Executive Summary

On August 2, 1990, Iraqi armed forces invaded Kuwait; within 5 days, the United States began to deploy troops to Operation Desert Shield. Intense air attacks against the Iraqi armed forces began on January 16, 1991, and opened a phase of the conflict known as Operation Desert Storm. Oil-well fires became visible by satellite images as early as February 9, 1991; the ground war began on February 24, and by February 28, 1991, the war was over. The oil fires were extinguished by November 1991. The last troops to participate in the ground war returned home on June 13, 1991. In all, approximately 697,00 U.S. troops had been deployed to the Persian Gulf area during the conflict.

Although considered an extraordinarily successful military operation with few battle casualties and deaths, veterans soon began reporting health problems that they attributed to their participation in the Gulf War. Although the majority of men and women who served in the Gulf returned to normal activities, a large number of veterans have had a range of unexplained illnesses including chronic fatigue, muscle and joint pain, loss of concentration, forgetfulness, headache, and rash.

The men and women who served in the Gulf War theater were potentially exposed to a wide range of biological and chemical agents including sand, smoke from oil-well fires, paints, solvents, insecticides, petroleum fuels and their combustion products, organophosphate nerve agents, pyridostigmine bromide (PB), depleted uranium (DU), anthrax and botulinum toxoid vaccinations, and infectious diseases, in addition to psychological and other physiological stress. Veterans have become increasingly concerned that their ill health may be related to exposure to these agents and circumstances.

Department of Veterans Affairs (VA) ap-
ciences and requested that the Institute of
evaluate the published scientific literature
ne agents to which the Gulf War veterans
ealth effects. To carry out the VA charge,
Health Effects Associated with Exposures
began its deliberations in January 199 by
nds for study. The committee decided to
to the veterans. Following meetings with
organizations, the committee decided to
pleted uranium, chemical warfare agents
bromide, and vaccines (anthrax and botu-
will examine the remaining agents.

ns and leaders of veterans organizations
the study. These meetings were invaluable
ortant perspective on the veterans' experi-
discussions with and written input from
the manner in which the committee con-
its process.

act, two public laws were passed: the Ve

the committee reviewed studies of any human populations—including veterans—that had been exposed to the agent of concern at any dose. These studies come primarily from occupational, clinical, and healthy volunteer settings.

The committee began its task by talking with representatives of veterans' organizations, as an understanding of the veterans' experiences and perspectives is an important point of departure for a credible scientific review. The committee opened several of its meetings to veterans and other interested individuals. The committee held a scientific workshop and two public meetings. It also received information in written form from veteran organizations, veterans, and other interested persons who made the committee aware of their experiences or their health status and provided information about research. This process provided valuable information about the Gulf War experience and helped the committee to identify the health issues of concern.

The committee and staff reviewed more than 10,000 abstracts of scientific and medical articles related to the agents selected for study and then carefully examined the full text of over 1,000 peer-reviewed journal articles, many of which are described in this report. For each agent, the committee determined—to the extent that available published scientific data permitted meaningful determinations—the strength of the evidence for associations between exposure to the agent and adverse health effects. Because of the general lack of exposure measurements in veterans (with some exceptions), the committee reviewed studies of other populations known to be exposed to the agents of interest. These include uranium-processing workers, individuals who may have been exposed to sarin as a result of terrorist activity (e.g., the sarin attacks in Japan), healthy volunteers (including military populations), and clinical populations (e.g., patients with myasthenia gravis treated with PB). By studying health effects in these populations, the committee could decide, in some cases, whether the putative agents could be associated with adverse health outcomes. The committee's judgments have both quantitative and qualitative aspects, and reflect the evidence and the approach taken to evaluate that evidence. The committee's methodology draws from the work of previous IOM committees and their reports on vaccine safety (IOM, 1991, 1994a), herbicides used in Vietnam (IOM, 1994b, 1996, 1999), and indoor pollutants related to asthma (IOM, 2000).

The committee adopted a policy of using only peer-reviewed published literature to form its conclusions. It did not collect original data or perform any secondary data analysis. Although the process of peer review by fellow professionals—which is one of the hallmarks of modern science—is the best assurance that a study has reached valid conclusions, peer review does not guarantee the validity or generalizability of a study. Accordingly, committee members read each research article critically. The committee used only peer-reviewed publications in forming its conclusions about the degree of association between exposure to a particular agent and adverse health effects. However, this report describes some non-peer-reviewed publications, which provided background information for the committee and raised issues that will require further research. In their evaluation of individual research articles, committee members

considered several important issues, including the quality of the study; its relevance; issues of error, bias, and confounding; the diverse nature of the evidence; and the study population.

The committee classified the evidence for association between exposure to a specific agent and a health outcome into one of five previously established categories. The categories closely resemble those used by several IOM committees that evaluated vaccine safety (IOM, 1991, 1994a), herbicides used in Vietnam (IOM, 1994b, 1996, 1999), and indoor pollutants related to asthma (IOM, 2000). Although the categories imply a statistical association, the committee had sufficient epidemiologic evidence to examine statistical associations for only one of the agents under study (i.e., depleted uranium); the epidemiologic evidence for the other agents examined (i.e., sarin, pyridostigmine bromide, and anthrax and botulinum toxoid vaccines) was very limited. Thus, the committee based its conclusions on the strength and the coherence of the data in the available studies. In many cases, these data distinguished differences between transient and long-term health outcomes related to the dose of the agent. Based on the literature, it became incumbent on the committee to similarly specify the differences between dose levels and the nature of the health outcomes. This approach led the committee to reach conclusions about long- and short-term health effects, as well as health outcomes related to the dose of the putative agents. The final conclusions represent the committee s collective judgment. The committee endea v ored to express its judgments as clearly and precisely as the available data allowed. The committee used the established categories of association from previous IOM studies, because they have gained wide acceptance for more than a decade by Congress, government agencies, researchers, and veteran groups.

- *Sufficient Evidence of a Causal Relationship.* Evidence is sufficient to conclude that a causal relationship exists between the exposure to a specific agent and a health outcome in humans. The evidence fulfills the criteria for sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose–response relationship,[1] consistency of association, temporal relationship, specificity of association, and biological plausibility.
- *Sufficient Evidence of an Association.* Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between an exposure to a specific agent and a health outcome in human studies in which chance, bias, and confounding could be ruled out with reasonable confidence.
- *Limited/Suggestive Evidence of an Association.* Evidence is suggestive of an association between exposure to a specific agent and a health outcome in

[1]A dose–response relationship refers to the finding of a greater health effect (response) with higher doses of an agent.

humans, but is limited because chance, bias, and confounding could not be ruled out with confidence.

- *Inadequate/Insufficient Evidence to Determine Whether an Association Does or Does Not Exist*. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure to a specific agent and a health outcome in humans.
- *Limited/Suggestive Evidence of No Association*. There are several adequate studies covering the full range of levels of exposure that humans are known to encounter that are mutually consistent in *not* showing a positive association between exposure to a specific agent and a health outcome at any level of exposure. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

These five categories describe different strengths of association, with the highest level being sufficient evidence of a causal relationship between exposure to a specific agent and a health outcome. The criteria for each category sound a recurring theme: An association is more likely to be valid to the extent that the authors reduced common sources of error in making inferences—chance variation, bias in forming a study cohort, and confounding. Accordingly, the criteria for each category express varying degrees of confidence based upon the extent to which it has been possible to exclude these sources of error. To infer a causal relationship from a body of observational evidence, the committee relied on long-accepted criteria for assessing causation in epidemiology (Hill, 1971; Evans, 1976). The following sections provide a discussion and conclusions regarding the putative agents (DU, PB, sarin, and vaccines).

DEPLETED URANIUM

Depleted uranium is a by-product of the enrichment process used to make reactor-grade uranium. Natural uranium is considered a low-level radioactive element. Because of the different percentages of uranium isotopes, the specific activity (a measure of radioactivity) of depleted uranium (14.8 mBq/μg) is 40 percent lower than that of naturally occurring uranium (25.4 mBq/μg) and considerably lower than that of enriched uranium (approximately 1,750 mBq/μg) (Harley et al., 1999). However, the chemical properties of depleted uranium are the same as those of the enriched and naturally occurring forms.

The U.S. military used depleted uranium in the Gulf War for offensive and defensive purposes (OSAGWI, 1998). Heavy armor tanks had a layer of depleted uranium armor to increase protection. Depleted uranium was also used in kinetic energy cartridges and ammunition rounds. U.S. personnel were exposed to depleted uranium as the result of friendly fire incidents, cleanup operations, and

accidents (including fires). DU-containing projectiles struck 21 Army combat vehicles (OSAGWI, 1998). After the war, assessment teams and cleanup and recovery personnel may have had contact with DU-contaminated vehicles or DU munitions. In June 1991, a large fire, which occurred in Camp Doha near Kuwait City, led to a series of blasts and fires that destroyed combat-ready vehicles and DU munitions. Nearby troops and cleanup crews may have been exposed to DU-containing dust or residue. Other troops may have been exposed through contact with damaged vehicles or inhalation of DU-containing dust (Fahey, 200).

The primary routes of exposure to uranium for humans are through ingestion or inhalation; the effects of dermal exposure and embedded fragments have also been studied. The amount of uranium retained in the body depends on the solubility of the uranium compounds to which the individual is exposed. Inhaled insoluble uranium concentrations may remain within the pulmonary tissues, especially the lymph nodes, for several years. Ingested uranium is poorly absorbed from the intestinal tract.

Conclusions on the Health Effects of Depleted Uranium

Although depleted uranium is the form of uranium that was present in the Gulf War, there are only a few studies of its health effects. Therefore, the committee studied the health effects of natural and processed uranium in workers at plants that processed uranium ore for use in weapons and nuclear reactors. The literature on uranium miners and on populations exposed to external radiation is largely not relevant to the study of uranium because the primary exposures of these populations were to other sources of radiation (e.g., radon progeny or gamma radiation). While studies of uranium processing workers are useful, these studies have several shortcomings. Although several studies involved tens of thousands of workers, even these studies were not large enough to identify small increases in the risk of uncommon cancers. Few studies had access to consistent, accurate information about individual exposure levels. Further, in these industrial settings, the populations could have been exposed to other radioisotopes (e.g., radium ore, thorium) and to a number of industrial chemicals that may confound health outcomes. Finally, no studies had reliable information about cigarette smoking, which may also confound outcomes of lung cancer. However, these cohorts of uranium processing workers are an important resource, and the committee encourages further studies that will provide progressively longer follow-up, improvements in exposure estimation, and more sophisticated statistical analyses.

Lung Cancer

Lung cancer mortality has been the focus of attention in many cohort studies of workers employed in the uranium processing industry. Many of these studies were large and had a long period of follow-up. Lung cancer mortality

was not increased among occupationally exposed persons in most of these cohorts. The strongest studies used internal controls, used multivariate analysis to adjust for possible confounders, had at least 30 years of follow-up, and measured the cumulative radiation exposure of individual workers.

In a large study of employees at Oak Ridge, Tennessee, uranium processing and research facilities (Frome et al., 1990), the entire group experienced a small increase in lung cancer mortality. Despite its shortcoming in measuring radiation exposure, the committee felt the Frome study was important because of its large size and multivariate analysis. The analysis showed that radiation exposure was not associated with lung cancer mortality. It also demonstrated the relative importance of several confounders. Socioeconomic status strongly predicted lung cancer risk. The study by Dupree and colleagues (1995) combined data from four separate studies and utilized quantitative estimates of individual cumulative exposures to uranium to form a dose–response analysis. The large number of cases of deaths from lung cancer (787) made it possible for Dupree and colleagues to perform a detailed dose–response analysis, while adjusting for confounders. This study found that the dose–response analysis did not suggest any increase in lung cancer risk up to 25 cGy. Above this level, there were too few cases to draw any conclusions. The strongest suggestion of an association with lung cancer appeared in the recent report by Ritz (1999), in which large and statistically significant increases in lung cancer mortality occurred in the small group of workers with a cumulative internal dose of 200 mSv or more. The committee viewed this finding with caution because the subgroup with the elevated risk had only three cases of lung cancer and because the author could not adjust for cigarette smoking, which had been an important factor in the Dupree study. Nevertheless, the data based on the well-characterized exposure levels in this study do suggest that after controlling for external dose, internal doses up to 200 mSv are not associated with excess risk of lung cancer.

The committee concludes that there is limited/suggestive evidence of no association between exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy. However, there is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to uranium and lung cancer at higher levels of cumulative exposure.

Renal Function

Although uranium is a heavy metal that can cause transient renal dysfunction, the preponderance of evidence indicates little or no clinically important renal effects of exposure to uranium. A few studies have shown functional changes in renal function (Lu and Zhao, 1990; Zamora et al., 1998), but the number of cases has been quite small. Perhaps the strongest evidence is the absence of kidney damage in workers who had been exposed to high levels of

soluble uranium compounds and in veterans exposed to DU from embedded shrapnel. Kidney function was normal in Gulf War veterans with embedded DU fragments years after exposure, despite urinary uranium concentrations up to 30.74 µg/g creatinine (McDiarmid et al., 2000).

The committee concludes that there is limited/suggestive evidence of no association between exposure to uranium and clinically significant renal dysfunction.

Other Health Outcomes

The information on other health outcomes in humans comes from epidemiologic studies of uranium processing workers and case reports of workers or other individuals accidentally exposed to large doses of uranium compounds. While the studies did not suggest that uranium has adverse health effects, the studies were of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association in humans.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to uranium and the following health outcomes: lymphatic cancer; bone cancer; nervous system disease; nonmalignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on hematological parameters, reproductive or developmental dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects, or musculoskeletal effects).

SARIN

Sarin is a highly toxic nerve agent produced for chemical warfare. It was synthesized in 1937 in Germany in a quest for improved insecticides (Somani, 1992). Although its battlefield potential was soon recognized, Germany refrained from using its stockpiles during World War II. Sarin s first military use did not occur until the Iran–Iraq conflict in the 1980s (Brown and Brix, 1998).

High-level exposures to sarin can be fatal within minutes to hours. In vapor or liquid form, sarin can be inhaled or absorbed, respectively, across the skin, eyes, or mucous membranes (Stewart and Sullivan, 1992). Because of its extreme potency, "high" sarin exposure for humans is quite low: Exposure to as little as 100 mg across the skin, or 50±00 mg/min/m ^{3} by inhalation, is lethal to 50 percent of exposed individuals (Somani, 1992).

Sarin, or isopropyl methylphosphonofluoridate, is a member of a class of chemicals known as organophosphorus esters (or organophosphates). A few highly toxic members of this large class are chemical warfare agents, but most are insecticides (Lotti, 2000). The drug pyridostigmine bromide is pharmacologically

similar to sarin and other organophosphates, but it is a member of a different chemical class, the carbamates. Both PB and sarin exert their effects by binding to and inactivating the enzyme acetylcholinesterase (AChE).[2] The binding of sarin to AChE is irreversible, whereas the binding of PB to AChE is reversible.

In March 1991, during the cease-fire period, troops from the U.S. 37th and 307th Engineering Battalions destroyed enemy munitions throughout the occupied areas of southern Iraq (PAC, 1996). One of the sites destroyed was a large storage complex at Khamisiyah, Iraq, consisting of more than 100 bunkers, which contained stacks of 122-mm rockets loaded with sarin and cyclosarin[3] (Committee on Veterans' Affairs, 1998). U.S. troops performing demolitions were unaware of the presence of nerve agents. In October 1991, inspectors from the United Nations Special Commission on Iraq (UNSCOM) first confirmed the presence of a mixture of sarin and cyclosarin (Committee on Veterans' Affairs, 1998). At the time of the demolition, there were no medical reports by the U.S. Army Medical Corps of military personnel with signs and symptoms of acute exposure to sarin (PAC, 1996). Further, a 1997 survey mailed by the Department of Defense (DoD) to 20,000 troops within a 50-mile radius of Khamisiyah found that more than 99 percent of respondents (n = 7,400) reported no acute cholinergic effects (CIA–DoD, 1997). Nevertheless, low-level exposure could have occurred without producing acute cholinergic effects.

Conclusions on the Health Effects of Sarin

The committee reached the following conclusions after reviewing the literature on sarin. The committee was unable to formulate any conclusions about cyclosarin because of the paucity of toxicological and human studies.

The committee concludes that 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.

In humans, exposure to high doses of sarin produces a well-characterized acute cholinergic syndrome. This syndrome, as evidenced by acute cholinergic signs and symptoms, is evident seconds to hours after exposure and usually resolve in days to months. The syndrome is produced by sarin's irreversible inhi-

[2]AChE is an enzyme necessary to remove acetylcholine (ACh). ACh transmits nerve signals at the cholinergic neuromuscular junction or synapses in the central nervous system. Anticholinesterase agents inhibit (inactivate) AChE, resulting in an accumulation of acetylcholine. The accumulation repetitively activates the ACh receptors, resulting in exaggerated responses of the organ (e.g., excess salivation).

[3]Cyclosarin is an organophosphate nerve agent. The committee examined the literature on this agent but found a very limited amount of information available on the health effects of this compound.

bition of AChE. Inactivation of this enzyme, which normally breaks down the neurotransmitter acetylcholine, leads to the accumulation of acetylcholine at cholinergic synapses. Excess quantities of acetylcholine result in widespread overstimulation of muscles and nerves. At high doses, convulsions and death can occur.

The committee concludes that there is limited/suggestive evidence of an association between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects.

After sarin exposure, many health effects are reported to persist (e.g., fatigue; headache; visual disturbances such as asthenopia, blurred vision, and narrowing of the visual field; asthenia; shoulder stiffness; symptoms of posttraumatic stress disorder; and abnormal test results, of unknown clinical significance, on the digit symbol test of psychomotor performance, electroencephalogram records of sleep, event-related potential, visual evoked potential, and computerized posturography).

These conclusions are based on retrospective controlled studies of three different exposed populations who experienced acute cholinergic signs and symptoms after exposure to sarin. One population consisted of industrial workers accidentally exposed to sarin in the United States; the other two populations were civilians exposed during terrorism episodes in Japan. The health effects listed above were documented at least 6 months after sarin exposure, and some persisted up to a maximum of 3 years, depending on the study. Whether the health effects noted above persist beyond the 3 years has not been studied.

The committee concludes that 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 health effects.

On the basis of positive findings in a study of nonhuman primates and studies of humans exposed to organophosphate insecticides, it is reasonable to hypothesize that long-term adverse health effects can occur after exposure to low levels of sarin. Studies of industrial workers exposed to low levels of organophosphate insecticides consistently show a higher prevalence of neurological and/or psychiatric symptom reporting. However, there are no well-controlled studies of long-term health effects in humans exposed to sarin at doses that do not produce acute signs and symptoms.

PYRIDOSTIGMIN

Pyridostigmine bromide was used duri
exposure to nerve agents. It has been used
treatment of myasthenia gravis and may b
sal of neuromuscular blockade (Williams,

PB, a reversible cholinesterase inhi
Hoffman-La Roche Laboratories in Switzer
Mestinon bromide (Williams, 1984). PB is
cholinesterase compounds, which general
Compounds in this category are poorly abso
are excluded by the blood brain barrier (Wil

Mestinon was approved by the Food
1955 as safe for the treatment of myasther
injectable form known as Regenol for rev
formulations (Rettig, 199). In the treatmer
oral dose is 120–600 mg per day (in divid
quency of the dose must be adjusted to the
sicians' Desk Reference, 2000). The drug
stration, and peak plasma levels occur 2 to
eliminated almost exclusively via the kidne

Side effects of PB are generally relat
thenics; in surgical patients, adverse reac
administration of atropine (Williams, 198
of PB are due to stimulation of muscarin
acetylcholine (ACh). Muscarinic reaction
abdominal cramps, increased peristalsis,
chial secretions, miosis, and heavy persp
muscle cramps, fasciculations, and weakne

PB binds reversibly to AChE and pre
versibly with nerve agents. PB pretreatmer
20 percent inhibition of whole-blood AChl
an antidote and has no value when adminis
not a substitute for atropine or 2-pralidoxi
efficacy (Madsen, 1998).

The DoD reported that 5,328,710 dos
that approximately 250,000 personnel took
plied as a 21-tablet blister pack; the dosa
every 8 hours. Variation in use occurr
administered and was to be taken only w
(PAC, 1996). Thus, veterans actual expos
few examples of documentation in either
ords (PAC, 1996).

ffects of Pyridostigmine Bromide

s have reported that PB causes acute tran-
unteers, patients given PB as a diagnostic
n, and myasthenia gravis patients treated
hen used as a diagnostic test, PB is gener-
- to 180-mg dose, which produces acute
inority of patients and normal volunteers.
25 percent of subjects experience abdomi-
estive sounds, pain, diarrhea, and nausea),
ms (skeletal muscle and tongue fasciccula-
arthria) that typically last 1² hours (see,
et al., 1990a,b,c, 1996a,b; Giustina et al.,
993; Bellone et al., 1992; O Keane et al.,
ang et al., 1995; Coiro et al., 1998). The
t, and tolerable; seldom require medical
ed by central nervous system symptoms.
his report did not show a relationship be-
e side effects, none was designed specifi-
e relationship. There is, however, a trend
igher PB doses among subjects given sev-

is to control muscle weakness in myas-
usually range from 120 to 600 mg. About
one or more side effects, which are usually
e gastrointestinal in origin. A few patients
ns such as hypersalivation, increased per-
bronchial secretion, and blurred vision.
ecause of side effects.

lental poisoning with PB in doses ranging
to-moderate cholinergic symptoms occur-
tion and lasting up to 24 hours. Patients
s (e.g., abdominal cramps, diarrhea, nau-
ry incontinence, and transient muscle fas-
were self-limited and were well tolerated.

vailable on the acute effects of PB comes
f growth hormone deficiency and its thera-
e doses of PB in these applications are
is during the Gulf War, yet these studies
and effective in clinical applications. Side
tinal and muscular, do not last long, and

es, in both clinical and healthy volunteer
testinal and muscular side effects, which

are transient and characteristically mild. Idiosyncratic reactions occur at a much lower rate.

> *The committee concludes that there is sufficient evidence of an association between PB and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes.*

Since unexplained Gulf War-related illnesses have been chronic, possible long-term effects of PB are of great interest. There are no reports of chronic toxicity related to human PB exposure in clinical or military populations. Haley and Kurt (1997) suggested that unexplained Gulf War-related symptoms could be a unique manifestation of organophosphate-induced delayed neuropathy associated with PB exposure alone or in combination with other wartime exposures, in the absence of acute symptoms of organophosphate toxicity. There is evidence that some AChE inhibitors may be associated with chronic neurological changes. Haley and Kurt provide evidence that a small number of ill Gulf War veterans have neurological impairment compared to a small number of well veterans from the same unit. The committee felt that the validity of this association, and the possible causal relationship between PB and the neurological findings, are uncertain. Among the reasons for withholding judgment are the large potential for selection and information biases[4] in this study population, the lack of a nondeployed comparison group, and the lack of clinical validity in the measures of neurological damage. Haley and Kurt's hypothesis requires further investigation.

Haley and Kurt (1997) have also suggested that chronic neuropsychological syndromes derived from factor analysis are linked to acute responses to administration of PB. The evidence that they present has several shortcomings. The major limitation was the lack of comparable studies in a nondeployed group of veterans. There is uncertainty about how the authors selected, administered, and interpreted the neuropsychological tests. The study population consisted of self-selected individuals who replied to a survey (41 percent of the battalion). The data on exposure to PB were self-reports of events that had occurred many years before.

The epidemiologic data do not provide evidence of a link between PB and chronic illness in Gulf War veterans. Most epidemiologic studies of Gulf War veterans have focused on whether a unique Gulf War syndrome exists and defining its characteristics. Only two epidemiologic studies specifically investigated the possible association of PB use and chronic symptoms among Gulf War veterans (Haley and Kurt, 1997; Unwin et al., 1999). This summary has already noted the limitations of the small, selected population studied by Haley and colleagues. Based on factor analysis, they defined three syndromes associated with

[4]Selection bias can occur in the recruitment of study subjects to a cohort when the study and control groups differ from each other by a factor, often unknown, that is likely to affect the results. Information bias results from the way in which the data are collected (e.g., measurement errors, imprecise measurement, misdiagnosis). Bias may also result from misclassification of study subjects with respect to the outcome variable.

Gulf War service. These factor-derived syndromes were not associated with taking PB or with the dose of PB. Haley and Kurt found an association between two of the three syndromes and self-reported symptoms that are consistent with adverse effects of PB. Because the study cohort was not assembled from a random sample of Gulf War veterans, this apparent association may be the result of inadvertent selection for veterans with both adverse health syndromes and adverse effects of PB. The evidence is not strong enough to conclude that an association exists between Gulf War illnesses and side effects of PB. In the second epidemiologic study (Unwin et al., 199), all exposures studied (PB, diesel or petrochemical fumes, oil fire smoke, viewing dismembered bodies, etc.) showed an association of similar magnitude with adverse symptoms in U.K. servicemen. The lack of specificity of the association between the type of exposure and symptoms suggests that PB itself is not the cause of the symptoms. Recall bias and reporting bias[5] may explain this finding. Thus, neither of these two studies provides good evidence for a specific association between PB and chronic adverse health effects.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association does or does not exist between PB and long-term adverse health effects.

VACCINES

During the Gulf War, a number of different immunobiologics (e.g., cholera, meningitis, rabies, tetanus, and typhoid vaccines) were sent to the war theatre to protect military personnel against potential exposures to biological threats (Committee on Veterans Affairs, 198). Concerns about Iraq s offensive bi ological warfare capabilities led to the decision that available vaccines should be utilized as preventive measures against biological warfare agents. The military sent approximately 310,000 doses of FDA-licensed anthrax vaccine to the Gulf War theatre, and it is estimated that 150,000 U.S. troops received at least one anthrax vaccination (Christopher et al., 1997; Committee on Veterans' Affairs, 1998). Approximately 137,850 doses of botulinum toxoid were sent to the Gulf, and it is estimated that 8,000 military personnel were vaccinated (Committee on Veterans Affairs, 1998). However, medical records from the Gulf War contain little or no information about who received these vaccines, how frequently the vaccines were administered, or the timing of vaccinations relative to other putative exposures (OSAGWI, 1999).

[5]Common sources of information bias are due to the inability of study subjects to

Anthrax Vaccine

The primary use of the anthrax vaccine in humans was initially for the protection of occupationally exposed individuals (e.g., persons working with animal hair or hide, including goat hair mill workers, tannery workers, and veterinarians). Protective antigen, one of the three toxin proteins produced by the anthrax bacillus, is the immunogenic component of both the U.S. and the U.K. vaccines. The U.S. vaccine is an aluminum hydroxide-adsorbed cell-free culture filtrate of an unencapsulated anthrax strain (Pile et al., 1998). Product licensure for Anthrax Vaccine Adsorbed was granted on November 10, 1970. It is estimated that 68,000 doses of the U.S. anthrax vaccine were distributed from 1974 to 1989, 268,000 doses in 1990, and 1.2 million doses from 1991 to July 1999 (Ellenberg, 199). The exact number of people who received the vaccine is not known. The current dosing schedule is 0.5 ml administered subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months, followed by yearly boosters.

In December 1997, the Secretary of Defense announced that all U.S. military forces would receive anthrax vaccinations for protection against the threat of biological warfare. The Anthrax Vaccine Immunization Program began vaccinations in March 1998.

Conclusions on the Health Effects of the Anthrax Vaccine

There is a paucity of published peer-reviewed literature on the safety of the anthrax vaccine. Brachman and colleagues (1962) conducted the only randomized clinical trial of vaccination with a protective antigen anthrax vaccine.[6] The clinical trial was conducted among eligible workers at four goat hair processing mills in which some raw materials were contaminated by anthrax bacilli. Participants were examined 24 and 48 hours following each vaccination to assess both local and systemic reactions to the vaccine. There were no reports of subsequent active or passive surveillance for possible adverse effects beyond 48 hours after each vaccination (however, there was further monitoring for the vaccine's efficacy). The typical reaction is described as a ring of erythema (1–2 cm in diameter) at the injection site, with local tenderness that lasted 24–48 hours. Some subjects (a number was not given) reported more extensive edema, erythema (more than 5 cm in diameter), pruritus, induration, or small painless nodules at the injection site (lasting up to several weeks). Twenty-one individuals had moderate local edema that lasted up to 48 hours. The only systemic reactions were reported in two individuals (0.9 percent of the actively vaccinated subjects) who experienced "malaise" lasting 24 hours following vaccination. The study notes that three individuals who received the placebo (0.1 percent

[6]Although the vaccine used in this study was similar to the vaccine currently available in the United States in that it was a protective antigen vaccine, the manufacturing process has since changed and a different strain of anthrax bacillus is now used (GAO, 1999).

alum) had mild reactions. However, studies of the anthrax vaccine have not used active surveillance to systematically evaluate long-term health outcomes. Unfortunately, this situation is typical for all but a few vaccines.

The committee concludes that there is sufficient evidence of an association between anthrax vaccination and transient acute local and systemic effects (e.g., redness, swelling, fever) typically associated with vaccination.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health effects.

Botulinum Toxoid

Botulinum toxins, known primarily for causing cases of foodborne botulism, are produced by the anaerobic bacterium *Clostridium botulinum*. Different strains of the bacillus produce seven distinct botulinum toxins (A G). These toxins are among the most toxic compounds per body weight of agent, with an LD_{50} of 0.001 μg/kg in mice (USAMRIID, 1996).

Work on modifying the botulinum toxin to the nontoxic form of a toxoid began in 1924. A bivalent toxoid (for serotypes A and B) was developed in the United States in the 1940s. Further research led to a pentavalent toxoid (serotypes A E) first produced in large lots by Parke, Davis, and Company in 1958 under contract to the U.S. Army (Anderson and Lewis, 1981). The current botulinum toxoid vaccine, a pentavalent toxoid (serotypes A–E), is in Investigational New Drug status. The toxoid has been administered to volunteers for testing purposes and to occupationally at-risk workers. The schedule for the pentavalent toxoid calls for subcutaneous injections at 0, 2, and 12 weeks, followed by annual boosters. Recent advances in molecular cloning techniques and new knowledge about the molecular mechanisms of action of the toxins have opened up avenues for new botulinum vaccine development (Middlebrook, 1995).

Conclusions on the Health Effects of Botulinum Toxoid

Early studies of the initial univalent botulinum toxoids in the 1940s reported a significant number of local and systemic reactions (Middlebrook and Brown, 1995). Several studies that primarily focused on the efficacy of the botulinum toxoid vaccine (Fiock et al., 1962, 1963) noted moderate local or systemic reactions. Studies of the botulinum toxoid vaccine have not used active surveillance to systematically evaluate long-term health outcomes.

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The committee concludes that there is sufficient evidence of an association between botulinum toxoid vaccination and transient acute local and systemic effects (e.g., redness, swelling, fever) typically associated with vaccination.

The committee concludes that there is inadequate/insufficient evidence to determine whether an association does or does not exist between botulinum toxoid vaccination and long-term adverse health effects.

Multiple Vaccinations

Military personnel often receive several vaccinations as they prepare for service in an environment with many endemic diseases. People have expressed concerns that multiple vaccinations prior to and during Gulf War service may have caused adverse health effects.

Conclusions on the Health Effects of Multiple Vaccinations

Certain multiple vaccination regimens can lead to suboptimal antibody responses, but there is little evidence, largely because of a lack of active monitoring, of adverse clinical or laboratory consequences beyond the transient local and systemic effects seen frequently with any vaccination.

A group of 99 employees at Fort Detrick, Maryland, who received many vaccinations related to occupational requirements, were followed for up to 25 years to investigate the potential subclinical effects of intensive vaccination. The participants underwent physical examinations and laboratory testing in 1956, 1962, and 1971 (Peeler et al., 1958, 1965; White et al., 1974). No clinical sequelae attributable to intense long-term immunization could be identified in this cohort. None of the subjects suffered unexplained clinical symptoms requiring them to take sick leave that could be attributed to the vaccination program. There was some evidence of a chronic inflammatory response, as characterized by certain laboratory test abnormalities. However, these changes cannot necessarily be attributed to the vaccinations, because the workers studied were occupationally exposed to a number of virulent microbes. This series of longitudinal clinical studies had several shortcomings. However, the studies were valuable because careful monitoring did not disclose any evidence of serious unexplained illness in a cohort that received a series of intense vaccination protocols over many years.

Several studies of U.K. Gulf War veterans provide some limited evidence of an association between multiple vaccinations and long-term multisymptom outcomes, particularly for vaccinations given during deployment (Unwin et al., 1999; Hotopf et al., 2000). There are some limitations and confounding factors in these studies, and further research is needed.

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tion does or does not exist between
rm adverse health effects.

EASED RISK OF ADVERSE
ONG GULF WAR VETERANS

e scientific evidence in the peer-reviewed
s about associations between the agents of
ll populations (see Table 1). The commit-
es that reflect the strength of the evidence
to the agent and health outcomes. The
kelihood that Gulf War veterans health
ed by these agents. To address this issue,
re the rates of health effects in Gulf War
nts with the rates of those who were not
ation about the agents to which individual
es. However, as discussed throughout this
rding the actual agents and doses to which
xposed. Further, to answer questions about
ar veterans, it would also be important to
fferences between exposed and unexposed
health outcomes. This information is also
lation. Indeed most of the evidence that the
ons about the association of the putative
n studies of populations exposed to these
tings, rather than from studies of Gulf War
data on veterans, the committee could not
in the studies that it reviewed to the level
us, the committee could not determine the

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onship

that a causal relationship exists between the
outcome in humans. The evidence fulfills the
sociation (below) and satisfies several of the
h of association, dose–response relationship,
ationship, specificity of association, and bio-

endent acute cholinergic syndrome that is evi-
exposure and resolves in days to months.

TABLE 1 *Continued*

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between an exposure to a specific agent and a health outcome in human studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

- Pyridostigmine bromide and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes.
- Anthrax vaccination and transient acute local and systemic effects.
- Botulinum toxoid vaccination and transient acute local and systemic effects.

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between exposure to a specific agent and a health outcome in humans, but is limited because chance, bias, and confounding could not be ruled out with confidence.

- Exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects.

Inadequate/Insufficient Evidence to Determine Whether an Association Does or Does Not Exist

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure to a specific agent and a health outcome in humans.

- Exposure to uranium and lung cancer at higher levels of cumulative exposure (>200 mSv or 25 cGy).
- Exposure to uranium and lymphatic cancer; bone cancer; nervous system disease; nonmalignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on hematological parameters, reproductive or developmental dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects, or musculoskeletal effects).
- Pyridostigmine bromide and long-term adverse health effects.
- Exposure to sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse health effects.
- Anthrax vaccination and long-term adverse health effects.
- Botulinum toxoid vaccination and long-term adverse health effects.
- Multiple vaccinations and long-term adverse health effects.

Limited/Suggestive Evidence of No Association

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, that are mutually consistent in not showing a positive association between exposure to a specific agent and a health outcome at any level of exposure. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

- Exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy.
- Exposure to uranium and clinically significant renal dysfunction.

likelihood of increased risk of adverse health outcomes among Gulf War veterans due to exposure to the agents examined in this report.

RESEARCH RECOMMENDATIONS

The committee s charge was to review the scientific literature on the potential health effects of agents to which Gulf War veterans may have been exposed. Of the many stressors and biological and chemical agents in the Gulf War theater, this report has reviewed the literature on the agents that were of most concern to the veterans and their representatives. Subsequent IOM studies will examine the literature on other Gulf War-related agents.

The committee considered the evidence for each of the agents in turn, as if each one were the only risk factor for adverse health effects. It did so because committee members sought to learn how each agent, in the absence of all of the others, might affect human health. The committee realized through the course of this study, however, that there may also be a need to examine the impact of the total experience of deployment and war on veterans health. Such an approach may help elucidate the nature of the illnesses in Gulf War veterans in a way that is not possible by examining single agents. Unfortunately, most of the studies conducted to date focus only on single agents. Yet integrating the various stressors, biological and chemical exposures, the complexities faced by military personnel during all phases of deployment, and the issues surrounding war may provide a more realistic approach toward understanding veterans health issues and may provide insights for preventing illnesses in future deployments.

The committee has developed the recommendations in Table 2 for future research, based on its review of the literature on each of the putative agents. These recommendations highlight areas of scientific uncertainty and, if implemented, will help to resolve important questions about the effect of the Gulf War on the health of the veterans.

Finally, this report takes its place alongside several other recent IOM reports on the health of Gulf War veterans. Although the conclusions and recommendations presented here will not end the controversy surrounding Gulf War veterans' illnesses, this report will provide a scientific basis for consideration by the Department of Veterans Affairs as they develop a compensation program for veterans. The committee hopes that its deliberations, along with the work of many others, will add to the body of accumulating knowledge about the health of Gulf War veterans.

TABLE 2 Research Recommendations

Biological, Chemical, and Psychological Interactions

- Research on the interactions among the multiple agents and stressors to which military personnel were exposed as a result of the Gulf War conflict.

Depleted Uranium

- Continued follow-up of the Baltimore cohort of Gulf War veterans with DU exposure. Long-term studies of the health of other Gulf War veterans at high risk for DU exposure (e.g., cleanup or radiation control units).
- Continued follow-up of the cohorts of uranium processing workers.
- Additional studies of the effects of DU in animals.

Sarin

- Long-term follow-up of populations exposed to sarin in the Matsumoto and Tokyo terrorist attacks.
- Studies in experimental animals to investigate the long-term effects of an acute, short-term exposure to sarin at doses that do not cause overt cholinergic effects and minimal acetylcholinesterase inhibition.
- Research on genetic factors that may alter susceptibility to sarin toxicity.

Pyridostigmine Bromide

- Research on chemical interactions between PB and other agents such as stress, and certain insecticides.
- Research on genetic factors (e.g., genetic polymorphisms of butyrylcholinesterase, paraoxonase) that may alter susceptibility to the effects of PB.
- Epidemiologic studies on the possible long-term health effects of PB.

Vaccines

- Long-term longitudinal studies of participants in the Anthrax Vaccine Immunization Program that would actively monitor and systematically collect and analyze data about symptoms, functional status, and disease status.
- Long-term systematic research to examine potential adverse effects of anthrax and botulinum toxoid vaccination in multiple species and strains of animals.
- Careful study of current symptoms, functional status, and disease status in cohorts of Gulf War veterans and Gulf War-era veterans for whom vaccination records exist.

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