Free Executive Summary

Gulf War and Health: Updated Literature Review of Sarin

Committee on Gulf War and Health: Updated Literature Review of Sarin

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Executive Summary

The Gulf War in 1990–1991 was considered a brief and successful military operation, with few injuries or deaths of US troops. The war began in August 1990, and the last US ground troops returned home by June 1991. Although most Gulf War veterans resumed their normal activities, many soon began reporting a variety of nonexplained health problems that they attributed to their participation in the Gulf War, including chronic fatigue, muscle and joint pain, loss of concentration, forgetfulness, headache, and rash.

Because of concerns about the veterans' health problems, the Department of Veterans Affairs (VA) requested that the Institute of Medicine (IOM) review the scientific and medical literature on the long-term adverse health effects of agents to which the Gulf War veterans may have been exposed. Congress also passed legislation for a similar study (the Persian Gulf War Veterans Act of 1998, PL 105-277, and the Veterans Programs Enhancement Act of 1998, PL 105-368).

In response to those requests, IOM has convened committees to evaluate the health effects of various chemicals used in the Gulf War. The first evaluated the health effects of depleted uranium, pyridostigmine bromide, sarin and cyclosarin, and vaccines (anthrax and botulinum toxoid) and produced *Gulf War and Health, Volume I*, hereafter referred to as *GW1*. The second reviewed the health effects of solvents and pesticides and produced *Gulf War and Health, Volume 2*, hereafter referred to as *GW2*. Another committee is reviewing the health effects of the combustion products of oil-well fires, fuels, and synthetic compounds potentially used as propellants for SCUD missiles.

Because of continued concerns of veterans, especially in light of recent toxicologic studies of low-dose exposure to the chemical-warfare agent sarin, the

VA requested that IOM conduct an updated evaluation of the health effects of sarin. A new committee, made up of some of the members of the committee responsible for *GW2*, was convened to conduct this review.

CHARGE TO THE PRESENT COMMITTEE

The present committee was charged to review the peer-reviewed literature published since earlier IOM reports on health effects associated with exposure to sarin and related compounds, including relevant epidemiologic studies. With regard to the toxicologic literature, the committee used review articles to obtain and present a broad overview of the toxicology of sarin and cyclosarin, and to assess biologic plausibility with respect to the compounds in question and health effects; individual toxicologic research papers were evaluated as warranted. The committee based determinations on the strength of the evidence of associations between the compounds and human health effects. If published, peer-reviewed information was available on the magnitude of sarin and cyclosarin exposure of Gulf War veterans, the committee addressed the potential health risks posed to the veterans. The committee also considered other relevant issues, such as exposure to multiple chemicals and genetic susceptibilities. The committee's review included recommendations for additional scientific studies to resolve continued scientific uncertainty as warranted.

The committee was not charged with determining whether a unique Gulf War syndrome exists, nor was it to make judgments regarding magnitudes of exposure of veterans to the putative agents. Moreover, the committee was not charged to focus on broader issues, such as the potential costs of compensation for veterans or policies regarding such compensation. Those decisions remain the responsibility of the secretary of veterans affairs. This report does, however, provide an assessment of the scientific evidence regarding health effects that may be associated with exposures to specific agents that were present in the Gulf War. The secretary may consider those health effects as the VA develops a compensation program for Gulf War veterans.

APPROACH TO THE CHARGE

The committee's first step was to identify the literature to be reviewed. The search was conducted by using the names of sarin and cyclosarin and their synonyms. Titles and abstracts were reviewed to determine their relevance to the committee's charge; potentially relevant studies were retrieved and evaluated. The literature was also searched for epidemiologic studies on organophosphorus (OP) compounds published and catalogued since August, 1999, when the last search was conducted for the preparation of *GW2*, and such studies were reviewed.

Animal studies had a small role in the committee's assessment of association between putative agents and health outcomes. In general, animal data were used

for making assessments of biologic plausibility in support of the epidemiologic data rather than as part of the weight of evidence to determine the likelihood that an exposure to a specific agent might cause a long-term outcome.

The committee classified the evidence of an association between exposure to sarin and cyclosarin and a specific health outcome into five categories: sufficient evidence of a causal relationship, sufficient evidence of an association, limited/suggestive evidence of an association, inadequate/insufficient evidence of an association, and limited/suggestive evidence of no association. The categories are modified from established categories of association from previous IOM studies that have gained wide acceptance over more than a decade by Congress, government agencies, researchers, and veterans groups.

POTENTIAL US TROOP EXPOSURE TO SARIN AND CYCLOSARIN

Sarin (GB; *o*-isopropyl methylphosphonofluoridate) and cyclosarin (GF; cyclohexyl methylphosphonofluoridate) are highly toxic OP nerve agents produced for chemical warfare. During a cease-fire period in March 1991, a large storage complex at Khamisiyah, Iraq, was destroyed. Two sites in the complex contained rockets loaded with sarin and cyclosarin. The total amount released, according to the most recent estimates, is 371 kg of sarin and cyclosarin combined. US troops performing demolitions were unaware of the presence of nerve agents, and no air monitoring was conducted at the time of the demolition.

Modeling has been conducted to determine potential exposures of US troops. According to model estimates, no troops were exposed to doses greater than would cause "first noticeable effects", which would set off chemical alarms and cause visible signs of the acute cholinergic syndrome. There were no medical reports by the US Army Medical Corps at the time of the release that were consistent with signs and symptoms of acute exposure to sarin. That information is consistent with the absence of reports of symptoms of an acute cholinergic syndrome by medical personnel or veterans.

TOXICITY, EXPERIMENTAL ANIMAL AND MECHANISTIC DATA

Neurotoxicity

OP compounds are absorbed rapidly and produce local and systemic effects. Clinical signs of toxicity associated with organophosphate-induced inhibition of acetylcholinesterase (AChE) depend on dosage. Toxicity in humans and animals includes the signs associated with overstimulation of muscarinic receptors[1] of the

[1]Muscarinic receptors are a subtype of receptors to which acetylcholine (ACh) binds. Binding of ACh to muscarinic receptors activates those receptors. Excessive activation of those receptors can lead to overstimulation of muscles and nerves.

autonomic nervous system by acetylcholine (ACh)—salivation, sweating, meiosis, tremor, lacrimation, urination, defecation, emesis, and bradycardia.

The principal mechanism of acute toxicity of sarin and cyclosarin, like that of other OP compounds, is inhibition of AChE. AChE is responsible for the hydrolysis of ACh at the synapse, and inhibition of that enzyme leads to a rise in ACh and overstimulation at cholinergic synapses. Obvious signs of the acute cholinergic syndrome do not generally appear until nervous system AChE inhibition approaches 70%. Some effects of sarin, however, do not appear to be related to inhibition of AChE.

Long-term changes in the electroencephalogram (EEG) of rhesus monkeys have been seen after a single high dose of sarin or a series of 10 small doses. The high dose was sufficient to produce the acute cholinergic syndrome, whereas each small dose produced few, if any, signs of acute poisoning. Changes persisted for 1 year after sarin administration, although the changes did not appear to have any behavioral or psychologic significance. Similar effects were not seen in marmosets or in guinea pigs except when they were exposed to doses that caused the acute cholinergic syndrome.

Recently, research has been conducted to resemble more closely the sarin exposures that might have occurred in the Gulf War. The highest concentration tested was one-tenth the lethal concentration. No consistent effects on locomotor activity or body temperature of rats were seen. Brain was examined histopathologically 30 days after exposure; no lesions or evidence of cell death were present. No effect was seen on total brain AChE measurements, but AChE was decreased in some brain regions—mostly in areas of the forebrain (the cerebral cortex, striatum, olfactory bulb, and the CA1 region of the hippocampus). Brain cytokine concentrations were affected by both sarin treatment and heat stress. Receptor density was measured for the M1, M2, and M3 subtypes of muscarinic receptors. M1 receptors were decreased in a dose-dependent manner in some brain regions. Sarin did not affect M3 receptor density under normal conditions, but under heat stress there was an increase in the number of M3 receptors in some brain regions. Some of those changes remained for the duration of the experiment (30 days). The results related to receptor density are suggestive of a potential mechanism through which sarin could cause long-term effects on the nervous system and indicate the desirability of future toxicologic and epidemiologic research.

The performance of rats in a T-maze and a Y-maze after exposure to sarin or sarin plus oximes was somewhat affected, but the performance of some of the control animals was also lower than expected in some of the studies with oximes. Many of the effects were reversed by 3 months.

Some studies have looked at expression of astroglial markers 1 and 2 hours and 1, 3, and 7 days after treatment. Glial fibrillary acidic protein and vimentin were increased in the areas of the brain studied (cortex, midbrain, cerebellum, brainstem, and spinal cord), and vimentin induction occurred sooner. Some effects on expression of both could still be detected 7 days after treatment.

Immunotoxicity

Both in vivo and in vitro immune effects have been seen, but they are not consistent and they depend on the cell types studied. Recent studies have investigated persistent effects of sarin on the immune system. Modest and inconsistent effects on lymphocyte proliferation and production of *N*-oxides were seen in rats 3 months after a single or repeated (three times in 1 week) 1-hour inhalation-chamber exposure.

Genotoxicity and Carcinogenicity

In general, genotoxicity studies (of mutagenesis, chromosomal damage, unscheduled DNA synthesis, or sister chromatid exchange) are negative. In a subchronic (90-day) toxicologic study of sarin (three different doses that produced profound inhibition of AChE and some deaths), one of two formulations of sarin was associated with one neoplastic lesion, a lymphoma, in one male in the high-dose group.

No chronic animal studies have been conducted to determine the carcinogenic effects of exposure to sarin.

Genetic Susceptibility

One of the mechanisms of sarin inactivation is hydrolysis with the enzyme paraoxonase (PON1), an esterase synthesized and secreted by the liver. The human PON1 gene has polymorphisms that affect serum PON1 activity and therefore might significantly alter susceptibility to the toxicity of sarin. The relationship between illness in Gulf War veterans and PON1 genotype and serum activity has been investigated. The results of one study suggested that low PON1 activity due to the polymorphism might be a risk factor for illness in Gulf War veterans, but another study did not find any differences in PON1 activity between symptomatic and asymptomatic Gulf War veterans.

HUMAN HEALTH OUTCOME DATA

Four populations have been studied in large epidemiologic studies after exposure to sarin: military volunteers who were exposed several decades ago to nonlethal doses of sarin and other chemical-warfare agents, industrial workers with documented acute exposure to sarin, victims of the sarin terrorist attacks in Matsumoto City in 1994 and Tokyo in 1995, and Gulf War veterans. Studies of Gulf War veterans include studies of veterans potentially exposed to sarin after demolition of rockets at Khamisiyah and a number of studies on Gulf War veterans that evaluate the relationship between symptoms and possible exposures on

the basis of a self-reporting questionnaire, including possible exposures to sarin or cyclosarin.

Neurologic Effects

A number of studies have evaluated the possible relationship between exposure to sarin or cyclosarin and neurologic effects in humans. Those outcomes have been the focus of the largest number of studies because of the neurotoxic actions of the chemicals.

Studies of British and US military servicemen who volunteered for an experimental study of the health effects of low-dose exposure to sarin and other chemical-warfare agents did not demonstrate any long-term health effects of exposure to cholinesterase inhibitors. In both the US and British studies, some subjects experienced the acute cholinergic syndrome.

Studies have followed the health effects in people who exhibited the acute cholinergic syndrome after terrorist attacks in Matsumoto and Tokyo, Japan. Three years after the Matsumoto attack, fatigue, headache, and the visual disturbances asthenopia, blurred vision, and narrowing of visual field were more common among people who reported signs of the acute cholinergic syndrome than among those who lived near the sarin release site who did not have signs of the syndrome. An English-language abstract also showed visual-field constriction and abnormal EEG 45 months after the attacks. Some 6–8 months after the Tokyo attack, symptom-free survivors of intermediate to high exposures were impaired on only one of nine neurobehavioral tests, and significant changes on some EEG results and postural sway tests were seen in females. Three years after the Tokyo attack, a dose-effect relationship was found in previously poisoned people on a measure of memory performance (the backward digit span test), and tapping interval for the dominant hand and stabilometry measures with eyes open were affected in exposed people. An uncontrolled study of patients after the Tokyo attack showed ocular effects (tiredness of eyes, dim vision, and difficulty in focusing), tiredness, fatigue, stiff muscles, and headache up to 5 years after the attack.

Studies have been conducted on US troops who were potentially exposed to sarin after munitions demolition at Khamisiyah. There are no reports that any troops had signs of the acute cholinergic syndrome. Studies of veterans showed no differences between troops who were and who were not present at Khamisiyah. However, when they were divided into those who reported that they had or had not witnessed the explosion and were questioned about symptoms present 8 years after the explosion, those who reported witnessing the explosion were more likely to have self-reported changes in memory, difficulty in sleeping, persistent fatigue, and depression.

In addition to the studies of troops potentially exposed to sarin at Khamisiyah, a number of studies have been conducted on cohorts from the Gulf War that

included analyses of possible indicators of sarin exposure on questionnaires. Self-reports indicating exposure to "chemical-warfare agents" were associated with various neurologic findings in a number of studies. The outcomes in the different studies were cognitive dysfunction, depression, and fibromyalgia; major depression and anxiety; a syndrome termed "confusion–ataxia" (problems with thinking, disorientation, balance disturbances, vertigo, and impotence); mood, memory, and cognitive deficits (profile of mood states, tension and confusion scales, three tests of recall memory, and the WMS-R backward digit span test of memory); and musculoskeletal, neurologic, neuropsychologic, and psychologic symptoms.

Some studies have not shown such effects. In a study of Danish Gulf War veterans, all of whom were involved in peacekeeping or humanitarian roles after the end of the war, self-reported exposure to "nerve gas" was not significantly associated with the neuropsychologic symptoms in the Gulf War cohort. Exposure of those troops to sarin, however, was unlikely. One study of US troops reported no association with symptoms of cognitive dysfunction, chronic fatigue, and fibromyalgia.

Posttraumatic stress disorder (PTSD) has been seen in survivors of the Matsumoto and Tokyo sarin terrorist attacks and in British veterans who reported either wearing "nuclear, biological, and chemical warfare suits", hearing chemical alarms, or having a "chemical/nerve gas attack". Other studies, however, found no relationship between PTSD and "wearing chemical protective gear or hearing alarms sounding", and PTSD was not more common among Khamisiyah-exposed than nonexposed Gulf War veterans. It is not known whether PTSD would be caused by the chemical itself or by the traumatic event.

Cardiovascular Effects

There have been some reports of persistent cardiovascular effects following the sarin attacks in Japan—sudden palpitation and electrocardiographic (ECG) changes—but other studies report that no ECG changes were evident in recovered victims 6–8 months after the Tokyo attack. A study of military personnel deployed during the time of Khamisiyah found one (cardiac dysrhythmias) of 10 specific self-reported physician cardiac diagnoses to be more frequent in the exposed versus nonexposed people. Other studies of veterans showed various cardiovascular effects, but only for deployed versus nondeployed veterans, with no analysis for exposure to sarin.

Other Health Effects

The presence of multisymptom illness, Gulf War illness, or unexplained illness and the relationship of any of them to possible indicators of exposure to chemical-warfare agents has been studied in Gulf War veterans. A case of Gulf

War illness was associated with "use of gas masks". Another study found that responding yes to "thought biological or chemical weapons were being used" was associated with meeting the criteria for a severe or mild to moderate case of multisymptom illness; and another found an association between high frequency of "placement on formal alert for chemical and biological warfare" and mild to moderate or severe multisymptom illness. The prevalence of multiple chemical sensitivity was also associated with hearing chemical alarms and self-reports of having a chemical or nerve-gas attack; and chronic fatigue syndrome was associated with hearing chemical alarms in a study of British soldiers. In all those studies, the exposure assessment is not a reliable indicator of actual sarin or cyclosarin exposures.

HEALTH OUTCOME CONCLUSIONS

The present committee weighed the strengths and limitations of all the epidemiologic evidence reviewed in this report and in *GW1* and reached its conclusions by interpreting the new evidence in the context of the entire body of literature. It assigned each health outcome being considered to one of five categories on the basis of that evidence. The definitions of the categories and the criteria for assigning particular health outcomes to each category are described in Table ES-1; the health outcomes assigned to each category are also listed in the table.

It should be noted that the committee was charged with reviewing the scientific data, not with making recommendations regarding VA policy; therefore, conclusions are not intended to imply or suggest policy decisions. Furthermore, the conclusions are related to associations between exposure to chemicals and health outcomes in human populations, not to the likelihood that any one person's health problem is associated with or caused by exposure to sarin or cyclosarin.

The committee's conclusions are presented in Box ES-1.

TABLE ES-1 Summary of Findings Regarding the Association Between Specific Health Outcomes and Exposure to Sarin or Cyclosarin

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, biologic plausibility, and a temporal relationship.

- **Exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months**

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance[1] and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality[2] study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they are not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not[3] due to bias, including confounding.

- **Exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and a variety of subsequent long-term neurological effects[4]**

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

- **Exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse neurological health effects**
- **Exposure to sarin and subsequent long-term cardiovascular effects**

Continued

TABLE ES-1 Continued

Limited/Suggestive Evidence of No Association

Evidence from well-conducted studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

[1]Chance refers to sampling variability.

[2]Factors used to characterize high-quality studies include the statistical stability of the associations, whether dose–response or other trends were demonstrated, whether or not the association was among numerous comparisons that were made, and the quality of the assessments of exposure and outcome. Specifically, the quality of exposure assessment refers to specificity and sensitivity in relation to the association of interest. For instance, for insecticides, studies assessing specific insecticides (such as chlorpyrifos) have more specificity than those assessing classes of insecticides (such as organophosphorus), which in turn are more specific than those assessing pesticides more generally. With respect to sensitivity, studies are judged by the instruments used to measure exposure. Biologic monitoring data are theoretically the most preferable but are almost never obtainable in the context of a nonpersistent chemical and a disease with long latency, like cancer. Other kinds of efforts can obtain sensitive measures of exposure, such as use of occupational or environmental monitoring data, use of more extensive industrial hygiene assessments, use of interview techniques that help to minimize recall bias (for example, photos of products and home and workplace walkthroughs). Similarly, there are questions about quality of outcome assessment—whether an outcome has been verified by a medical diagnosis in a consistent fashion.

[3]Factors used to make this judgment include the data on the relationship between potential confounders and related health end points in a given study, information on subject selection, and classification of exposure.

[4]See Chapters 3 and 4, and Box ES-1 for further details.

BOX ES-1
Health Outcome Conclusions

Short-Term Neurological Effects Following Acute Exposures

There is sufficient evidence of a causal relationship between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months.

The acute cholinergic syndrome has been recognized for decades. The syndrome, as well as cholinergic signs and symptoms, is evident seconds to hours after exposure and usually resolves in days to months.

Long-Term Neurological Effects Following Acute Exposures

There is limited/suggestive evidence of an association between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and a variety of subsequent long-term neurological effects.

Many health effects are reported in the literature to persist after sarin exposure: fatigue, headache, visual disturbances (asthenopia, blurred vision, and narrowing of the visual field), asthenia, shoulder stiffness, and symptoms of PTSD. Sarin exposure has been followed by abnormal test results, of unknown clinical significance, on the digit symbol test of psychomotor performance, EEG records of sleep, event-related potential, visual evoked potential, and computerized posturography.

Persistent Neurological Effects Following Low-Level Exposures

There is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse neurological health effects.

In the absence of carefully designed human studies expressly of sarin or cyclosarin's long-term health effects at doses that do not produce acute signs and symptoms, the committee concludes that the data remain inadequate or insufficient to determine whether such effects exist.

Persistent Cardiovascular Effects Following Low-Level Exposures

There is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to sarin and subsequent long-term cardiovascular effects.

Studies of persistent cardiovascular effects after sarin exposure have been inconsistent. Therefore, the committee concluded that the data are inadequate or insufficient to determine whether an association exists.

GULF WAR and HEALTH

Updated Literature Review of Sarin

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Board on Health Promotion and Disease Prevention

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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COMMITTEE ON GULF WAR AND HEALTH: UPDATED LITERATURE REVIEW OF SARIN

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report:

Margit L. Bleecker, Director, Center for Occupational and Environmental Neurology, Baltimore, Maryland
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of

this report was overseen by **Lauren A. Zeise,** Chief, Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, California Environmental Protection Agency. Appointed by the National Research Council and Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Following the Iraqi invasion of Kuwait in August of 1990, approximately 700,000 US troops were deployed to the Persian Gulf in 1990 and 1991. Although the duration of combat was short and casualties few, upon their return many of the Gulf War veterans began experiencing unexplained symptoms, such as muscle and joint pain, fatigue, difficulties of cognition, and headaches. Studies have shown that the prevalence of these symptoms clearly was higher among veterans who had been deployed to the Persian Gulf than among either those not deployed or those sent to other wars. This has led many to consider the possibility that exposures unique to the Persian Gulf Theater could be the source of the illnesses.

In 1998, in response to the health concerns of veterans and their families, the Department of Veterans Affairs contracted with the Institute of Medicine (IOM) to study the scientific evidence concerning possible adverse health effects of multiple agents to which veterans may have been exposed. To carry out this assignment, the IOM has convened three committees. The first committee report addressed the effects on health of four sets of compounds: depleted uranium, sarin and cyclosarin, pyridostigmine bromide, and vaccines against botulinum toxin and anthrax. The second committee reported on the health effects of exposure to insecticides and solvents. The third committee is currently reviewing the combustion products of oil-well fires, fuels, and compounds potentially used as propellants for Scud missiles.

Our ad hoc committee was asked to update the first committee's report on outcomes of exposure to sarin and cyclosarin, in light of more recent studies of sarin exposure from terrorist attacks in Japan; possible sarin exposure of veterans

at Khamisiyah, Iraq, during the Gulf War; and more recent toxicological studies on low-dose exposure to sarin. In as much as no veterans of the Gulf War are known to have had symptoms of acute sarin toxicity, our focus was on the long-term effects of low-dose exposure. In addition, since sarin and cyclosarin are strong acetylcholinesterase inhibitors, we also reviewed recent studies on organophosphorus insecticides, which also are cholinesterase inhibitors.

I am deeply appreciative of the fine work and great expertise of committee members, William Daniell, MD, MPH; Rose Goldman, MD, MPH; Richard Mayeux, MD, MSc; Samuel Potolicchio, MD; and Joseph Rodricks, PhD. Further, the study could not have been successfully completed without the superb efforts of study director Michelle Catlin and research assistant Deepali Patel.

Jack M. Colwill, MD

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