against many intracellular microbes, i.e., viruses, fungi, and some bacteria.

103. Dennis, 232-235.

104. Jose B. Cibelli, Robert P. Lanza and Michael D. West, with Carol Ezzell, "The First Human Cloned Embryo," *Scientific American*, January 2002.

105. Gina Kolata with Andrew Pollack, "A Breakthrough on Cloning? Perhaps, or Perhaps Not Yet," *New York Times*, 27 November 2001, A1-12.

106. Cibelli, x.

107. Gina Kolata, "Company Says It Produced Embryo Clones," *New York Times*, 26 November 2001, A-14.

108. Sharon Begley, "Brave New Monkey," *Newsweek*, 22 January 2001, 50-52.

109. Block, 63-65.

110. Garrett, 226-233.

111. Block, 65-68.

112. Zilinskas, 18.

113. Block, 68-71.

114. Fraser and Dando, 2.

115. Block, 51.

116. Dando, 41.

117. Fraser and Dando, 3.

118. Block, 47-48; Dando, 125-129.

119. Dennis, 232-235.

120. Fraser and Dando, 4; see also Dando, 127. Polymorphisms are differences in a specific gene. Single nucleotide polymorphisms (SNP) arise from the change of just one base pair in the DNA sequence. SNPs are markers that may lead to the genetic basis of many diseases. Theoretically, a SNP or sets of SNPs may provide new targets for new drugs, toxins, or bioregulators.

121. Peters, 30.

122. Mildred K. Cho, David Magnus, Arthur L. Caplan, Daniel McGee and the Ethics of Genomics Group, "Ethical Considerations in Synthesizing a Minimal Genome," *Science*, Vol 286, 10 December 1999, 2087-2090.

123. Zilinskas, 13-15.

124. Fraser and Dando, 3.

125. Rick Weiss, "A Terrorist's Fragile Footprint," *The Washington Post*, 29 November 2001, 1.

126. Broad, B1-8.

127. Fraser and Dando, 3.

128. Robins, 158. See footnote 102 for definitions of humoral and cell-mediated immunity.

129. Zilinskas, 21.

130. Dennis, 232-235.

131. Fraser and Dando, 3.

132. William A. Haseltine, "Beyond Chicken Soup," *Scientific American*, November 2001, 56-63.

133. Peters, 30.

134. Dennis, 232-235.

135. Dando, 11.

136. Block, 71.

137. Zilinskas, 5-6.

138. Alexander, 119-121, 196.

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