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GULF WAR and HEALTH

VOLUME 1

Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines

INSTITUTE OF MEDICINE

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Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines

Carolyn E. Fulco, Catharyn T. Liverman, Harold C. Sox, *Editors*

Committee on Health Effects Associated with Exposures During the Gulf War

Division of Health Promotion and Disease Prevention

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

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Preface

Although the Gulf War lasted but a few days, many combat troops have suffered lingering health problems that they attribute to their wartime service. Their health problems and illnesses have features in common with illnesses suffered by veterans of earlier wars, including the difficulty that their physicians have had in making a diagnosis. As yet, these illnesses remain unexplained by medical science, which has prompted some people to wonder if troops in the Persian Gulf theater were exposed to an agent or combination of agents that caused these illnesses. Research on this question continues. Another important question is whether an agent in the environment in the Persian Gulf theater could cause known conditions like heart disease or cancer.

In an effort to respond 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 associations between the agents to which Gulf War veterans may have been exposed and adverse health effects. To carry out this assignment, the IOM convened the Committee on Health Effects Associated with Exposures During the Gulf War. In planning its work, the committee contacted representatives of veterans' organizations for advice in setting its priorities for this study. The veterans and their representatives advised the committee to begin the project by studying depleted uranium, sarin, pyridostigmine bromide, and vaccination against botulinum toxin and anthrax. Reports on other agents will follow, as the Institute of Medicine and the Department of Veterans Affairs have a long-term commitment to study all of the agents to which the veterans may have been exposed. Further, the IOM will issue updated reports as new evidence appears in the scientific literature.

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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 697,000 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.

in a locale with uranium-contaminated drinking water varied from 1 to 33 years, and in the high-exposure group, it varied from 3 to 59 years. The indicators of kidney function included urinary excretion of glucose, creatinine, protein, and beta$_2$-microglobulin (BMG). The markers for cell toxicity were alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), and *N*-acetyl-beta-*D*-glucosaminidase (NAG). For males and females, the urinary glucose levels differed in the high- and low-exposure groups, and the amount increased with increasing uranium intake. Increases in ALP and BMG also correlated positively with increasing uranium intake. In contrast, there was no evidence for glomerular injury, as measured by normal serum creatinine concentration and no proteinuria. The authors suggest that intakes of uranium between 0.004 µg/kg and 9 mg/kg body weight are associated with altered kidney function but that the proximal tubule, rather than the glomerulus, is the site of this effect.

Fragments of depleted uranium. Uranium concentrations in the urine of Gulf War veterans have been found at higher levels in those with retained DU shrapnel than in those without when measured at 2, 4, and 7 years after first exposure (Hooper et al., 1999; McDiarmid et al., 2000). A recent study found that levels of urinary uranium ranged from 0.01 to 30.74 µg/g creatinine[4] in veterans with retained shrapnel fragments (McDiarmid et al., 2000). The concentration of uranium in the urine of nonexposed veterans ranged from 0.01 to 0.047 µg/g creatinine. Despite much higher levels of urinary uranium in the veterans with retained fragments of DU, renal function parameters (serum creatinine, BMG, and retinol-binding and urine proteins) were the same in the two groups, strongly suggesting that years of exposure to uranium does not damage the kidneys (McDiarmid et al., 2000).

Conclusions on Nonmalignant Renal Disease

Although uranium is a heavy metal that causes transient renal dysfunction, the preponderance of evidence indicates little or no clinically important renal effects of exposure to uranium. A few studies have shown 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 that had been exposed to high levels of soluble uranium compounds (Kathren and Moore, 1986) 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).

[4]The unit of measurement for urinary uranium is expressed as micrograms per gram creatinine.

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

Nonmalignant Neurological Disease

The committee carefully examined the studies on neurological outcomes as these outcomes are of interest in the study of Gulf War-related illnesses. Uranium has been shown in several animal studies to enter the brain of animals exposed through either inhalation or implantation of fragments of depleted uranium (see toxicology section). The mortality experiences of uranium processing workers (Table 4.15) generally show no excess neurologic disease mortality risks, with the exception of one study in which workers at a nuclear fuels fabrication plant had an SMR of 346 (95% CI 126–753) for death from diseases of the nervous system (Hadjimichael et al., 1983). There were 6 deaths from diseases of the central and peripheral nervous system and only 1.7 expected deaths. However, the number of cases was small, and the 95% CI was very wide. It is important to note that mortality is not a good measure for neurologic outcomes as they may not be the cause of death noted on the death certificate.

Several case studies have examined neurological outcomes or symptoms. Moore and Kathren (1985) studied three individuals 38 years after they were exposed to high concentrations of uranium (estimates of initial lung deposition of 40–50 mg of uranium) after an industrial accident. Shortly after the accident an examination found "mental status changes believed in excess of what which would be caused by fear reaction." No other details were provided. Examination of two of these individuals 38 years after the accident revealed no clinical findings attributable to uranium exposure (Moore and Kathren, 1985; Kathren and Moore, 1986). Neurological symptoms were also absent in an examination of a male worker 6 days after he had a 5-minute accidental exposure to uranium tetrafluoride powder (an estimated radioactivity of 197 nCi/m^3; 6,905.6 Bq/m^3) (Lu and Zhao, 1990).

A case report described a 44-year-old man who developed foot cramps, leg pain, a gait disorder, and a tendency to fall backward (Goasguen et al., 1982). The symptoms progressed and he developed an extrapyramidal syndrome with ataxia, nystagmus, and peripheral neuropathy. Although the authors claimed that the etiology of his illness was related to a bar of metallic uranium that he handled frequently during the first 3 years of his illness, they presented no estimates of the level of exposure of this patient to uranium and did not make a convincing argument for its causal role in his illness.

The committee found no studies of neurological symptoms after human exposure to uranium by either the oral or the dermal route.

McDiarmid and colleagues (2000) studied a cohort of Gulf War veterans who had fragments of depleted uranium in their soft tissues. As noted in the preceding section, the veterans excreted substantial amounts of uranium, presuma-

TABLE 4.15 Nonmalignant Neurologic Disease Mortality

Reference	Study Site	Study Group (*n*)	No. of Observed Deaths	No. of Expected Deaths	SMR (95% CI)	Disease Classification
Polednak and Frome, 1981	Y-12 uranium processing plant, Oak Ridge, TN	18,869	38	49.3	77 (49–105)[a]	Diseases of the nervous system
Hadjimichael et al., 1983	Nuclear fuels fabricating plant, Connecticut	2,613 males in industrial jobs	6	1.7	346 (126–753)	ICDA-8: 340–359
Stayner et al., 1985	Phosphate fertilizer production facility, Florida	3,199	3	8.73	34 (9–89)[b]	Diseases of the nervous system
Brown and Bloom, 1987	Uranium enrichment plant, Portsmouth, OH	5,773	13	32.7	40 (21–68)	ICD-7: 330–334, 345
Frome et al., 1990	Y-12 and K-25 uranium enrichment facilities and research laboratory, Oak Ridge, TN	28,008	76	81.76	93 (71–115)[a]	ICDA-8: 320–389

NOTE: ICD = *International Classification of Diseases;* ICDA = *International Classification of Diseases, Adapted.*

[a]The confidence interval was calculated by the committee; it was not stated in the study.
[b]90% CI.

bly as a result of gradual dissolution of DU fragments. Results from a battery of computer-based neurocognitive tests suggest a statistical relationship between elevated urinary uranium levels and "problematic performance on automated tests assessing performance efficiency and accuracy" (McDiarmid et al., 2000). Traditional tests of neurocognitive function (pen-and-pencil tests) did not show any statistical differences in performance between the veteran cohort and a control group.

The committee found several methodological issues that make it difficult to draw firm conclusions from this study. The authors did not adequately define their neurocognitive testing methods or the method for deciding the expected level of performance. The procedures involved calculating two "impairment indexes" for each test subject—one for the automated and one for the traditional neurocognitive measures. They calculated the impairment indexes for the neurocognitive tests by dividing the total number of scores that were below the expected score by the total number of scores obtained from each test battery. However, the investigators did not indicate how they chose the cutoff value that defined "expected" performance, nor did they explain how they chose the decision cut points.

As acknowledged by the authors, the number of individuals with high uranium levels in urine was small, "and it appeared that a few veterans with complex histories may have contributed appreciably to the observed variance." Further studies may help explain the lack of correlation between the computer-based tests, which showed abnormalities, and the standard written tests, on which the subjects performed normally. Continued follow-up of this cohort will provide insight into any potential neurocognitive effects of depleted uranium.

In summary, the evidence regarding exposure to uranium and diseases of the nervous system is not strong enough to form a firm conclusion. In studies on Gulf War veterans, the search for evidence of neurological effects will require careful neurocognitive measurements, correlation of these with clinical dysfunction, and comparison of exposed veterans to control groups chosen to illuminate various facets of the complex exposure history of Gulf War veterans.

Conclusion on Nonmalignant Neurological Disease

The committee concludes that there is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to uranium and diseases of the nervous system.

Nonmalignant Respiratory Disease

Nonmalignant respiratory effects from inhaled uranium aerosols will depend in part on where in the lung the inhaled particles come to rest. Deposition depends primarily on particle size and solubility. Particle clearance mechanisms will remove a portion of deposited particles primarily by mucociliary action, which operates in the upper respiratory tract to sweep particles up to the pharynx

The committee has developed the following additional recommendations for research based on its review of the literature on each of the putative agents (Chapters 4–7). These recommendations highlight areas of scientific uncertainty and gaps in research.

DEPLETED URANIUM

While a group of veterans exist with depleted uranium in their tissues, the majority of veterans' exposure to DU is unknown. The committee urges the continuation and expansion of efforts to model potential exposures to DU in various military settings (e.g., inside and outside vehicles damaged by DU munitions, other areas potentially contaminated by the dispersion of DU particles). Such efforts may result in a quantitative assessment of Gulf War veterans' exposure to depleted uranium. Further, the committee urges publication of the results in the peer-reviewed literature so that the studies may receive broad review.

The committee recommends the following avenues of research to complement our current knowledge of the health effects of depleted uranium.

The committee recommends long-term follow-up of veterans exposed to depleted uranium, including the Baltimore cohort and other veterans potentially exposed to depleted uranium (e.g., those involved in cleanup operations or radiation control units).

Long-term follow-up of the cohort of veterans who have undergone evaluation at the Baltimore Veterans Administration (VA) Medical Center since 1993 will continue to improve our understanding of the health effects of exposure to depleted uranium. The committee recommends expanding the cohort of DU-exposed veterans and including control cohorts of non-DU-exposed Gulf War-deployed veterans in this study.

Additionally, controlled, long-term morbidity and mortality studies of additional cohorts of Gulf War veterans, particularly those that may have been exposed to DU through different routes of exposure (e.g., those involved in cleanup operations and in radiation control units), would further the knowledge on health effects related to DU exposure.

The committee recommends continued follow-up of the cohorts of uranium processing workers, particularly studies that will incorporate more sophisticated analyses of the data.

The majority of the evidence on the human health effects of exposure to uranium is from studies of workers in uranium processing mills and other facilities. These cohorts are a valuable information resource, as they are, in many cases, large groups that have been studied for many years. Additionally, researchers have analyzed data across several of these cohorts to enable comparisons between the cohorts and to increase the possibility of observing rare health outcomes. The committee encourages studies that will provide continued long-term follow-up of uranium processing workers, particularly those that incorporate new methods of measuring dose and utilize sophisticated statistical analyses.

The committee recommends additional studies in experimental animals to investigate specific effects of depleted uranium.

Animal studies provide the opportunity to carefully study the effects of depleted uranium in isolation from other exposures. Controlled experimental conditions provide a contrast with studies of veterans or workers in industrial settings as both populations have concomitant exposures to many other potential hazards. Of particular importance are studies of cognitive function, neurophysiological responses, brain DU concentrations, and the transport kinetics of DU.

SARIN

The committee recommends the following avenues of research to augment our understanding of long-term effects of exposure to sarin.

The committee recommends careful long-term follow-up of populations exposed to sarin in the Matsumoto and Tokyo terrorist attacks.

The Matsumoto experience shows that direct exposure to sarin, particularly in intermediate to high doses, is associated with the acute cholinergic syndrome. Further, follow-up studies of Matsumoto demonstrate that significant chronic symptoms from sarin exposure persist and include visual disturbances, fatigue or asthenia, and headache. These chronic symptoms appear to be dose dependent. Follow-up studies, with well-defined control populations, will provide information related to possible long-term health effects.

The Tokyo sarin experience also confirms that intermediate doses of sarin leads to the acute cholinergic syndrome. Visual disturbances are frequent sequelae of acute exposure. Neurophysiological testing of a small group of asymptomatic people exposed to sarin shows chronic changes in visual and event-related evoked potentials and vestibulocerebellar function months after the acute syndrome had subsided. While these neurophysiological data are suggestive of subtle, persistent central nervous system (CNS) effects from sarin, long-term follow-up studies are required.

Of particular importance is a study that would include a group of individuals that presented symptoms of acute sarin poisoning at the time of exposure, as well as a group that was involved in the incidents but did not experience acute illness. These two groups, together with an unexposed matched control group, would provide important information on whether the long-term sequelae already reported occur in those who have been exposed to subsymptomatic levels of sarin. Studies should include neuropsychological testing, electroencephalogram (EEG), evoked potentials, and vestibular testing.