INTRODUCTION

While chemical warfare agents have been used in military conflict for decades, it is only in the last two decades that increased attention has been paid to the acute and chronic health effects associated with exposure to these agents. The subsequent reports of ill-defined illnesses in the veterans of the Gulf War of 1991, followed by the 1995 sarin terrorist attack in the Japanese subway system, focused attention on the capacity of deliberate or accidental exposure to chemical warfare agents, resulting in significant human death and subsequent disability.

Epidemiological studies of chemical warfare agents have suffered problems in determining exposure. Other than epidemiological investigations following the Japanese terrorist event, little objective epidemiological evidence is available. In this chapter, the major studies that have been conducted on populations exposed to the chemical warfare agents are discussed and methodological issues summarized.

PRE-WORLD WAR II

The first full-scale deployment of chemical agents in battle was during World War I in 1915, when the Germans used them against French, Canadian, and Algerian troops. Casualties were relatively heavy, though there were few deaths. A total of 50,965 tons of pulmonary, lachrymatory, and vesicant agents were deployed by both sides of the conflict, including chlorine, phosgene, and mustard gas. Official figures declare about 1,176,500 nonfatal casualties and 85,000 fatalities directly caused by chemical agents during the course of the war (Heller, 2005). In 1925, 16 of the world’s major nations signed the Geneva Protocol, pledging never to use gas in warfare again; however, there were subsequent reports of its use. In 1935, Italy used mustard gas during the invasion of Ethiopia in the Second Italo-Abyssinian War with 15,000 chemical casualties reported. In this military conflict and subsequent wars in which chemical agents were used, no systematic attempt was made to accurately describe the epidemiology of the exposures, nor were any accurate data collected to monitor the health of exposed populations after the acute exposures.

Concern regarding the potential long-term effects of these exposures continued to be an issue, and in 1975, a longitudinal follow-up study of the mortality experience of three samples of World War I veterans was conducted to determine if a single exposure to mustard gas with respiratory injury was associated with increased risk of lung cancer in later life (Norman, 1975). Rosters of men born between 1889 and 1893 (2,718 exposed to mustard gas, 1,855 hospitalized with pneumonia in 1918, and 2,578 with wounds of the extremities (controls)) were traced via the Veterans Administration’s death records. The 4,136 deaths reported were 95% of that expected. Observed deaths from lung cancer numbered 69 (2.5%) for the mustard gas group, as compared to 33 (1.8%) for the pneumonia group and 50 (1.9%) for the controls. The risk of death from lung cancer among men who were gassed relative to that for the controls was estimated as 1.3, with 95% confidence limits of 0.9–1.9.

WORLD WAR II

In 1938, the chemical structure of sarin nerve gas was discovered by the Germans, followed by the discovery
of the nerve agent soman in the spring of 1944 (Schmaltz, 2006). However, chemical warfare agents were not extensively used by either side, due in part to fear of a devastating Allied retaliatory attack. There was one account of an exposure to mustard gas among Allied troops when several US ships were sunk by the Germans in 1943, including one carrying mustard gas intended for use in retaliation by the Allies if German forces initiated gas warfare. Because the presence of the gas was highly classified, authorities treating casualties ashore had no idea that they were seeing the effects of mustard gas; as a result, they prescribed improper treatment. This incident was not uncovered for many years, and military records indicate that 628 of the casualties hospitalized after the raid suffered from mustard gas exposure and 69 deaths were attributed in whole or in part to this cause (US Naval Historical Center, 1943). The due impact of the gas exposure to military and civilian populations was not accurately reported because of the high secrecy regarding the exposure and the difficulty discerning the effect of gas exposure from other types of injuries.

During the Holocaust, the Nazis used the insecticide Zyklon B containing hydrogen cyanide to kill several million people in extermination camps and reportedly used poison gases during the Warsaw ghetto uprising in 1943. In addition, experiments were conducted on concentration camp prisoners using mustard gas and phosgene.

In 1994, a US Senate report, entitled “Is Military Research Hazardous to Veterans’ Health? Lessons Spanning a Half Century,” stated that US military personnel were used as human subjects in the 1940s to test two chemical agents, mustard gas and a similar compound, Lewisite. This testing was done to determine how to best protect military troops from the effects of chemical warfare agents (Pechura and Rall, 1993).

During the war, the US military conducted a secret research program aimed at determining how best to protect military personnel against the effects of mustard gas and Lewisite (Pechura and Rall, 1993). Up to 4,000 men took part in the program, which required participants to wear gas masks and clothing that had been treated in an attempt to keep the gas from reaching the skin. Men were required to remain in the sealed test room from 1 to 4h. Some men were tested in the field, where they were required to stay in an area that had been bombarded with mustard gas anywhere from 1h to 3 days. In 1992, the US Department of Veterans Affairs (VA) began to allow compensation for seven conditions that can result from mustard gas exposure: laryngitis, chronic bronchitis, emphysema, asthma, chronic conjunctivitis, chronic keratitis, and corneal opacities. Following publication of a report by the National Academy of Sciences (Pechura and Rall, 1993), the VA extended the list to include respiratory cancers (nasopharyngeal, laryngeal, and lung except for mesothelioma), skin cancer, chronic obstructive pulmonary disease, and acute nonlymphocytic leukemia.

Bullman and Kang (2000) conducted a 50-year mortality follow-up study of veterans exposed to low levels of mustard gas. The subjects were World War II Navy veterans who received low-level nonlethal exposures to mustard gas while participating in mustard gas chamber tests at Bainbridge, MD, between 1944 and 1945. These veterans were exposed to mustard gas while wearing protective clothing and masks. A control group consisted of 2,663 Navy veterans who served at the same location and time as the exposed people, but did not participate in chamber tests. The investigators found no excess of any cause-specific mortality associated with varying levels of mustard gas exposures that were sufficient to cause skin reactions. A significant strength of this study was that the length of time in the exposure chamber, the dose of exposure, and documentation of any observable acute effect were available for each of the exposed subjects so that a dose–response analysis could be done.

Schnurr et al. (2000) reported on the prevalence of current posttraumatic stress disorder (PTSD) associated with participation in these secret military tests of mustard gas exposure. Using the registry established by the VA, 363 male military veterans were randomly sampled and found to have a current prevalence of 32% for full PTSD and 10% for partial PTSD. Prevalence of PTSD varied as a function of risk and protective factors, including volunteering, physical symptoms during the tests, and prohibited disclosure. Veterans with full PTSD reported poorer physical health, a higher likelihood of several chronic illnesses and health-related disability, greater functional impairment, and higher likelihood of healthcare use than those with no PTSD. Veterans with partial PTSD also had poorer outcomes than did veterans with no PTSD in a subset of these domains.

Schnurr et al. (1996) postulated that these exposures involved elements of “contamination stressors,” in which information about the exposure or the lack of information serve as the stressors, rather than the actual exposure to the chemical. Lack of information during the time of exposure, and the notification decades later could have led to vague or diffuse fear with unknown consequences, contributing to the development of PTSD. The contamination stressor led to a future orientation; a worry about what problems will develop as a result of the previous exposure.

POST-WORLD WAR II

Development of other agents, such as the O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX) nerve agent continued during the 1950s, and in
1961, the United States was producing large amounts of VX and performing its own research into nerve agents. In 1952, the US Army patented a process for developing the powerful toxin ricin.

In 1969, 23 US servicemen and one US civilian stationed in Okinawa, Japan, were exposed to low levels of the nerve agent sarin while repainting the depot’s buildings. When the exposure was publicized, the United States moved the weapons in 1971 to Johnston Atoll. Between 1951 and 1969, various chemical and biological agents were tested at the Dugway Proving Ground. From 1962 to 1973, more than 5,800 military personnel participated in a series of tests on the vulnerability of warships to biological and chemical attacks. Only some of the involved military personnel consented to these tests. Many of them used chemical warfare simulants, which were thought at the time to be harmless. The results of the tests were reported in classified documents (SHAD report). In 2000, the US Department of Defense (DoD) released the names of the participants and information about the testing that occurred. In 2002, the Institute of Medicine (IOM) agreed to undertake a scientific study of potential long-term health effects associated with these exposures. The IOM assembled a comparable control group and conducted a health survey by telephone. Mortality records were also examined. The primary outcomes of interest were mortality, general health, and medical conditions. The SHAD participants were divided into four groups:

- Group A consisted of 3,000 participants whose exposure was limited to either Bacillus globigii (BG) or methylacetoacetate (MAA).
- Group B consisted of 850 participants whose only potential exposure was to triethyl phosphate (TEHP) and contained a large number of Marines.
- Group C consisted of 720 participants who were in tests where active chemical warfare agents were used.
- Group D consisted of 850 subjects potentially exposed to simulants who were not in group A, B, or C.

Control groups were assembled for each of the exposed groups. Of the nearly 12,500 Navy and Marine subjects, 9,600 were assumed alive (i.e., no evidence of death from available records sources) and were surveyed. The response rate for the SHAD participants was 60.8% and 46.6% for controls. No differences were observed in all-cause mortality between SHAD participants and controls, although the SHAD participants had a statistically significant higher risk of death due to heart disease. Lack of cardiovascular risk factor data makes this difference difficult to interpret. SHAD participants also reported statistically significantly worse health than controls, but no specific patterns of illness were found. Group C, the only group with potential exposure to active chemical or biological agents, reported the smallest differences in overall health compared to controls. Small differences in memory and attention as well as somatization were observed and SHAD participants had higher levels of neurodegenerative conditions. SHAD participants also reported higher rates of symptoms, thought to be related to reporting bias. There were no significant differences in self-reported hospitalizations.

This report was significant in that it was the first epidemiological investigation of a military population with documented exposure to chemical agents or simulants. The survey was conducted, however, 30 years after the exposure and, with the exception of mortality records, was limited to self-reported measures of health. A mortality follow-up study of the SHAD cohort was published by Kang and Bullman (2009) in which the cause-specific mortality of 4,927 SHAD veterans was compared to 10,927 other Navy veterans of that era. The SHAD veterans had an increased risk of overall mortality, due primarily to heart disease; therefore, this heightened risk was not attributed to exposure to active chemical or biological warfare agents. This study was limited due to lack of information on other potential exposures, particularly exposure to Agent Orange, a defoliant used in Vietnam, and the possibility of error was introduced by exposure misclassification.

In 2012, the IOM was commissioned to conduct a second epidemiological study comparing the health status of the SHAD veterans with a comparison population. This research, currently underway, will build on knowledge gained from the first study and use veteran and Medicare data as well as death certificate data. The anticipated date for completion of the study is February 2015.

**IRAN–IRAQ WAR**

Saddam Hussein received chemical weapons from many countries, including the United States, West Germany, the Netherlands, the United Kingdom, France, and China (Lafayette, 2002). In 1980, Iraq attacked Iran, employing mustard gas and tabun, in a war that lasted 8 years. A total of 5% of all Iranian casualties were directly attributable to the use of these agents. Iran sustained approximately 387 chemical attacks during this war (Shemirani et al., 1993). About 100,000 Iranian soldiers, along with significant numbers of civilians, were chemical warfare victims. Nerve gas agents killed about 20,000 Iranian soldiers immediately. Shortly after the war ended in 1988, the Iraqi Kurdish village of Halabja was exposed to multiple chemical agents, resulting in the death of 10% of the 50,000 residents.

The extensive assault on military and civilian populations, terrible as it was, has resulted in some of the
I. INTRODUCTION, HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY

A. Best-designed epidemiological studies of the effects of exposure to chemical warfare agents in recent years. Hashemian et al. (2006) reported on the results of a cross-sectional, randomized survey of 153 civilians in three towns exposed to military conflict in northwestern Iran: Oshnaviveh (low-intensity conventional warfare), Rabat (high-intensity conventional warfare), and Sardasht (both high-intensity conventional warfare and chemical weapons). The surveys measured full or partial PTSD diagnosis and symptoms of anxiety and depression. Compared with individuals exposed to low-intensity warfare, those exposed to high-intensity warfare and chemical weapons were at a higher risk for lifetime PTSD (odds ratio (OR), 18.6; 95% confidence interval (CI), 5.8–59.4), current PTSD (OR, 27.4; 95% CI, 3.4–218.2), increased anxiety symptoms (OR, 14.6; 95% CI, 6.0–35.6), and increased depressive symptoms (OR, 7.2; 95% CI, 3.3–15.9). Exposure to high-intensity warfare but not to chemical weapons was also significantly associated with lifetime PTSD (OR, 5.4; 95% CI, 1.7–17.6), compared with those in the low-intensity warfare group. Further, compared with individuals exposed to high-intensity warfare alone, those exposed to both high-intensity warfare and chemical weapons were at higher risk for lifetime PTSD (OR, 3.4; 95% CI, 1.5–7.4), current PTSD (OR, 6.2; 95% CI, 2.0–20.1), increased anxiety symptoms (OR, 5.6; 95% CI, 2.5–12.6), and increased depressive symptoms (OR, 3.7; 95% CI, 1.8–7.2).

Sulfur mustard is rated by the International Agency for Research on Cancer (IARC) as a human carcinogen and is a known risk factor for occupational lung cancer (Nishimoto et al., 1987; Ghanei and Vosoghi, 2002). Zafarghandi et al. (2012) described the incidence of cancer in 7,570 Iranian sulfur mustard-exposed veterans compared to 7,595 unexposed subjects in a 25-year follow-up study. Cancer incidence was significantly increased with exposure to sulfur mustard. The incidence rate ratio for cancer was 1.81 (95% CI 1.15–2.34); however, no increased risk of site-specific cancers were found. The hazard ratio of cancer occurrence was 2.02 (95% CI 1.41–2.88).

The long-term clinical consequence of sulfur mustard exposure was looked at by the Sardasht-Iran Cohort Study (Ghazanfari et al., 2009), which included 372 individuals from Sardasht as the exposed group and 128 non-exposed individuals from Rabat. As part of this research, Ghanei et al. (2010) studied pulmonary complications and found that blistering at the time of exposure was associated with more respiratory symptoms and worse lung function, but not with air trapping, bronchiectasis, and mosaic parenchymal attenuation detected with computed tomography (CT) of the thorax. This cohort was also used to examine the long-term effects of sulfur mustard on civilian’s mental health 20 years post exposure. There were significant differences in somatization, obsessive-compulsion, depression, anxiety, and hostility between the exposed and unexposed groups, suggesting significant long-term effects of sulfur mustard exposure.

Comparisons of the effects of sulfur mustard and nerve agents have also been conducted in this population. Emadi et al. (2012) compared late cutaneous complications between the two exposure groups of 154 sulfur mustard-exposed cases and 175 nerve agent exposed cases. Only 18.1% of the mustard-exposed group was asymptomatic, compared to 62.4% of the nerve agent exposures. A number of mustard-induced dermatologic lesions were reported, including scars, intertrigo, xerosis, cherry angioma, hyperpigmentation, pilar keratosis, poikiloderma, and malignant tumors.

1991 GULF WAR

Given the past use of chemical weapons of Iraq on its own citizens, there was much concern that Saddam Hussein would again employ these weapons during the conflict against coalition forces. The only known exposure to anticholinesterase chemical warfare agents during the Gulf War was during the destruction of munitions containing 8.5 metric tons of sarin/cyclosarin housed in Bunker 73 at Khamisyah, Iraq, on March 4, 1991, and additional destruction of sarin/cyclosarin rockets in a pit at Khamisyah on March 10, 1991. The US DoD reported that the exposure levels were too low to activate chemical alarms or to cause symptoms at the time of the detonation; however, several studies have been conducted to assess long-term health effects associated with this exposure. The DoD conducted modeling of the air plume that resulted from the detonation and estimated the extent of troops potentially exposed to the plume.

McCauley et al. (1999) conducted a computer-assisted telephone survey of 2,918 Gulf War veterans from Oregon, Washington, California, North Carolina, and Georgia to evaluate the prevalence of self-reported medical diagnoses and hospitalizations among this potentially exposed population and among comparison groups of veterans who were deployed and not deployed to the Southwest Asia theater of operations. Troops reported to be within 50 km of the Khamisyah site did not differ from other deployed troops in terms of reporting any medical conditions or hospitalizations in the 9 years following the Gulf War. Hospitalization rates among deployed and nondeployed troops did not differ. Deployed troops were significantly more likely than nondeployed troops to report diagnoses of high blood pressure (OR = 1.7), heart disease (OR = 2.5), slipped disk or pinched nerve (OR = 1.5), PTSD (OR = 14.9), hospitalization for depression (OR = 5.1), and periodontal disease (OR = 1.8). There was a trend for deployed veterans to report more diagnoses of any cancer (OR = 3.0).
Smith et al. (2003) investigated postwar morbidity for Gulf War veterans, contrasting those who may have been exposed to low levels of nerve agents at Khamisyah and those unlikely to have been exposed. Cox regression modeling was performed for hospitalizations from all causes and hospitalizations from diagnoses within 15 categories during the period March 10, 1991 through December 31, 2000, for the duration of active-duty status. Veterans possibly exposed to nerve agents released by the Khamisyah demolition were not found to be at increased risk for hospitalization from most chronic diseases nearly 10 years after the Gulf War. Only 2 of 37 models suggested that personnel possibly exposed to subclinical doses of nerve agents might be at increased risk for hospitalization from circulatory diseases, specifically cardiac dysrhythmias.

Bullman et al. (2005) reported the results of a mortality study of troops exposed to chemical warfare agents based on the air plume models that were developed after the detonation. The cause-specific mortality of 100,487 exposed veterans was compared with that of 224,480 unexposed US Army Gulf War veterans. The risks for most disease-related mortality were similar for exposed and unexposed veterans. However, exposed veterans had an increased risk of brain cancer deaths (relative risk = 1.94; 95% CI = 1.12, 3.34). The risk of brain cancer death was larger among those exposed 2 or more days than those exposed 1 day when both were compared separately to all unexposed veterans.

This same team of investigators also conducted a study to examine the association of exposure to the Khamisyah plume with subsequent self-reported morbidity (Page et al., 2005). The study sample included 1,056 deployed Army Gulf War veterans who responded to the National Health Survey of Gulf War Era Veterans in 1995 and who were resurveyed in 2000. Half of the subjects had been notified of potential exposure to chemical warfare agents. Comparing notified and nonnotified subjects, there were no statistically significant differences with respect to bed days, activity limitations, clinic visits, or hospital visits. Among 71 self-reported medical conditions and symptoms, there were five statistically significant differences, four of which were for lower rates of illness among notified subjects.

Page and colleagues also published a similar study undertaken to investigate whether possible chemical warfare exposure was associated with morbidity among Army Gulf War veterans using morbidity data for 5,555 Army veterans who were deployed to the Gulf region (Page et al., 2005). Responses to 86 self-assessed health measures, as reported in the 1995 National Health Survey of Gulf War Era Veterans, were evaluated. They found little association between potential exposure and health after adjusting for demographic variables. The investigators concluded that potential exposure to sarin or cyclosarin at Khamisyah did not seem to have adversely affected self-perceived health status, as evidenced by a wide range of health measures.

More recently, Heaton examined the association between modeled estimates of sarin/cyclosarin exposure levels and volumetric measurements of gross neuroanatomical structures in 1991 Gulf War veterans with varying degrees of possible low-level sarin/cyclosarin exposure (Heaton et al., 2007). A total of 26 veterans recruited from the Devens Cohort Study participated. Magnetic resonance images (MRIs) of the brain were acquired and analyzed using morphometric techniques, producing volumetric measurements of white matter, gray matter, right and left lateral ventricles, and cerebrospinal fluid. Volumetric data were analyzed using exposure estimates obtained from refined models of the presumed exposure hazard area in Khamisyah. No differences were observed in the 13 exposed veterans when compared to 13 nonexposed veterans in volumetric measurements of discrete brain tissues. However, linear trend analyses showed a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter (adjusted parameter estimate = 4.64, P < 0.0001) and increased right lateral ventricle (adjusted parameter estimate = 0.11, P = 0.0288) and left lateral ventricle (adjusted parameter estimate = 0.13, P < 0.0001) volumes. These findings suggest subtle but persistent central nervous system pathology in Gulf War veterans potentially exposed to low levels of sarin/cyclosarin.

This investigative team also compared previous neurobehavioral performance results collected prior to notification of veterans who were potentially exposed during the Khamisyah detonation (Proctor et al., 2006). They hypothesized that the exposure to sarin and cyclosarin would be associated with poorer performances on objective neurobehavioral tasks in specific functional domains (particularly in visuospatial abilities and psychomotor functioning) in a dose-dependent manner. They found that sarin and cyclosarin exposure was significantly associated with less proficient neurobehavioral functioning on tasks involving fine psychomotor dexterity and visuospatial abilities 4–5 years after exposure. They concluded that the findings suggest a dose–response association between low-level exposure to sarin and cyclosarin and specific functional central nervous system effects 4–5 years after exposure.

To determine the generalizability of these findings in the Devens Cohort, investigators from the University of California, San Francisco studied a second cohort of Gulf War veterans with suspected sarin/cyclosarin exposure (Chao et al., 2010). They studied 40 Gulf War veterans categorized as exposed to sarin/cyclosarin at Khamisyah in comparison to a control group of 40 nonexposed veterans. MRI data of the brain were analyzed, with
volumetric measurements of gray matter, white matter, cerebrospinal fluid and hippocampus. Exposed veterans had reduced total gray matter and hippocampal volumes compared to controls (P < 0.01). While no group differences were observed on measures of cognitive function or total white matter volume, there were significant positive correlations between total white matter volume and measures of executive function and visuospatial abilities in exposure sarin/cyclosarin. While limited in accurate exposure assessment and specific unit information, the authors argue that these findings in conjunction to those found by Heaton, Proctors, and colleagues point to the need for a follow-up study with more subjects and more sophisticated imaging technology.

TERRORISM

Two terrorist attacks with the nerve agent sarin affected populations in Matsumoto and Tokyo, Japan, in 1994 and 1995, killing 19 and injuring more than 6,000. Morita et al. (1995) described the acute effects, including instantaneous death by respiratory arrest in four victims in Matsumoto. In Tokyo, 2 people died in station yards, and another 10 victims died in hospitals within a few hours to 3 months after the poisoning. A total of six victims with serum cholinesterase (ChE) below 20% of the lowest normal levels were resuscitated from cardiopulmonary arrest (CPA) or coma with generalized convulsion. Of those, five recovered completely and one remained in a vegetative state due to anoxic brain damage. Electroencephalogram (EEG) abnormalities were observed for up to 5 years in certain victims. Miosis and copious secretions from the respiratory and gastrointestinal tracts (muscarnic effects) were common in severely to slightly affected victims. Weakness and twitches of muscles (nicotinic effects) appeared in severely affected victims. Neuropathy and ataxia were observed in a small number (less than 10%) of victims, in which findings disappeared between 3 days and 3 months. Leukocytosis and high serum creatine kinase (CK) levels were common. Hyperglycemia, ketonuria, low serum triglycerides, and hypokalemia were observed in severely affected victims, and these abnormalities were attributed to damage of the adrenal medulla.

The Matsumoto government assembled a committee of city government, local hospitals and physicians from Shinsu University to monitor the immediate and long-term effects of the exposure, resulting in the most comprehensive epidemiological studies of acute and residual effects of exposure to chemical warfare agents. Three weeks after the attack, community residents (n = 2052) residing in an area within 1,000–850 m of the attack were surveyed and categorized as severely affected if they were admitted to the hospital, moderately affected if treated in outpatient clinics, and slightly affected if they had symptoms but did not seek medical attention. At the time of this follow-up survey, 28% of the affected residents remained symptomatic (69% of the severely affected, 42% of the moderately affected, and 14% of the slightly affected). The most frequent persisting symptoms were fatigue, dysesthesia of extremities, and ocular pain. Visual problems continued in about 10% of severely affected victims (Yanagisawa et al., 2006).

In the Tokyo subway attack, 640 victims were seen within hours of the incident. Of these people, 5 were critically injured and required mechanical ventilation, and another 107 were moderately injured with systemic symptoms and signs of respiratory, digestive, or neurological damage, in addition to ocular problems. The large majority (n = 528) had only eye damage or symptoms and were released after several hours of observation (Yanagisawa et al., 2006).

There have been a number of investigations of the health of the survivors of the Tokyo subway attack. Yokoyama et al. (1998a) conducted a study of 18 victims 6–8 months after the attack. At that time, their mean plasma ChE was 72.1, lower than the normal range of 100–250 IU/L. In neurobehavioral testing at that time, sarin cases had significantly lower scores on the digit symbol test than the control group. Cases were more likely to have higher scores on both the General Health Questionnaire, an indication of psychological distress, and fatigue measures than controls, and PTSD scores were also increased. Postural balance was also different in victims, suggesting that integration of visual input might have been impaired (Yokoyama et al., 1998b). P300 and VEP (P100) latencies in the sarin cases were significantly prolonged in these victims compared with the matched controls (Murata et al., 1997). In the sarin cases, the CVRR (electrocardiographic R-R interval variability) was significantly related to serum ChE levels determined immediately after exposure; the PTSD score was not significantly associated with any neurophysiological data despite the high PTSD score in the sarin cases. These findings suggest that asymptomatic after effects to sarin exposure, rather than PTSD, persist in the higher and visual nervous systems beyond the turnover period of ChE.

The National Police Academy (1999) conducted a survey of 1,247 residents who reported to the police department that they had contact with sarin at the incident. More than half complained of physical symptoms, such as asthmnia and decrease in visual acuity; and 17% reported psychological trauma from the event, with 14% still unable to ride on subways 3 years after the incident.

There continue to be follow-up studies describing the residual effects of the attack. Ohtani et al. (2004) followed 34 victims 5 years after the attack. Not only PTSD, but also nonspecific mental symptoms, persisted in the victims at a high rate. A total of 11 victims were diagnosed with current
or lifetime PTSD. Victims with PTSD showed higher anxiety levels and more visual memory impairment.

Yamasue et al. (2007) conducted a 5 year follow-up study to identify persistent morphological changes subsequent to the attack. In the research, 38 victims of the sarin attack who had been treated in the emergency department for sarin intoxication and 76 control subjects underwent weighted and diffusion tensor MRIs. ChE values were compared to levels immediately after the attack. The voxel-based morphometry exhibited smaller than normal regional brain volumes in the insular cortex and neighboring white matter, as well as in the hippocampus, in the victims. The reduced regional white matter volume correlated with decreased serum cholinesterase levels and with the severity of chronic somatic complaints related to interoceptive awareness. Voxel-based analysis of diffusion tensor MRIs further demonstrated a significantly lower than normal fractional anisotropy in the victims. These findings suggest that sarin intoxication might be associated with structural changes in specific regions of the human brain.

Rescue and safety workers have also been studied. Nishiwaki et al. (2001) looked at 27 male rescue team staff and 30 police officers 3–45 months after the event. The subjects showed decreased performance on the digit span test; however, no effects on stabilometry and vibration perception threshold were found. Li et al. (2004) followed 27 male firefighters and 25 male police officers 3 years after the attack for genotoxic effects. They found an elevated frequency of sister chromatid exchanges in lymphocytes of the victims, which were related to the percentage of ChE inhibition observed just after the attack.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

This chapter described the major epidemiological studies of populations who have been exposed to chemical warfare agents. Many of the studies of military populations have suffered from inaccurate exposure assessment and lack of clinical data. However studies in the past decade of terrorist attacks, as well as the Iran–Iraqi cohort studies, provide the most comprehensive data to date on the scope of health outcomes associated with these exposures. These reports point to the need for long-term follow-up studies of victims of such events. The data from the terrorist events and military assaults point to the prevalence of PTSD in populations with real or threatened exposure.

References


