The History and Science of CBRNE Agents, Part I

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Abstract

Various unconventional forms of warfare have existed throughout history and include intentional contamination, poisoning, and delivery of a variety of weapons—virulent microorganisms, deadly toxins, and high-yield explosives, including atomic weapons. Such weapons have been studied and utilized on the battlefield, in political struggles, and in terrorist activities for centuries. Chemical, biological, radiological, nuclear, and explosive (CBRNE) substances assumed a new prominence in the public consciousness following recent terror attacks. These agents pose a public health risk; thus, scientific professionals, including biochemists, should understand the history of CBRNE agents, their potential for harm, and the technologies—both common and advanced—used when handling a suspected CBRNE incident.

Introduction

The acronym *CBRNE* (pronounced SEA-BURN- EE), meaning Chemical-Biological-Radiological- Nuclear-Explosive, has replaced the passé acronyms NBC (Nuclear, Biological, Chemical) and ABC (Atomic, Biological, Chemical), employed to describe agents used by some party to intentionally inflict harm on another party. The official definition from 18 U.S.C. Section 2332a is:

> Any explosive, incendiary, poison gas, bomb, grenade, or rocket having a propellant charge of more than four ounces [113 g], missile having an explosive or incendiary charge of more than one-quarter ounce [7 g], or mine or device similar to the above. (2) Poison gas. (3) Any weapon involving a disease organism. (4) Any weapon that is designed to release radiation at a level dangerous to human life. 1

The separate words that comprise the acronym CBRNE describe each agent that could be employed malevolently (e.g., *Biological* describes microbial agents such as *Bacillus anthracis*). Another analogous term currently en- vogue and heard often in media reports and political circles is *weapons-of-mass-destruction* (WMD). Historically, the planning and use of such agents was reserved for warfare between opposing state forces, but recent events have shown a new, frightening utility for CBRNE among terrorist groups (both domestically and abroad), who have shown an interest and willingness to use the agents to spread fear and chaos among civilian populations for political and ideological reasons.

Scientific professionals will be among the first to respond to the aftereffects of any CBRNE incident. Imperatively, biochemists must understand: the history of

CBRNE to grasp the injurious potential of past usage; agent biochemistry (modes of action, infection, etc.); and the usefulness of traditional and new laboratory methods for diagnosis.

The History of CBRNE

The malicious use of chemical and biological agents is not a recent phenomenon. Evidence exists that prehistoric humans used arrowheads and spears dipped in feces. 2 As early as 1000 B.C. during the late Bronze Age 3, the Chinese recorded hundreds of recipes for compounds that were mixed with gunpowder in hopes of producing a toxic smoke to incapacitate their enemies; mixtures such as “soul-hunting fog” (containing arsenic) and “five-league fog” (enriched with wolf excrement) were described in detail and still used over ten centuries later.

The first suspected use of a biological agent occurred circa 500 B.C. during the Classical Age 3, when it is believed the Assyrians poisoned their enemy’s water supply using rye ergot, a poisonous mycotoxin obtained from diseased rye. 4 Even the Spartans utilized an early form of chemical warfare, when they harnessed toxic smoke from tar-and-sulfur-soaked burning wood and used it against the Athenians during the Peloponnesian War. Later, hellebore roots were used by Solon of Athens to taint a tributary used by Cirrhaeans as a water source. 5

In 1155 A.D., Barbarossa contaminated his enemy’s wells with the bodies of his dead troops during the Battle of Tortona. 6 During the Hundred Years War at the siege of Thun l'Eveque in 1340 A.D. (as the Plague began rampaging in one of its many historical epidemics), the practice of propelling animal carcasses at enemy fortifications was grasped more as a harassment technique versus an intentional means of spreading disease. Jean Froissart, a contemporary chronicler, stated the besiegers "...cast in deed horses, and beestes stynking..." and that "...the ayre was hote as in the myddes of somer: the stynke and ayre was so abominable.” Such was the misery of the defending contingent that they surrendered, though no record of consequential illness exists.5

In thirteen years, the dreaded Plague had traveled from Asia to the Middle East, arriving in 1346 A.D. Once it manifested at the walled port city of Kaffa in present-day Feodosiya, Ukraine, inventive, retreating Turkish besiegers decided to catapult their own plague-ridden dead over the walls of the city. 7 Thus was born the first confirmed use of a microbial agent to inflict harm, though no one believes these warriors understood the exact etiology of the disease; the use of cadavers as a source of contagion, or “bad air”, obviously was understood. 5 The supposition that warriors believed decaying matter tainted the air and caused disease was definitely confirmed in 1422 A.D.; Corbut launched dead soldiers and loads of feces amidst his enemies at Carolstein, such that “a great number of the defenders fell victim to the fever which resulted from the stench.” 6 Spanish

troops attempted to induce disease in French soldiers by using wine tainted with the blood of lepers in 1495 A.D., but this effort was unsuccessful. 6

Around 1500 A.D., the use of fomites as agent vectors became a new strategy of biological warfare. Pizarro used clothing contaminated with smallpox as “gifts” for the natives of South America. The British would resurrect Pizzaro’s fomite vector tactic again in 1754 A.D. during the French-Indian War; blankets from a smallpox hospital were presented to Native Americans camped around Fort Pitt, causing disease that quickly spread throughout the tribes. However, it was not confirmed that the fomites were the direct cause of the disease, as it was already endemic in Native American tribes at that juncture. 6

The American Civil War marked an era of advancing military technology, though several archaic methods of biological warfare were revisited. In 1863, Dr. Luke Blackburn, a Confederate physician, was incarcerated for importing clothing from yellow fever and smallpox patients and selling them to Union troops; only one Union officer was purportedly killed by this scheme. During the summer of that same year, General W.T. Sherman wrote that, as the Union retreated from Vicksburg, Confederate troops deliberately shot farm animals and deposited them in ponds to slow the Union withdrawal. 6

The truly modern era of biological and chemical warfare commenced during World War I. The early Twentieth Century was a milestone in microbiology, with new erudition on the causative agents of disease and culturing techniques. Germany developed the first-known comprehensive biological warfare program; their plan was to use *Bacillus anthracis* (anthrax) and *Burkholderia mallei* (Glanders) to infect Allied livestock, but success cannot be certain, as these are naturally occurring diseases in certain farm animals. A German physician, Anton Dilger, suffered a nervous breakdown and was discharged from the German army in 1915; subsequently, he traveled to the United States to live and rest with his parents in Virginia at a time when America was still neutral in the conflict. Dilger brought with him cultures of *B. anthracis* and *B. mallei*, which he gave to a German operative, Captain Frederick Hinsch, who inoculated horses bound for Allied troops in Europe. German agents would use this tactic of infecting horses and livestock extensively during the period between 1915 and 1917. 6

The chemists were not to be outdone by the biologists in the First World War. The Second Battle of Ypres on April 22, 1915 marked the very first widespread usage of synthesized chemical agents in full-scale war, when the Germans attacked French and Algerian forces with chlorine gas. A total 50,965 tons of pulmonary, lacrimatory, and vesicant agents, including numerous variants of chlorine (Cl_2), phosgene, and mustard gas, were utilized by both the Central and Allied powers, causing 176,500 non-fatal casualties and 85,000 fatalities directly. 8

The horrors of World War I led many statesmen to question the justness and

humaneness of biological and chemical agents. The *1925 Geneva Protocol for the Prohibition of the Use in War of Asphyxiation, Poisonous, or Other Gases, and of Bacteriologic Methods of Warfare* was the first worldwide attempt to halt proliferation of these agents, but effectively became a “no-first-use” policy when the French, Soviets, and British proclaimed they would use the agents if first attacked with them. Possession of the agents was not forbidden under the Geneva Protocol; therefore, proliferation was paradoxically assured. Although a signatory, the United States Senate did not ratify the Geneva Protocol until 1975. 6 In 1918, the Japanese formed a special military division to investigate the practicality of biological weapons; the Japanese would later take up their newfound knowledge when occupying China during World War II. 2 8

During World War II, Germany further expanded on the embryonic chemical agent technology of World War I through its discovery of the nerve agents tabun (Figure 1), sarin (Figure 2), and soman (Figure 3). Although the Nazis developed and manufactured several chemical agents during this period, neither the Axis nor the Allied Powers used them in the European theater. Documents recovered in Germany after the war showed that Germany believed the Allies also had access to nerve agents, and so fear of retaliation is believed to have discouraged their use by the Nazis. However, the Axis Powers did not completely ignore these agents. Japan used mustard gas (Figure 4) and another recently developed blister agent Lewisite (Figure 5) against Chinese troops during the Japanese occupation. The Japanese also experimented with biological warfare agents, intentionally testing the agents of cholera, dysentery, typhoid, plague, and anthrax on enemy human subjects during their occupation of Manchuria from 1931 until their eventual surrender in 1945. 8 9 Ultimately, the United States would overlook the atrocities of the implicated Japanese scientists during the war crimes tribunals following the war. Intelligence had long indicated a robust Japanese bioweapons program, including purported plans to attack North America using paper balloons containing bioagents. 9 Given U.S. isolationism and reluctance to enter World War II, American biological and chemical weapons research had lagged behind other world powers for decades. 9

A senior Palestinian Islamic religious authority, Haj Amin el-Husseini (a close ally of Hitler), spearheaded a chemical attack on Jews in Palestine that was ineffective. Agents carrying canisters of German “fine white powder” were instructed to empty the canisters at strategic points in the Tel Aviv water system. Each of the five canisters was described as containing enough chemical agent to kill 25,000. 8 With Adolf Eichmann’s effort to address “The Final Solution of the Jewish Question,” the Nazis utilized the insecticide Zyklon B, containing hydrogen cyanide (HCN) gas, to murder hundreds of thousands of unsuspecting Jews and other “undesirable” victims in the “showers” of the concentration camps during the Holocaust. 8 10

A new, terrifying weapon ended the struggle of the Japanese in August 1945, when the first atomic weapons were employed by the United States against the

Japanese mainland in the cities of Hiroshima and, later, Nagasaki. For the first time ever, entire cities could be leveled in mere seconds, with thousands of instantaneous fatalities and the subsequent casualties resulting from radiation toxicity and contamination. Paralleling the mid-war U.S. rush to acquire biological and chemical weapons technology, the United States heavily invested resources in the race to be the first nuclear power ahead of Germany and Japan, who were also working towards nuclear weapons programs at the time. 11 12 Debates still rage about whether the U.S. should have used this new, powerful weapon to end the war, but there is no doubt that the 1945 employment let the nuclear “cat out of the bag” and helped trigger arms races that have not yet resolved.

Captured German and Japanese technology (and scientists) fueled the arms races of the succeeding Cold War. The United States and the Soviets both recovered German artillery shells containing nerve agents and used them to expand their own chemical weapons arsenals. 8 German rocket technology was the basis of the U.S.-U.S.S.R. space race and complex CBRNE missile delivery systems, which would relegate atomic bomb technology to obsolescence.

Since World War II and the conclusion of the Cold War, several nations acquired or are believed to possess nuclear weapons, such as the United States, former Soviet Republics (e.g., Russia), France, the United Kingdom, Pakistan, India, and Israel. The nuclear stockpiles of the world are believed adequate to destroy the world many times over. 13 Nuclear proliferation by unstable Third World countries (such as Iran and North Korea) is a present, vehement focus in U.S. national security and foreign policy circles. In 1969, President Richard Nixon signed an executive order that renounced U.S. preparations for biological war; the U.S. limited its research efforts to vaccines and defensive measures. Between 1971 and 1973, offensive stockpiles of biological weapons were destroyed at Ft. Detrick, Pine Bluff Arsenal, and Rocky Mountain Arsenal. A small portion of biological agents was retained at the newly established United States Army Medical Research Institute for Infectious Diseases (USAMRIID) for defensive studies. 6

Early in the Iraq-Iran War that started in 1980, Iraq began to employ mustard gas (Figure 4) and tabun (Figure 1) against Iranian forces, causing 5% of all Iranian casualties. Iran was also alleged to have used chemical weapons manufactured by Iraq and the United States, but this was never confirmed. After the war ended in 1988, the Iraqi Kurdish village of Halabja was exposed to mustard, sarin (Figure 2), tabun, and VX (Figure 6) by Saddam Hussein’s regime, killing about one-tenth of the town's 50,000 residents. 8

However, accidents, both related to CBRNE proliferation and benign civilian purposes, managed to exemplify for civilian populations on both sides of the Cold War just how deadly CBRNE agents are. The Three-Mile Island incident was a near disaster for the U.S., with widespread nuclear contamination only narrowly avoided. Chernobyl was the nuclear power disaster that Three-Mile Island could

have been, with vast, detectable radiological contamination “...subsequent[ly] transport[ed] across Asia to Japan, the North Pacific, and the west coast of North America.” Neither disaster, however, equaled the levels of radiation released in the atmosphere from Cold War nuclear weapons tests. 14 There were also accidents involving bioweapons or potential bioweapons in the Soviet Union and United States. In April 1979, the Soviet city of Sverdlosk experienced an accidental release of weaponized anthrax spores from a military research facility, which caused a small-scale epidemic. 6 In 1989, a research facility in Reston, Virginia had a scare when a certain strain of *Ebola* virus (typically a highly virulent, usually fatal hemorrhagic Filovirus) was discovered in a group of imported research monkeys. There have been subsequent outbreaks of this strain, *Ebola- Reston*, among research primates imported from the Philippines, with human seroconversion but fortunately no illness. 15

The United States experienced its first case of confirmed bioterrorism in 1984. Followers of the Indian cult leader named Bhagwan Shree Rajneesh deliberately contaminated several restaurant salad bars with *Salmonella typhimurium* causing 751 cases of gastroenteritis. 6

Japan experienced chemical terrorism in 1995 with a release of sarin nerve gas into the Tokyo subway system by members of the Aum Shinrikyo cult, which resulted in 12 fatalities and over 3,000 injuries. The cult had previously attempted bioterror attacks with several potential bioweapons, including botulinum toxin. 6 About one month after the September 11, 2001 terror attacks in Washington, D.C. and New York City, several cases of cutaneous and inhalational anthrax appeared among employees of media outlets and the U.S. Postal Service. The source was determined to be letters sent through a post office in New Jersey, and additional letters bound for prominent U.S. politicians were intercepted. A massive epidemiological investigation ensued, but those responsible for this latest bioterror attack in the United States have not been apprehended. 6 The source of the weaponized anthrax (a product beyond the capabilities of the layman) was never definitively determined.

The history of CBRNE agents is long and sordid, and this brief, historical timeline is by no means complete. The past has shown the threat of these agents will never be eliminated, either in warfare or terrorism. The most recent events of history have shown a remarkable, rapid escalation in technology that has unfortunately included improvements in CBRNE technology.

CBRNE Agents

This two-part article will look at specific examples of probable CBRNE agents in each category—those chemical, biological, and radioactive compounds most likely to have the greatest deleterious effects with the least expense and difficulty for the perpetrators.

> In attempting to evaluate and discuss agents that can be used as WMDs, the question, "What can cause a *maximum credible event*?" is hopefully answered. A overwhelming use of civilian healthcare resources. For an agent to be considered capable of causing a maximum credible event, it should be highly lethal, inexpensively and easily produced in large quantities, stable in aerosol form, and have the ability to be dispersed (1-5 mm). The ideal agent also is communicable from person to person and has no treatment or vaccine. 16

Scientists and medical professionals must be familiar with key CBRNE agents that could be encountered in the current uncertain sociopolitical climate, either via state-initiated warfare or through terrorist plots and actions. Radical idealists of every persuasion, though small in number, can cause exceptional harm and panic with considerably few resources.

Time and space do not permit an adequate treatment of every possible agent; indeed, many common household or agricultural products could be used as CBRNE agents. The 1995 bombing of the Federal Building in Oklahoma City is one such example, where fertilizer was used as a key ingredient in a high-yield explosive, which erased the front half of a large, multistory building. Even something as familiar as carbon monoxide (CO) could be employed as a CBRNE agent in the right circumstances. Therefore, it is important be aware of the plethora of agents, both known and unforeseen, to provide the best support to providers and investigators (i.e., FBI, CDC, epidemiologists, toxicologists, etc.) during any incident. In many situations, symptoms and mechanisms of action discussed in this paper are similar among many disparate agents; therefore, the professional should attempt to glean how routine laboratory results might apply to agents not discussed in this study (e.g., pulmonary agents would obviously cause hypoxia with a low PO2).

In addition to examining the biochemical pathways and mechanisms of each agent type, this article will also examine probable clinical presentations (i.e., symptoms, routine test results, etc.) when known; possible means of delivery (i.e., vectors); and other investigative, confirmatory test methods employed in the laboratory to aid in mitigating the effects of a CBRNE incident.

Chemical Agents

In a sense, all CBRNE agents produce their insidious effects on living tissue at the molecular level. The mechanisms of biological agents, for example, are ultimately biochemical in nature, even if they do not involve the actions of synthetic chemical compounds. However, this section focuses solely on synthetic chemical compounds in four main groups: blood agents, mostly based on cyanide, which cause chemical asphyxiation at the cellular level; vesicants (the so-called blister agents), such as mustard gas, that cause blistering of the skin; pulmonary agents (or choking agents), such as chlorine, that suffocate by

hindering the lungs; and, perhaps the most lethal, nerve agents, such as sarin and VX, that inhibit the breakdown of the neurotransmitter acetylcholine in nervous tissues. 8

This section will not discuss incapacitating or lachrymatory chemical agents (such as tear gas or pepper spray), which are typically non-lethal compounds producing short, temporary physiological or mental effects. Such agents are used by law enforcement for crowd and riot control, offering limited utility for the terrorist or combatant at war.

Chemical Delivery Vectors

Salts and other solids have been used for years in various poisons, but solids offer limited utility in causing widespread damage. At first, tainting a water supply might seem a good means of inflicting harm, but water quickly dilutes any agent and mitigates its effects. Another possible delivery tactic is solid or vapor dispersal from low-flying aircraft, but weather, as with gaseous vapors from munitions, can confound the applicability of this strategy.

In military applications, the most effective, proven means of delivery has been in the vaporized form via large munitions (e.g., bombs or missiles), as smaller munitions fail to provide adequate air volume saturation. Typically, liquid agents are volatile by nature or design; therefore, liquid agents that will rapidly vaporize are employed to cause the greatest damage with greatest ease of storage and maintenance.17

Whether vectored to target by munitions or aircraft, attackers must carefully plan for changes in weather (especially wind direction and speed) to achieve maximum effect with the least damage to one's own side. In terrorist incidents such as the Aum Shinrikyo subway attacks, a non-explosive, vaporizing mechanism proved useful at incapacitating large numbers of people in a relatively confined space; an explosion preceding dispersal could alarm intended victims, speed their escape, and prevent the maximum effects of the agent.

Blood Agents

Cyanide, such as the Nazi's infamous Zyklon B, is a deadly agent that interferes with oxygen utilization at the cellular level. Typical volatile forms of this agent are seen in cyanogen chloride (ClCN) and hydrogen cyanide (HCN). The use of the term "blood agent" is actually a misnomer; it has no direct effect on erythrocytes or plasma. 18 Rather, cardiac and nervous tissue damage accounts for its lethal effects.

The active atom in any such compound, whether as a gas or salt, is the cyanide ion (CN^-), which is a metabolically aggressive species causing immediate injury to the optical and respiratory systems. Symptoms of exposure are lethargy or

coma, dyspnea, tachypnea, tachycardia, and hypotension. Severe poisoning results in bradypnea, bradycardia, cardiovascular collapse, and ultimately death. 19 20 Patients may report smelling bitter almonds. 17 Multiple clinical presentations of this type would constitute evidence as to its use.

Cyanide's toxic effects stem from its inhibition of electron transfer in the mitochondria along the electron transfer chain to oxygen during ATP synthesis. Cyanide binds to a crucial enzyme called cytochrome oxidase, which is utilized in the mitochondria for aerobic respiration. With the impairment of oxidative phosphorylation, ADP , H+, Na+ (sodium pump failure), and Mg2+ accumulate in the mitochondria and cytosol, and ATP is quickly depleted. 21 Lactic acid increases as anaerobic respiration attempts to fill the void left by the failure of aerobic respiration. 17 Therefore, major cellular respiration and energy production is rapidly hindered, and cell, tissue, and organ death ensues.

In the clinical laboratory, metabolic and lactic acidosis is seen, with an unexplained high anion gap ([Na+] – {[Cl-] + [HCO3-]}) and elevated lactate levels (if such testing is available). Blood gases show an elevated oxygen level, and all these presentations are due to the disruption of oxidative phosphorylation. 20 22

Confirmation would constitute a whole blood cyanide level greater than 0.05 µg/mL. 20 Methods are diverse and difficult, as cyanide is an elusive poison. The "gold standard" for all chemical toxins is the ubiquitous, time- consuming gas-chromatograph-mass-spectrometer (GC/MS). This technique involves first vaporizing a substance before injecting it into a GC column, which separates the substance into distinct compounds. The separated molecules immediately enter the MS, where they are ionized by a high-energy electron beam, transported and separated from uncharged species (based on mass-to-charge ratios), and detected. 23 Tung et al. introduced a more rapid method for determining blood cyanide levels by first binding cyanide to a sodium hydroxide trap 24; with the addition of methemoglobin as the colorimetric indicator, cyanide levels can be determined spectrophotometrically, much like the traditional method for determining hemoglobin levels.

Blister Agents

As the name implies, these agents cause large, fluid-filled blisters to develop on exposed skin and other mucosal surfaces. Vesicants such as Lewisite (Figure 5) made their combat appearance during the First World War and caused more casualties than all other agents combined, including chlorine, phosgene, and cyanogen chloride. 25 The use of Lewisite was later abandoned when an effective antidote was synthesized to counteract the active arsenic component. 26

Following Lewisite, mustard agents were introduced in two forms—complexed to sulfur (Figure 7) and soon after to nitrogen (Figure 4). The name mustard is derived from the characteristic color of the impure gas and the garlic or mustard plant odor often accompanying its release. 26 No effective antidote yet exists for this vesicant agent. 25 This paper will focus on the biochemistry of the vesicant sulfur mustard, as it has not been rendered obsolete. Nitrogen mustard has never been used; its effects are uncertain. 25

A major complication of mustard use is its stealthy nature. Pain and blisters are major symptoms that do not manifest for hours after exposure, whereas Lewisite's effects are immediate. 25 Even if one survives exposure, which is likely given that mustard is not usually fatal 25, a strong correlation with lung cancers and mustard inhalation has been shown. 21 Sulfur mustard victims develop deep, itching or burning blisters where the agent contacts the skin; exposed eyes become sore and swollen, increasing the risk of conjunctivitis and blindness. Breathing high concentrations causes bleeding and blistering within the respiratory system, leading to pulmonary edema. The greatest danger of fatality comes with extreme dosages (LD50 = 100 mg/kg). 25 26

The biochemistry of mustard is not clearly understood, which accounts for the lack of available antidotes. Mustards are strong alkylating agents; they act through cyclization with ethylene groups forming a strong sulfonium electrophilic center that reacts powerfully with any of the important macromolecular nucleophiles involved in a variety of metabolic processes, such as peptides and nucleic acids. In the case of nucleic acids, mustard is thought to cause breaks in DNA strands that increases the activity of the repair enzyme poly (ADP- ribose) polymerase, or PADPRP. The increased activity rapidly depletes stores of NAD+, a crucial cofactor in glycolysis, causing a buildup of glucose-6-phosphate, and this buildup stimulates the hexose monophosphate shunt, which triggers cellular proteases. Proteases in basal epidermal cells are thought to cleave adherent fibrils connecting the basal epidermal cell layer to the basement membrane, resulting in the characteristic blisters. 25

Another theory involves mustard's inactivation of the free radical scavenger glutathione; in such a situation, sulfhydryl groups are inactivated and a loss of free radical protection ensues. Calcium and magnesium adenosine triphosphotases are laden with sulfhydryl groups, so their quiescence would result in high calcium levels within the cell, triggering the activation of several cleavage enzymes, such as proteases and endonucleases. The final step in the hypothetical glutathione cascade is cell death. 25 No specific test for mustard exposure exists. Standard laboratory panels would show leukocytosis, hyperglycemia, and hypercalcemia. Increased levels of thiodiglycol, a mustard metabolite, have been demonstrated in the urine of patients using GC/MS up to two weeks post-exposure. 25 27

Pulmonary Agents

As the name implies, pulmonary or choking agents interfere with breathing and cause suffocation, and the main agents include chlorine gas (Cl2 – a yellow-green gas), chloropicrin (Figure 8), phosgene (Figure 9), and diphosgene (Figure 10), all containing chlorine in varying molecular configurations. 28 Other toxic inhalational agents exist and work by similar mechanisms, such as zinc oxides, nitrogen oxides, phosphorous smokes, and titanium tetrachloride 25. For the purposes of this treatment, the focus will be on chlorine-containing gases, as history and science provide adequate data on these similar agents from which to draw conclusions.

The acute symptoms associated with pulmonary agents are all very similar; for example, chlorine and phosgene can cause skin irritation, ocular involvement, spasmodic coughing, a choking sensation, substernal tightness, aphonia, stridor, hemoptysis, dyspnea, tracheobronchitis, pneumonitis, and bronchopneumonia; peribronchial and perivascular fibrosis follow chronically in the case of chlorine. Phosgene causes acute pulmonary edema and bronchiolitis obliterans (as can lone chlorine in sufficiently high doses). Exertion, asthma, or other conditions that increase the respiration rate intensifies and hastens the effects of any respiratoryagent.21 25 29

The biochemistry of chlorine gases is insidious. Soon after exposure, water in the lungs combines with the compound to form carbon dioxide, hypochlorous acid, and hydrochloric acid, the latter of which simply begin dissolving lung tissue. 30 The reaction can be summarized as follows: Cl2 + H2O -> HCl (hydrochloric acid) + HOCL (hypochlorous acid)

Segal discussed the somewhat controversial assertion that tissue damage is also caused by the generation of free oxygen radicals. 30 This once accepted, now debated method of generation is summarized in the following reaction: Cl2 + H2O -> 2 HCl + [O-] (nascent oxygen) In addition, phosgene, a gas often emitting a smell of freshly cut grass, hay, or green corn, is an alkylating agent and carcinogen, as it interferes with DNA replication. 31

Arterial blood gases (ABG) provide convincing clues as to the use of these agents. PO2 levels provide nonspecific information as to the severity of the resulting hypoxia, as do increased CO2 levels. ABG levels returning to normal within 4 to 6 hours post-exposure indicate a decreased risk of mortality. 25 One might also expect to see decreased pH and increased chloride values, depending on the level of absorption, but no concrete research exists describing the usefulness of these laboratory values 32.

Testing for these agents after exposure is not plausible, as they are quickly reduced into the acid compounds described previously. Instead, first-responders will need to collect anecdotal evidence (i.e., witness accounts, circumstances at the scene, patient accounts, etc.) to determine whether these agents account for

the symptoms and clinical presentation. Military and civilian first-responders (i.e., firefighters, FBI investigators, etc.) possess equipment and reagents to detect a variety of residual chemical agents at the incident scene.

Nerve Agents

Nerve agents are perhaps the most deleterious of all chemical agents. They occur in forms discussed previously, such as sarin, cyclosarin, soman, tabun, and VX, the latter of which gets its two-letter moniker from a United Nations military designation—the “V” stands for venomous. 25 All nerve agents belong to a class of compounds designated as organophosphates, resulting from the esters of phosphoric acid in various configurations. As the term implies, nerve agents affect elements of the nervous system by interrupting the breakdown of the neurotransmitters that signal muscle tissues to contract, which prevents them from relaxing. 33 21 A lethal dose (LD50) of VX, the most reactive, deadly nerve agent, is only a mere 10 mg/70 kg for cutaneous exposure, while the least reactive (but still quite deadly) is sarin (LD50 = 1.7 g/70 kg). Lethal doses by inhalation require far less. 25

Initial symptoms of exposure include rhinorrhea, substernal tightness, and pupil dilation. Soon after, the victim experiences dyspnea, nausea, and salivation, followed by involuntary emesis, defecation, and urination. Muscle twitching progresses into convulsive involuntary spasms, and ultimately the victim becomes comatose and suffocates. 33 Effects on the parasympathetic autonomic nervous system result in bronchoconstriction, miosis, gastrointestinal symptoms, increased secretions, urination, and bradycardia; effects on the junctions between nerves and muscles result in tachycardia, hypertension, muscle fasciculation, tremors, weakness, and flaccid paralysis. 21 The effects of nerve agents are long lasting and cumulative with successive exposures; survivors of nerve agent almost invariably suffer from chronic neurological damage. 33 21

Nerve agents inhibit the key cholinergic enzyme, acetylcholinesterase (AChE). Esterases (as a class of enzymes) catalyze the hydrolysis of esters, and AChE has a high affinity for the esters of acetylcholine (ACh), a neurotransmitter of the autonomic nervous system. 25 Free, unbound ACh builds up at the endings of autonomic nerves due to the inhibition of AChE by the organophosphate agent, causing continuous electrical stimulation and the resulting physical symptoms. Nerve agents actually inhibit AChE by binding to a serine hydroxyl group at the enzyme’s active site, forming a stable, phosphorylated, inactive enzyme. Dephosphorylation of the enzyme-agent complex is the rate-limiting step. 21

Respiratory impairment involved in nerve agent intoxication produces expected abnormalities in arterial blood gas values, including a reduction in PO2. Hypokalemia has been reported in sarin exposure, although the mechanism has not been ascertained. No standard laboratory tests exist to measure nerve agent

levels directly; however, indirect evidence can be gathered. 34 One method of determining exposure via standard laboratory testing involves measuring erythrocytic cholinesterase (RBC ChE) and pseudocholinesterase (plasma butylcholinesterase or BuChE) levels, which are reduced 20-25% by the agent; however, baseline values are most useful when using suspected post-exposure enzyme levels for comparison. RBC ChE and BuChE levels that remain unchanged over time run counter to exposure, but conclusions and treatments should be based foremost on symptoms. 25 34

End of Part I

In this article, we examined the long history of CBRNE agents and introduced various chemical agents. In Part II, we will discuss radiological and biological agents, which also ultimately do their insidious work at the biochemical level.

List of Figures

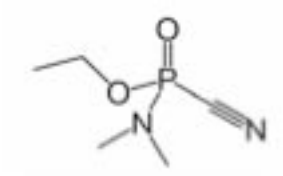
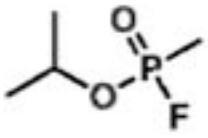


Figure 1. Ethyl N,N- dimethylphosphoramidocyanidate- tabun nerve agent



2-(fluoro-methyl-phosphoryl)oxypropane

Figure 2. Molecular structure of sarin

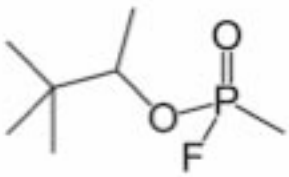


Figure 3. 3-(fluoro-methyl-phosphoryl)oxy-2,2- dimethyl-butane -soman nerve agent

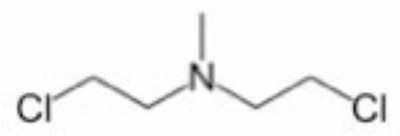


Figure 4. bis(2-chloroethyl)methylamine

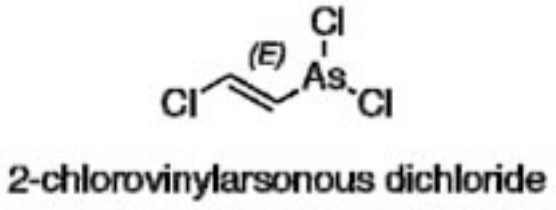


Figure 5. Molecular structure of predominant lewisite isomer

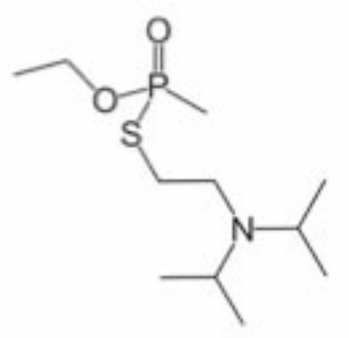


Figure 6. O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothioate - VX nerve agent

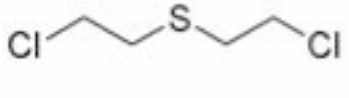


Figure 7. Molecular structure of sulfur mustard agent

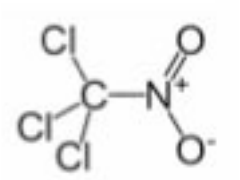


Figure 8. Trichloronitromethane - chloropicrin gas

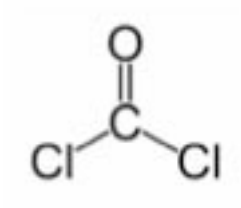


Figure 9. Carbonyl chloride - phosgene gas

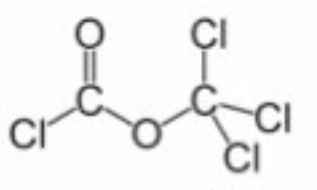


Figure 10. Trichloromethyl chloroformate - diphosgene gas

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