Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

chapter 64

Future Biologic and Chemical Weapons*

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HISTORICAL PERSPECTIVE

Biologic and chemical weapons have been used throughout history.[1] For millennia, indigenous South American peoples deliberately used plant-derived arrow poisons such as curare and toxins from poison dart frogs, although these preparations were used mainly for hunting. Similar toxins were used in Africa. The ancient Greeks, for whom *toxikon* meant "arrow poison," tipped arrows with winter aconite, and this practice continued into medieval Europe and persisted into the seventeenth century in Spain and Portugal.[2] Soldiers in India used smoke screens, incendiary weapons, and toxic fumes as early as 2000 BCE, and the Sung Dynasty in China employed a wide variety of arsenical smokes and other poisons in battle. The military use of toxins dates from at least the sixth century BCE, when Assyrian soldiers poisoned enemy wells with ergot-contaminated rye. In 423 BCE, during the Peloponnesian War, Thracian allies of Sparta captured the Athenian fort at Delium by using a long tube and bellows to blow a poisonous smoke from coals, sulfur, and pitch into the fort. Greek fire (likely composed of rosin, sulfur, pitch, naphtha, lime, and saltpeter) was invented in the seventh century CE and proved to be a very effective naval weapon. Various poisons saw battlefield use during medieval times, and the use of poisons for murder (including assassinations) became widespread. Other examples before the twentieth century include the contamination of water by dumping the corpses of dead humans or animals into wells, the use of snakes and other creatures as poisonous vectors, and occasionally, fomites to transmit infections such as smallpox to unsuspecting victims. This latter technique was used with remarkable success during the French and Indian War (1754-1767), when Sir Jeffrey Amherst was alleged to have given "gifts" (blankets) harboring the pus and scabs from smallpox victims to unsuspecting Native American Indians. The Indians possessed no immunity against smallpox and thus experienced very high rates of infection and mortality as smallpox swept through the local tribes.[3]

During the late nineteenth and early twentieth centuries, the science and technology necessary for the development of sophisticated biologic and chemical weapons proceeded apace. World War I saw the first large-scale use of "poison gas," including lacrimators, chlorine, phosgene, arsenicals, cyanide, and sulfur mustard. By the end of the war, nearly one in every three rounds was a chemical munition. Dr. Shiro Ishii and other Japanese scientists in the infamous Unit 731 worked on the weaponization of anthrax, plague, smallpox, and tetrodotoxin as well as a variety of chemical agents during World War II. There are even suspicions that the bomb used in the assassination of Reinhard Heydrich in Czechoslovakia in 1942 contained botulinum toxin.[4] After World War II, ricin was used as an injectable assassination weapon, and in the 1970s and 1980s T-2 toxin, a trichothecene mycotoxin, was alleged to have been the toxic component of the "yellow rain" employed against H'Mong refugees from Laos. More recently, Iraq and Iran both used chemical weapons against each other in the Iran-Iraq War of the 1980s, and Iraq had a weapons program that included the development of sulfur mustard, nerve agents, "Agent 15" (an anticholinergic incapacitating agent), botulinum toxin, epsilon toxin from *Clostridium perfringens*, and aflatoxin.[5] Militia groups in the United States and terrorist groups throughout the world have used ricin for political purposes.

American scientists started developing chemical weapons as a response to the use of chemical warfare in Europe during World War I and conducted both offensive and defensive research on biologic and chemical weapons. However, in 1969, the United States unilaterally renounced the first use of chemical agents, halted chemical-agent production, and terminated its offensive biologic weapons program.

In 1972, the Biological Weapons and Toxins Convention was created; it was signed by representatives from 104 nations, including the United States (which ratified the Convention in 1975), the Soviet Union, and Iraq, although many signatories did not consider toxins to be biologic weapons and did not consider the treaty binding on toxin use. Since that time, at least 140 nations have either signed or ratified this treaty.[6] However, the

*The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the U.S. Army, U.S. Navy, any other U.S. military organization, or any of the places where Dr. Darling works, or any governmental organization.

Soviet Union and Iraq began violating the treaty in short order. In the Soviet Union, weapons scientists stepped up research and development of numerous biologic and chemical weapons as part of one of the largest and most comprehensive biologic-weapons programs in history. Soviet scientists created large stockpiles of weaponized anthrax, plague, smallpox, tularemia, nerve agent, mustard, and other biologic and chemical agents.[5]

In 1979, the world was put on notice of the devastating potential that biologic weapons pose to humanity. In that year, a small quantity of weapons-grade anthrax was accidentally released from a manufacturing plant located in the former city of Sverdlovsk (now Yekaterinburg) in Russia. Seventy-seven cases and 66 deaths were reported. Dr. Matthew Meselson, a Harvard scientist, was permitted to study the event many years later and reported the results of his work in a 1979 *Science* article. Meselson determined that the majority of the deaths had occurred among victims living in a narrow 4-km-wide band downwind from the plant. Animal deaths were confirmed as far as 30 km downwind. Meselson further concluded that less than 1 g of weapons-grade anthrax had been released from the plant.[7] If his calculations are accurate, weaponized anthrax possesses staggering potential as a biologic weapon given its stability, its relative ease of production, and its ability to be dispersed in a clandestine manner over great distances.

In March 1995, after having unsuccessfully attempted to deploy biologic agents, members of the Aum Shinri Kyo cult executed a coordinated attack with the nerve agent sarin (GB) on the Tokyo subway system. Over 5500 people sought medical treatment, and a dozen died. The Aum Shinri Kyo had used sarin in Matsumoto 9 months earlier in an attack that had exposed more than 300 people and had killed 7 in an attempt to assassinate judges unfavorable to their cause.[8,9]

The anthrax attacks in the fall of 2001 involved the use of letters containing weapons-grade anthrax mailed through the U.S. postal system. Five people died and 17 became ill with either cutaneous or inhalational anthrax. Buildings contaminated with spores included the Hart Senate Office building and the Brentwood postal facilities in Washington, DC. It cost millions of dollars to rehabilitate these buildings. The anthrax used in the attacks was determined to be extremely potent and could have caused far greater numbers of casualties had it been dispersed more widely.[10,11]

According to Dr. Ken Alibek, former Deputy Director of Biopreparat, the Soviet Union's nominally civilian medical research institute, Soviet scientists and physicians spent large sums of money and manpower during the 1980s and 1990s developing the most lethal and potent biologic weapons known to man. In addition to weaponizing the etiologic agents of anthrax, smallpox, Marburg fever, and others, they created antibiotic-resistant strains of *Yersinia pestis* (plague), *Francisella tularensis*, and other pathogens. Furthermore, by applying genetic engineering techniques, the Soviets are also alleged to have created pathogens with novel characteristics and strains of several organisms capable of defeating certain vaccines.[12]

As we enter the biotechnologic revolution of the twenty-first century, our understanding of molecular biology, genetics, and biochemistry is exploding. The human genome has been sequenced, and it is now possible to manipulate genes from disparate organisms to create new and novel pathogens. Scientists are also able to synthesize and weaponize a number of different endogenous biologic-response modifiers including cytokines, hormones, neurotransmitters, and plasma proteases. But even nature continues to surprise us. New, naturally occurring infections with the potential to cause large-scale human diseases and death continue to emerge at an ever-increasing rate throughout the world, and it is conceivable that these pathogens could also be weaponized by enterprising scientists.

This chapter briefly reviews the future of chemical and biologic weapons as we enter this new era of explosive growth in our understanding of the life sciences. We are presented with an extraordinary opportunity to solve a host of human afflictions or to create new classes of biologic and chemical weapons that have the capacity to destroy our civilization as we know it today.

FUTURE BIOLOGIC WEAPONS

The appearance of a new or reemerging infectious disease has global implications. During the past 20 years, over 30 new lethal pathogens have been identified.[13] A classic example of this emerging threat is pandemic influenza. In 1918, as World War I was coming to an end, the Spanish flu struck with devastating consequences. In less than 1 year, this virus was able to circumnavigate the globe and kill an estimated 40 million people.[14] More recently, the emergence of severe acute respiratory syndrome (SARS) in Southeast Asia resulted from a coronavirus that jumped species from animals to humans and rapidly spread to 29 countries in less than 90 days. Novel and dormant infectious agents such as SARS or influenza appear to be emerging or reemerging with increasing frequency and with greater potential for serious consequences. Many factors contribute to the emergence of new diseases: environmental changes, global travel and trade, social upheaval, and genetic changes in infectious agent, host, or vector populations. Once a new disease is introduced into a suitable human population, it often spreads rapidly and with devastating impact on the medical and public health infrastructure. If the disease is severe, it may lead to social disruption and have a profound economic impact. Outbreaks of emerging or reemerging diseases may be difficult to distinguish from outbreaks as a result of intentional introduction of infectious diseases for nefarious purposes.

As scientists develop more sophisticated laboratory procedures and increase their understanding of molecular biology and the genetic code, the possibility of bioengineering more virulent, antibiotic, and vaccine-resistant pathogens for military or terrorist uses becomes increasingly likely. It is already theoretically possible to synthesize and weaponize certain biologic response modifiers (BRMs) as well as to engineer genomic weapons capable of inserting novel DNA into host cells.

The potential to cause widespread disease and death with any of these weapons is incalculable and concerning. Scientists and policy makers have begun to address the issue with a robust research agenda to develop medical countermeasures.

Selected Emerging and Reemerging Infections with Weaponization Potential

Because emerging diseases are so diverse and endemic to different geographic locations, their complete description is beyond the scope of this chapter. However, some of these infections may become future threats as agents of biologic warfare or terrorism. The most worrisome emerging infectious disease may well be the one we don't know about. Recent experience with HIV, Ebola fever, SARS, monkeypox, West Nile fever, and hundreds of other "new" diseases reveal that we will continue to be surprised.

Avian Influenza

Avian influenza, or highly pathogenic avian influenza, has periodically caused human infections primarily through close contact with avian species, most often through occupational contact at chicken or duck farms in Southeast Asia. As of May 2004, a large outbreak of avian influenza involving the H5N1 strain and human cases has been reported in two countries from this region.[15] Thus far, no human-to-human transmission has been reported, but the potential exists for genetic reassortment between avian and human or animal strains of influenza. A recent report in the journal *Science* linked the influenza virus responsible for the 1918 epidemic to a possible avian origin.[16] If true, avian influenza may pose a much greater danger to human populations than previously reported. The disease presents in humans in a fashion similar to other types of influenza viruses. It usually begins with fever, chills, headaches, and myalgias and often involves the upper and lower respiratory tract with development of cough, dyspnea, and in severe cases, acute respiratory distress syndrome. Laboratory findings may include pancytopenia, lymphopenia, elevated liver enzymes, hypoxia, a positive reverse transcriptase-polymerase chain reaction test for H5N1, and a positive neutralization assay for H5N1 influenza strain. In vitro studies suggest that the neuraminidase (NA)-inhibitor class of drugs may have clinical efficacy in the treatment and prevention of avian influenza infection.[17]

Human Influenza

The threat for pandemic spread of human influenza viruses is substantial. The pathogenicity of human influenza viruses is directly related to their ability to alter their eight viral RNA segments rapidly; the new antigenic variation results in the formation of new hemagglutinin (HA) and NA surface glycoproteins, which may go unrecognized by an immune system primed against heterologous strains.

Two distinct phenomena contribute to a renewed susceptibility to influenza infection among persons who have had influenza illness in the past. Clinically significant variants of influenza A viruses may result from mutations occurring in the HA and NA genes and expressed as minor structural changes in viral surface proteins. As few as four amino acid substitutions in any two antigenic sites can cause such a clinically significant variation. These minor changes result in an altered virus able to circumvent host immunity. Additionally, genetic reassortment between avian and human or avian and porcine influenza viruses may lead to the major changes in HA or NA surface proteins known as *antigenic shift*. In contrast to the gradual evolution of strains subject to antigenic *drift,* antigenic shift occurs when an influenza virus with a completely novel HA or NA formation moves into humans from other host species. Global pandemics result from such antigenic shifts.

Influenza causes in excess of 30,000 deaths and over 100,000 hospitalizations annually in the United States. Pandemic influenza viruses have emerged regularly in 10- to 50-year cycles for the last several centuries. During the last century, influenza pandemics occurred three times: in 1918 ("Spanish influenza," a H1N1 virus), in 1957 (Asian influenza, a H2N2 subtype strain), and in 1968 (Hong Kong influenza, a H3N2 variant). The 1957-1958 pandemic caused 66,000 excess deaths, and the 1968 pandemic caused 34,000 excess deaths in the United States. The 1918 influenza pandemic illustrates a worst-case public health scenario; it caused 675,000 deaths in the United States and 20 to 40 million deaths worldwide.[16] Morbidity in most communities was between 25% and 40%, and the case-mortality rate averaged 2.5%. A reemergent 1918-like influenza virus would have tremendous societal effects, even in the event that antiviral medications were effective against this more lethal influenza virus.

SARS and SARS-associated Coronavirus

SARS-associated coronavirus (SARS-CoV) emerged as the cause of SARS during 2003. That year, SARS was responsible for approximately 900 deaths and over 8000 infections in people from at least 29 countries worldwide. Before a case definition had been clearly established, Chinese authorities reported to the World Health Organization (WHO) over 300 cases of an atypical pneumonia with five related deaths, all originated from Guangdong province in China during February 2003. The infection quickly spread as infected patients traveled to Hong Kong and from there to Vietnam, Canada, and other locations. Only eight laboratory-confirmed cases occurred in the United States, but there is concern that the U.S. population is vulnerable to a widespread outbreak of SARS such as the one that occurred in China, Hong Kong, Singapore, Toronto, and Taiwan in 2003.[18]

A SARS case definition evolved from this initial report to the WHO by Chinese health authorities in February 2003. A case was initially defined by clinical criteria; a suspected or probable case was defined as an illness that included potential exposure to an existing case and fever with pneumonia or respiratory distress syndrome. In April 2003, a confirmed case was defined as a case from which SARS-CoV was isolated from culture.[19] SARS-CoV

infections have an incubation period of 2 to 10 days. Systemic symptoms such as fever and chills followed by a dry cough and shortness of breath begin within 2 to 7 days. Patients may develop pneumonia and lymphopenia by days 7 to 10 of the illness. Most patients with SARS-CoV have a clear history of exposure either to a patient with SARS or to a setting in which SARS-CoV is known to exist. Laboratory tests may be helpful but do not reliably detect infection early during the illness. SARS-CoV should be suspected in patients requiring hospitalization for radiographically confirmed pneumonia or acute respiratory distress syndrome of unknown etiology and one of the following risk factors during the 10 days prior to the onset of illness: (1) travel to China, Hong Kong, or Taiwan, or close contact with an ill person having a history of such travel; (2) employment in an occupation associated with a risk for SARS-CoV exposure; or (3) inclusion in a cluster of cases of atypical pneumonia without an alternative diagnosis.

A "respiratory hygiene/cough etiquette" strategy should be adopted in all SARS-affected healthcare facilities. All patients admitted to the hospital with suspected pneumonia should receive the following measures: (1) They should placed in droplet isolation until it is determined that isolation is no longer indicated (standard precautions are appropriate for most community-acquired pneumonias; droplet precautions for non-avian influenza); (2) they should be screened for risk factors of possible exposure to SARS-CoV; and (3) they should be evaluated with a chest radiograph, pulse oximetry, complete blood count, and additional workup as indicated. If the patient has a risk factor for SARS, droplet precautions should be implemented pending an etiologic diagnosis. When there is a high index of suspicion for SARS-CoV disease, the patient should be treated in terms of SARS isolation precautions immediately (including airborne precautions), and all contacts of the ill patient should be identified, evaluated, and monitored.[19] Although ribavirin, high-dose corticosteroids, and interferons have been used in treatment, it is unclear what effect they have had on clinical outcome. No definitive therapy has been established. Empiric antibiotic treatment for community-acquired pneumonia by the current American Thoracic Society/Infectious Diseases Society of America guidelines is recommended pending etiologic diagnosis. Diagnostic tests for SARS-CoV include antibody testing using an enzyme immunoassay and reverse transcriptase-polymerase chain reaction tests for respiratory, blood, and stool specimens.[20] In the absence of known SARS-CoV transmission, testing is recommended only in consultation with public health authorities. Testing for influenza, respiratory syncytial virus, pneumococcus, chlamydia, mycoplasma, and legionella should be conducted, since the identification of one of these agents excludes SARS by case definition. Clinical samples can be obtained during the first week of illness with a nasopharyngeal swab plus an oropharyngeal swab and a serum or a plasma specimen. After the first week of illness, a nasopharyngeal swab plus an oropharyngeal swab and a stool specimen should be obtained. Serum specimens for SARS-CoV antibody testing should be collected when the diagnosis is first suspected and at later times as indicated. An antibody response can occasionally be detected during the first week of illness, is likely to be detected by the end of the second week of illness, and at times may not be detected until more than 28 days after the onset of symptoms. Respiratory specimens from any of several different sources may be collected for viral and bacterial diagnostics, but the preferred specimens of choice are nasopharyngeal washes or aspirates.[20]

Nipah and Hendra Viruses

The Nipah and Hendra viruses are closely related but distinct paramyxoviruses that compose a new genus within the family Paramyxoviridae. The Nipah virus was discovered in Malaysia in 1999 during an outbreak of a zoonotic infection, now called *Nipah virus encephalitis,* involving mostly pigs and some human cases.[21] Hendra, the causative agent of Hendra virus disease, was identified in a similar outbreak involving a single infected horse and three human cases in Southern Australia in 1994.[22] It is believed certain species of fruit bats are the natural hosts for these viruses and remain asymptomatic. Horses and pigs act as amplifying hosts for the Hendra and Nipah viruses, respectively. The mode of transmission from animal to humans appears to require direct contact with tissues or body fluids or with aerosols generated during butchering or culling. Personal protective equipment including gowns, gloves, and respiratory and eye protection is advised for agricultural workers culling infected animal herds. Thus far, human-to-human transmission of these viruses has not been reported.

In symptomatic cases, the onset of disease begins with flu-like symptoms and rapidly progresses to encephalitis with disorientation, delirium, and coma. Fifty percent of those with clinically apparent infections have died from their disease. There is currently no approved treatment for these infections, and therefore, therapy relies heavily on supportive care. The antiviral drug ribavirin has been used in past infections, but its effectiveness remains unproven in clinically controlled studies.[23] Although no person-to-person transmission is known to have occurred, barrier nursing and droplet precautions are recommended because respiratory secretions and other bodily fluids are known to harbor the virus. The clinical laboratory should be notified before specimens are sent because these may pose a laboratory hazard. Specimens for viral isolation and identification should be forwarded to a reference laboratory. Requests for testing should come through public health departments, which should contact the Centers for Disease Control and Prevention (CDC) Emergency Operations Center at 770-488-7100 before sending specimens.

Biologic Response Modifiers

BRMs direct the myriad complex interactions of the immune system. BRMs include erythropoietins, interferons, interleukins, colony-stimulating factors, granulocyte and macrophage colony-stimulating factors, stem-cell growth factors, monoclonal antibodies, tumor-necrosis-factor inhibitors, and vaccines.[24]

A growing understanding of the structure and function of BRMs is driving the discovery and creation of many novel compounds including synthetic analgesics, antioxidants, and antiviral and antibacterial substances. For example, BRMs are being used to treat debilitating rheumatoid arthritis by targeting cytokines that contribute to the disease process.[25] By neutralizing or eliminating these targeted cytokines, BRMs may reduce symptoms and decrease inflammation. BRMs may also be used as anticarcinogens, with the following goals: (1) to stop, control, or suppress processes that permit cancer growth, (2) to make cancer cells more recognizable, and therefore more susceptible, to destruction by the immune system, (3) to boost the killing power of immune system cells, such as T cells, natural killer cells, and macrophages, (4) to alter growth patterns in cancer cells to promote behavior like that of healthy cells, (5) to block or reverse the processes that change a normal cell or a precancerous cell into a cancerous cell, (6) to enhance the ability of the body to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, such as chemotherapy or radiation, and (7) to prevent cancer cells from spreading to other parts of the body.[26,27]

More of these promising new drugs are currently in development. It can be readily theorized that research to develop various BRMs can be subverted to a malicious end. That is, instead of using BRMs to suppress cancer growth or to decrease disease susceptibility, researchers could develop compounds to cause illness and death. Other drugs could be designed to alter certain metabolic processes or to alter brain chemistry to affect cognition or mood. The opportunity for mischief is limited only by the imagination of the person with ill intent.

Bioengineered Pathogens

The rapid advance of biotechnology has the potential to alter the present and future threat of biologic weapons. Already, complete or partial genomic sequence data for many of the most lethal human pathogens (such as anthrax, plague, and the smallpox virus) have been published and are widely available via the Internet.[28] In addition to the enormous explosion in our knowledge of human pathogens, there is a parallel increased understanding of the complexities of the human immune response to foreign agents and toxins. Such knowledge has led to a deeper understanding of the development of basic immunity to a variety of different human infectious diseases. With this increase in scientific knowledge has come the power to manipulate the immune system at its most fundamental level. As we prepare for future threats, we must not ignore the potential quantum leap that biotechnology offers our enemies in developing new biologic-warfare threats. In fact, there is mounting evidence that new biologic agents have already been produced by former adversaries. Examples of such new threat agents and the potential effects they might have on human subjects have been detailed in the scientific and popular literature. Examples of biologic threats that could be produced through the use of genetic engineering technology include the following: (1) microorganisms resistant to antibiotics, standard vaccines, and therapeutics, (2) innocuous microorganisms genetically altered to produce a toxin, a poisonous substance, or an endogenous bioregulator, (3) microorganisms possessing enhanced aerosol and environmental stability characteristics, (4) immunologically altered microorganisms able to defeat standard threat identification and diagnostic methods, (5) genetic vectors capable of transferring human and foreign genes into human cells for therapeutic purposes,[28] and (6) combinations of these with improved delivery systems.

POTENTIAL FUTURE CHEMICAL WEAPONS

Nature of the Problem

The threats associated with the use of chemical weapons as battlefield or terrorist weapons are not easy to assess.[29,30] Risk assessment of use must take into account national laws, international treaties and conventions, and the likelihood of adherence to these legal obligations. Loopholes in existing agreements can be exploited to develop weapons that are technically not proscribed by international law. Goals and objectives may vary depending on whether military use is planned at the strategic, tactical, or operational level and whether the developer is a national government, a breakaway republic, a kidnapped or recruited scientist, or a terrorist cell. Risk of use may also differ depending on whether the targets are military versus civilian, human versus nonhuman (animals or plants, including livestock and crops), or individual (as in assassinations) versus large groups, and depending on whether the aim is death versus incapacitation. Risk also depends on agent availability and on the technology available for production, storage, and dissemination; current advances in technology are associated with a higher risk of weaponization. The fallibility of intelligence can be illustrated by two examples from the twentieth century and one from the twenty-first:

1. During most of World War II, the Allied perception of risk from possible chemical-agent use by Axis powers focused on those agents, primarily pulmonary agents and vesicants, known from World War I. In fact, Germany had developed a new kind of chemical-warfare agent, the compounds later to be called G-series nerve agents. Their existence came as a complete surprise to Western governments when, in the waning days of the European campaign, Allied soldiers advancing into Germany discovered buried nerve-agent munitions and entire nerve-agent factories. Why these agents were never used on the battlefield is a topic of much speculation, but in retrospect they clearly posed the most lethal, yet unrecognized, threat from Germany.[31]
2. Assessment of the chemical threat posed by Saddam Hussein at the time of the Gulf War of 1991 centered on the known Iraqi use of sulfur mustard and nerve agents during the Iran-Iraq War in the 1980s. It was not until 1998 that Reuters News Agency reported the

discovery by British intelligence that Iraq had stockpiled large quantities of a "mental incapacitant" (incapacitating agent) known as Agent 15.[32]

3. The risk of use of chemical agents by Iraq after 2001 was assessed to be high partly because of the known stockpiles of sulfur mustard and nerve agents (as well as the suspected stockpiles of cyanide and the new revelations about Agent 15) from the time of the 1991 Gulf War. Although a full accounting has yet to be made, allegations have been made that most of the Iraqi chemical stockpile was actually destroyed in 1991 or soon afterward and that the risk of their use was actually very low. Whether those reports are true does not invalidate the argument that the risk from these agents was still very much debatable.

Chemical agents originally used during World War I are sometimes considered obsolete, especially in comparison to the more potent nerve agents and incapacitating agents. However, agent potency is only one part of the story. To deliver the 10 μg that represents a lethal dose for half of an exposed group (LD_{50}) of the nerve agent VX would seem to be easier than delivering the 3 to 7 g that constitute the LD_{50} of sulfur mustard and more difficult than delivering the much smaller lethal doses of toxins such as botulinum toxin. In fact, sulfur mustard is easier to synthesize than is nerve agent and is easy to disseminate in a clandestine manner to create delayed effects. Thus, mustard still lays claim to being the "King of Gases," and it has allegedly been used in a variety of venues since the end of World War II. Most known chemicals with toxicities equal to or greater than that of ammonia could theoretically be used as chemical-warfare or terrorism agents.

Existing Agents and Their Potential for Future Use

Existing chemicals capable of weaponization for military or terrorist use include the following:

1. Battlefield and riot-control agents
   a. Pulmonary agents (see Chapter 93)
   b. Vesicants (see Chapter 92)
   c. Cyanide (see Chapter 94)
   d. Nerve agents (see Chapter 91)
   e. Antimuscarinic agents such as BZ and Agent 15 (see Chapter 95)
   f. Riot-control agents (see Chapter 98)
   g. Defoliants and other herbicides
   h. Novichok
   i. New chemicals employed for physicochemical effects
2. Related compounds
   a. Battlefield incendiary agents, smokes (including standard military white obscurant smoke, or HC smoke), and other combustion products such as oxides of nitrogen and perfluoroisobutylene (PFIB)
   b. Opioids (see Chapter 97) and other anesthetic agents (see Chapter 100)
   c. Cholinergic agents (see Chapter 99)
   d. Psychedelic indoles and other hallucinogens (see Chapter 96)
3. Toxic industrial chemicals or materials (see Chapter 90)
4. Poisons
5. Toxins (see Chapters 131-137)
6. Combination of chemicals

Existing chemicals remain candidate agents for future use. Some compounds not developed to cause injury or incapacitation nevertheless can be very dangerous; HC smoke, for example, can cause the same type of pulmonary damage induced by phosgene. The CDC lists nearly 70 separate chemicals, including a variety of toxic industrial chemicals and poisons, as potential agents for terrorism. These include osmium tetroxide, long-acting anticoagulants, heavy metals, toxic alcohols, and white phosphorus.[33] A recent issue of the *Morbidity and Mortality Report* includes an even longer list.[34] Pyrolysis products from explosions and conflagrations may release large quantities of cyanide and other toxicants that, although different from the original chemicals present, may still cause death. Industrial chemicals are readily available in large quantities as preformed compounds and should be considered high on the list of potential terrorist agents.[35,36] Toxins, which are chemicals produced within biologic organisms, also represent high-threat agents.[37] New chemicals are currently being synthesized on rigid three-dimensional molecular skeletons, the most promising of which are the norbornanes. Building on norbornane geometry allows for a modular enhancement of the number of functional sites on a given molecule. Since many norbornane derivatives, such as the mixture of chlorobornanes known as the toxaphenes, are persistent and have significant acute and chronic toxicity, these derivatives have been considered potential candidates for new agents.[38]

Novichok[39-42] (Russian for "newcomer") refers to the alleged Russian development of a highly toxic binary nerve agent or generation of nerve agents (sometimes called "fourth-generation" agents). Only sketchy and unverifiable information is available in the unclassified literature, but the existence of these agents would demonstrate the possibility of creating new chemical compounds toxic enough to be used as chemical-warfare or terrorist agents. So-called GV analogs combining some of the properties of G-series and V-series nerve agents have also been suggested as potential new agents.[38] The use in 2002 of an incapacitating gas (thought to be an opioid compound derived from fentanyl and possibly mixed with another anesthetic agent) in the siege of a Moscow theater taken over by Chechen rebels was evidence either of the deployment of a preexisting anesthetic agent or of a new anesthetic compound.[43,44] Organofluorines have been investigated because of their reported ability to defeat protective-mask or chemical-filtrations systems.[38] Other incapacitating agents under development exert primarily physical rather than chemical effects and include immobilizing agents ("stickums"), antitraction gels ("slickums"), and malodorants.[45]

Technologic Modifications of Battlefield Chemical Agents and Delivery Systems

Ways in which existing or future battlefield chemical agents and delivery systems could be modified to

improve performance must be considered. These modifications include the following:

1. Agent thickening
2. Binarization
3. Micronization: "dusty agents"
4. Developments in delivery systems
   a. Dual-use cyberinsects and biorobots
   b. Nanotechnology

Small quantities of thickening agents, such as acrylates, can be added to chemical agents to increase their viscosity. Thickened agents are more persistent in the environment and in wounds than are nonthickened agents, and they are less easily decontaminated.[46] Although no nation is currently known to stockpile thickened agents, the technology for their production is relatively simple and requires only standard chemical-warfare agents and the right proportion of a thickener.[38a,38b,47] Many industrial chemicals and other poisons could theoretically be rendered more effective as battlefield or terrorist agents by thickening.

In the 1950s, the U.S. Army began to investigate the then-new technology of binarization, although production did not accelerate until the 1960s and deployment was not widespread until the 1980s.[39] A binary chemical weapon did not employ a new kind of agent but rather represented a novel way of producing and storing an already existing type of agent. The idea was to make storage of chemical rounds safer by stopping the production process at the penultimate synthetic step, resulting in two precursor compounds that when mixed would create the desired agent. These two precursors could then be stored separately. Just prior to use, one component could be inserted into a round, where it would be separated from the other precursor by a thin membrane. The impact and momentum of the launch of the projectile would burst the membrane to allow for mixing of the components and in-flight production of the chemical agent. In practice, this process was often not complete, but the 20% or so of ancillary reaction product was often extremely toxic by itself. Binarization or some similar production-arrest method could theoretically be used by a clandestine terrorist cell to help evade detection and to decrease the risks associated with the production, transportation, and use of chemical agents.

Micronization is a type of particularization involving the production of extremely fine particles onto which a chemical agent can be adsorbed. During World War II, Germany explored particularization of sulfur mustard onto small carrier particles of silica (silicon dioxide), although other powdered silicates (talc, diatomite, and pumice) and clays (kaolinite and Fuller's earth) can also be used.[48] The advantages of such "dusty agents" are increased volatility (used to facilitate the movement of relatively nonvolatile agents such as sulfur mustard and the persistent nerve agent VX into the alveoli) and increased penetration of clothing and chemical protective equipment.[49] Iraq used a "dusty mustard" composed of 65% sulfur mustard adsorbed onto silica particles ranging in diameter from 0.1 to 10 microns during its war with Iran. Micronization of a variety of chemical, biologic, and toxin agents requires a certain degree of technologic sophistication that is becoming increasingly easy to acquire.

Agent delivery can potentially be modified in a variety of ways in addition to thickening and micronization. The Jordanian government released a report in 2004 of the discovery of an elaborate plot by Al Qaeda terrorists for a two-stage attack using a massive vehicle-borne improvised explosive device followed by the release of toxic chemicals to include acetones, nitric acid, and sulfuric acid.[50] Similarly, enhanced-fragmentation munitions could be used in combination with chemical agents to drive the agents more effectively into the body.

Innovative new delivery systems taking advantage of advances in robotics include the proposed use of cyberinsects and biorobots to deliver biologic agents, chemical agents, or toxins.[51] Engineering on an even smaller scale is the purview of nanotechnology, also called "micromechanical engineering" and "microelectromechanical systems."[52] Nanotechnology takes advantage of the unique properties of materials on the scale of about a nanometer (10^{-9} meter)[53] and deals with the molecule-by-molecule or even atom-by-atom assembly of materials. Nanoparticles behave in unusual and unpredictable ways, are small enough to enter cells easily, and in fact are being developed to provide not only better storage and dispersal of pharmaceutical products but also more efficient transport of both biologic organisms (such as viruses) and chemical compounds into the body.[52] In some cases they may be surprisingly toxic, partly because of the ease with which they can cross membranes (including the blood-brain barrier) and enter cells.[54] This toxicity could be exploited by governments or terrorist organizations interested not only in small-particle delivery of chemical agents but also in the ancillary and perhaps synergistic effects of the carrier materials themselves.

Nanomaterials can be encapsulation compounds such as *fullerenes*, or buckyballs, which are hollow 60-carbon geodesic shells; *nanoshells* (for example, a gold shell surrounding an inert silica core); a "self-assembled, polyamino acid nanoparticles system" under development in France; or *dendrimers*, which are onion-like layers of shells surrounding a biologically active core.[53] Any of these materials could be used to deliver existing or new chemical agents. Other nanomaterials include self-assembling liquids composed of cylindrical nanofibers (each 6 to 8 nm in diameter) that solidify upon injection to form structured scaffolds capable of presenting ordered peptide signals to cells. A *ferrofluid* such as a colloidal suspension of nanoscale ferrous oxide can be coupled with antibodies in a laboratory to detect and concentrate rare human cells in a diagnostic setting, but this technology could easily be adapted to target those cells in vivo. *Quantum dots* are nanoscale semiconductor crystals that show promise in the in vitro and in vivo diagnosis of a variety of conditions; although their main use is projected to be in the laboratory, animal experimentation involving injected quantum dots has demonstrated successful targeting of lymph nodes and of prostate-cancer xenografts in mice.

Adverse health effects from any of these kinds of nanoparticles could represent a primary goal for military

or terrorist operatives in addition to the toxicity of any other chemicals delivered by the nanoparticles. Water-soluble fullerenes have caused brain damage in large-mouth bass,[55] dendrimers can cause osmotic and membrane damage and can activate the clotting and complement systems, and quantum dots composed of selenium, lead, and cadmium can release those metals into cells, depending on the composition of the surface coating of the dots.[53]

"Designer" Chemicals from Biotechnologic Processes

Biotechnology refers to "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."[56] Biotechnology includes such time-honored practices as the baking of bread and the brewing of beer, but in the twenty-first century refers in particular to genetic engineering, that is, the artificial transfer of genes from one organism to another and the consequent alteration of the genetic structure of a cell.[57] It is founded on the basic sciences of genomics (the study of the genetic composition of an organism) and proteomics (the study of the expression of the genome by means of protein synthesis). "Designer" chemicals could be produced from biotechnologic processes. These processes include the following: (1) combinatorial chemistry and ligand modification, (2) genomics and target identification, (3) microarrays, proteomics, and rational agent design, and (4) toxicogenomics, database mining, and the prediction of toxicity.[58]

Combinatorial chemistry is the production of complex sets, or so-called libraries, of related compounds, as in the case of the norbornane derivatives previously described. Automated screening techniques to select for library elements with desired toxic effects on specified target organs can process several hundred thousand compounds a day against several dozen different proteins. This obviously accelerates tremendously the development of new chemical agents.

Genomics has benefited enormously from three modern scientific efforts: the Human Genome Project, the Human Genome Diversity Project, and gene therapy.[59] Identification and cataloging of hundreds of single-nucleotide polymorphisms (individual sequence variations) allows for the selection of genomic sequences to be mass-produced for insertion into cells for the creation of a specific effect. Targeting unusual sequences of high prevalence in certain populations raises the specter of genomic, or ethnic, weapons, as previously described. Less appreciated is the potential for genomics to be used to develop drugs, chemical or toxin agents that can also be targeted to specific variants within a population of humans, animals, or crops. The widespread availability of genome libraries on the Internet makes it nearly impossible to control or restrict access to the already published genomic libraries on over a hundred microbial pathogens.[60]

Proteomics complements genomics by characterizing the protein expression of segments of the genome and by making it easier to develop compounds that target or produce a specific protein. Direct gene insertion, genetic delivery via virus or bacteria, or drug tailoring to affect a given protein can all be used. A scorpion toxin has already been successfully engineered into a virus that acts as a pesticide against caterpillars. Protein sequences in toxins are partly responsible for resistance to light, oxygen, moisture, and desiccation; the insertion of genes to create altered proteins or the introduction of chemical agents engineered to cause structural changes in expressed proteins could significantly alter the toxicity of a given compound.[58] Furthermore, the widespread use of DNA microarrays (glass slides or chips imprinted with thousands of specific single-stranded DNA sequences) allows for fast automated screening of candidate compounds.

Scientists involved in the selection and evaluation of specific chemical agents can now use toxicogenomics (the study of genetic variation of response to toxins) and data mining (the computerized analysis of databases of drug and chemical information via sophisticated neural nets) as tools to eliminate less likely candidates and to algorithmically predict compounds with high toxicity or with other desired characteristics relating to environmental persistence, toxicokinetics (absorption, distribution, biotransformation, and elimination), and toxicodynamics (mechanism of action). Such tools will undoubtedly lead to the development not only of new pharmaceutical agents but also of designer toxins for military or terrorist use.[58]

CONCLUSIONS

If history is any guide, new biologic and chemical weapons and novel "mid-spectrum" agents (e.g., toxins, bioregulators, synthetic viruses, and genocidal weapons) will be developed in the future, and new modifications will be found to improve the production, weaponization, storage, delivery, and action of existing agents.[61] Naturally occurring emerging infectious diseases provide examples of newly identified pathogens with weaponization potential, and mid-spectrum agents such as toxins and bioregulators will undoubtedly assume more prominence with the accelerating pace of nanotechnology (for improved delivery and for synergistic toxicity) and biotechnology. Agents of any category can theoretically be engineered to target specific genes or proteins with differential population prevalence to produce genomic or ethnic weapons; and advances in proteomics, toxicogenomics, and computerized database mining could be used for the rapid and efficient development of not only new drugs but also new chemical agents for terrorism.[62] Biotechnology has now advanced to the point that no special equipment is required beyond that available to any modern molecular-biology laboratory, and the scale of operations is also well within the means of governments and terrorist groups.[59] The threats from future modification of existing agents and from the development of new agents, new agent-development technologies, and innovative delivery systems should not and must not be underestimated.

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