AMYOTROPHIC LATERAL SCLEROSIS IN VETERANS

Review of the Scientific Literature
Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature

Committee on the Review of the Scientific Literature on Amyotrophic Lateral Sclerosis in Veterans

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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—Goethe
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COMMITTEE ON THE REVIEW OF THE
SCIENTIFIC LITERATURE ON AMYOTROPHIC
LATERAL SCLEROSIS IN VETERANS

RICHARD T. JOHNSON, MD (Chair), Distinguished Service Professor of Neurology, Microbiology, and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD
WALTER G. BRADLEY, DM, FRCP, Professor and Chair, Department of Neurology, Miller School of Medicine at the University of Miami, FL
BEATE R. RITZ, MD, PhD, MPH, Professor and Vice Chair, Department of Epidemiology, University of California, Los Angeles School of Public Health, Los Angeles
WALTER A. ROCCA, MD, MPH, Professor of Epidemiology and Neurology, Mayo Clinic College of Medicine, Rochester, MN
JEREMY M. SHEFNER, MD, PhD, Professor and Chair, Department of Neurology, State University of New York, Upstate Medical University, Syracuse
CHRISTINA WOLFSON, PhD, Professor of Epidemiology and Biostatistics, McGill University, Montreal, Canada

STAFF

ABIGAIL MITCHELL, PhD, Senior Program Officer
MICHAEL SCHNEIDER, MPH, Senior Program Associate
DEEPAI PATEL, Senior Program Associate
PETER JAMES, Research Associate
DAMIKA WEBB, Research Assistant
RENEE WLODARCZYK, Program Assistant
NORMAN GROSSBLATT, Senior Editor
ROSE MARIE MARTINEZ, ScD, Director, Board on Population Health and Public Health Practice
REVIEWERS

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:

CARMEL ARMON, MD, MSC, MHS, Tufts University and Baystate Medical Center, Boston, MA
CARLO DELUCA, PHD, Neuromuscular Research Center, Boston University, MA
LAWRENCE GOLDSTEIN, PHD, Department of Cellular and Molecular Medicine, University of California, San Diego and Howard Hughes Medical Institute
CLIFTON L. GOOCH, MD, EMG Laboratory of New York Presbyterian Hospital and Columbia Neuropathy Research Center, Columbia University College of Physicians and Surgeons, NY
FREYA KAMEL, MD, MPH, National Institute of Environmental Health Sciences, Research Triangle Park, NC
LORENE NELSON, PHD, Department of Health Research and Policy, Stanford University, CA
M. DONALD WHORTON, MD, MPH, Executive Vice President and Epidemiologist, WorkCare, Inc., Alameda, CA

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 Elena Nightingale, Scholar-in-Residence, Institute of Medicine. Appointed by the National Research Council, 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 author committee and the institution.
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Amyotrophic lateral sclerosis (ALS) is a progressive and nearly always fatal disease that affects a person’s nervous system. It is sometimes referred to as Lou Gehrig’s disease, after the famous baseball player who died from it. When a person develops ALS, nerve cells in the brain and spinal cord degenerate. The degeneration prevents communication between the nervous system and the voluntary muscles of the body, and the breakdown in communication leads to muscle paralysis. Eventually, the muscles responsible for breathing are affected, and respiration fails. There is no effective treatment for ALS.

ALS affects 20,000-30,000 men and women in the United States at any given time. It occurs in people of all races and ethnic backgrounds. About 5-10% of ALS cases are inherited; the cause of the remaining 90-95% of cases is not known.

Four recent epidemiologic studies have reported an association between development of ALS and prior service in the US military. Three of those studies1 evaluated veterans of the 1991 Persian Gulf War; the fourth2 evaluated veterans who served in the military in the period 1910-1982. Because of the findings of

those studies, the Department of Veterans Affairs (VA) asked the National Academies to conduct an independent assessment of the potential relationship between military service and the later development of ALS. The population of interest to VA encompasses all veterans, not only veterans who served in a specific deployment (for example, veterans of the Gulf War). The National Academies assigned the project to the Institute of Medicine (IOM), which appointed a committee and charged it with evaluating the scientific literature on ALS in veterans. In addition, if an association were found to exist between military service and the later development of ALS, the committee might make recommendations that would help to identify risk factors for ALS that are relevant to military service.

In 2001, Secretary of Veterans Affairs Anthony J. Principi made a policy decision to provide disability compensation to Gulf War veterans who served in the Southwest Asia Theater of Operations during the period August 2, 1990-July 31, 1991, and who later developed ALS. Other US veterans with ALS do not receive disability compensation for their illness.

**METHODOLOGY**

The committee began its work by identifying the medical and scientific literature on ALS. PubMed, a database created and managed by the National Library of Medicine, was searched for studies on ALS in the veteran population. The articles relevant to the committee’s task were identified, and copies were obtained. Next, the committee assessed the studies for methodologic rigor and for evidence of association between service in the military and development of ALS. For information on possible ALS risk factors, PubMed was searched for studies on ALS in nonveteran populations and review articles on ALS (including articles on studies conducted in laboratory animals).

The committee framed its conclusion on the basis of categories that qualitatively rank the strength of the evidence of an association (described in Box S-1). The categories are adapted from the system of the International Agency for Research on Cancer for evaluating evidence of the carcinogenicity of various
agents, and they have been used by many previous IOM committees.

CONCLUSION

The committee identified one high-quality cohort study\(^3\) that adequately controlled for confounding factors and reported a relationship between serving in the military and later development of ALS. Results of three other studies supported the association. One of the three\(^4\) was generally well conducted, but it was limited by the potential for underascertainment of cases in the comparison group. The other two\(^5\) had several methodologic limitations that made them less valuable for the committee’s evaluation. Another study\(^6\) did not report an association between military service and ALS; it also had methodologic limitations.

**On the basis of its evaluation of the literature, the committee concludes that there is limited and suggestive evidence of an association between military service and later development of ALS.**

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RECOMMENDATIONS

The committee developed recommendations to assist VA in gathering information on ALS in the veteran population so that it might be able to determine more definitively whether there is an association between military service and ALS. The committee also provided guidance for further study of risk factors that are most relevant to military service. The committee recommends the following:

- Explore the use of existing cohort studies designed for other outcomes and ongoing or completed high quality case-control studies of ALS for their suitability to assess the relationship between ALS and military service.
- Identify all putative ALS risk factors relevant to military service and conduct systematic reviews of the literature on them.
- Conduct further corroborative or exploratory studies to elucidate ALS risk factors relevant to military service.

<table>
<thead>
<tr>
<th>BOX S-1 Categories of Strength of Association</th>
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<tbody>
<tr>
<td><strong>Sufficient Evidence of a Causal Relationship</strong></td>
</tr>
<tr>
<td>This category would indicate that evidence is sufficient to conclude that there is a causal relationship between military service and ALS in humans. The evidence must be supported by experimental data and fulfill the guidelines for sufficient evidence of an association (below). The evidence must be biologically plausible and satisfy several of the guidelines used to assess causality, such as strength of association, dose-response relationship, consistency of association, and temporal relationship.</td>
</tr>
<tr>
<td><strong>Sufficient Evidence of an Association</strong></td>
</tr>
<tr>
<td>This category would indicate that evidence is sufficient to conclude that there is a positive association, that is, a consistent positive association has been observed between military service and ALS in human studies in which chance and bias, including confounding factors, could be ruled out with reasonable confidence. For example, several high-quality studies had reported consistent positive associations, and the studies were sufficiently free of bias, including adequate control for confounding factors.</td>
</tr>
<tr>
<td>Limited and Suggestive Evidence of an Association</td>
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<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>This category would indicate that evidence is suggestive of an association between military service and ALS in humans, but the body of evidence is limited by the inability to rule out chance and bias, including confounding factors, with confidence. For example, at least one high-quality study had reported a positive association that was sufficiently free of bias, including adequate control for confounding factors. Other corroborating studies might provide support for the association, but they were not sufficiently free of bias, including confounding factors. Alternatively, several studies of lower quality might show consistent positive associations, and the results were probably not due to bias, including confounding factors.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Inadequate or Insufficient Evidence to Determine Whether an Association Exists</th>
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<tbody>
<tr>
<td>This category would indicate that evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between military service and ALS in humans.</td>
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</table>

<table>
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<tr>
<th>Limited and Suggestive Evidence of No Association</th>
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<tbody>
<tr>
<td>This category would indicate that evidence is consistent in not showing a positive association between military service and ALS in humans 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 cannot be excluded.</td>
</tr>
</tbody>
</table>
INTRODUCTION

Amyotrophic lateral sclerosis (ALS)—also called Lou Gehrig’s disease, motor neuron disease, and Charcot disease—affects about 20,000-30,000 people in the United States. ALS is a neuromuscular disease that affects people of all races and ethnic backgrounds. The risk of developing ALS increases with age through the age of 70 years. The risk beyond the age of 70 years is uncertain because of difficulties in separating ALS from other conditions (Armon 2004; Mandrioli et al. 2003; McGuire et al. 1996; Sorenson et al. 2002). The risk is higher in men than in women of the same age, and there may be some variability among ethnic groups (Annegers et al. 1991; McGuire et al. 1996). The disease is often relentlessly progressive and almost always fatal. The rate of progression is quite variable from patient to patient.

ALS causes degeneration of the motor neurons in the cerebral motor cortex (called upper motor neurons) and in the brain stem and spinal cord (called lower motor neurons) (Rowland 2000). Motor neurons are nerve cells that provide communication between the highest levels of the nervous system and the voluntary muscles of the body. When the upper motor neurons degenerate, their connections to the lower motor neurons and spinal interneurons (neurons that convey impulses from one neuron to another) are disrupted. That disruption leads to weakness of muscles in a characteristic pattern and to spasticity. Lower motor neuron degeneration disrupts nerve contact with the muscles and results in muscle atrophy. Spontaneous muscle activity, called fasciculation, also occurs. Eventually those affected are unable to move their arms and legs and cannot speak or swallow. When the connections between the neurons and the muscles responsible for breathing are disrupted, patients either die from respiratory failure or require mechanical ventilation to continue to breathe. Most people who have ALS die from respiratory failure within 5 years of the onset of symptoms.
Some 5-10% of ALS cases are familial (inherited) (Rowland 2000; Siddique et al. 1999). Most cases of familial ALS are inherited in an autosomal dominant fashion (that is, one affected parent carries the mutant gene for ALS and passes it to about half of his or her children) (Siddique et al. 1997). A small number of cases of familial ALS are inherited in an autosomal recessive fashion (that is, both unaffected parents carry a mutant gene and the disease affects about a quarter of their children). The specific gene mutations that cause most familial ALS cases are unknown, but about 20% of familial cases are believed to be caused by a mutation in a gene that encodes the enzyme superoxide dismutase 1 (Siddique and Deng 1996).

The majority of ALS cases are nonfamilial. The cause of nonfamilial ALS is unknown. Despite a number of epidemiologic studies that have examined occupations (for example, Italian professional soccer, farming, and electrical work), physical trauma, strenuous physical activity, lifestyle factors (for example, diet, cigarette use, and alcohol consumption), ethnic group, and socioeconomic status, there are no consistent findings (Armon 2003; Armon 2004; Chio et al. 2005; Rowland 2000; Valenti et al. 2005).

ALS-like diseases have been reported in Guam, the Kii peninsula of Japan, and Papua New Guinea (Banack and Cox 2003; Banack et al. 2006; Cox et al. 2003; Cox et al. 2005; Cox and Sacks 2002; Murch et al. 2004a; Murch et al. 2004b; Siddique et al. 1999). The causes of the ALS-parkinsonism-dementia complex of Guam and similar neurodegenerative diseases in the Kii peninsula of Japan and Papua New Guinea have not been identified. The pathology of these ALS-like diseases is different from that of ALS, and they will not be addressed in this report.

THE DEPARTMENT OF VETERANS AFFAIRS REQUEST FOR THIS STUDY AND THE STATEMENT OF TASK

Several recent studies have reported a link between military service and ALS (Coffman et al. 2005; Haley 2003; Horner et al. 2003; Smith et al. 2000; Weisskopf et al. 2005). The Department of Veterans Affairs (VA) Office of Public Health and Environmental Hazards drafted an issue brief on that topic on
January 14, 2005 (Brown 2005). VA concluded that the recent publications “are suggestive but not definitive that military service increases ALS risk” and recommended that “to help clarify the science underlying possible service connection for ALS, VA could request the National Academy of Sciences to review the relevant literature and provide an independent opinion on this issue.”

VA sent a request to the National Academies to study the possible association between military service and later development of ALS. The National Academies assigned the project to the Institute of Medicine (IOM). IOM entered into a contract with VA to conduct the following study:

An IOM committee will review, evaluate, and summarize the scientific literature on ALS in veterans. If an association exists between military service and the development of ALS, then the committee might make recommendations that will help to identify risk factors.

The population of interest to VA encompasses all veterans, not veterans who served only in a specific deployment (for example, veterans of the Gulf War).

In 2001, Secretary of Veterans Affairs Anthony J. Principi made a policy decision to provide disability compensation to Gulf War veterans who served in the Southwest Asia Theater of Operations during the period August 2, 1990-July 31, 1991, and who later developed ALS (Department of Veterans Affairs 2001; Department of Veterans Affairs 2003). Other US veterans who have a diagnosis of ALS do not receive disability compensation for their illness.

**PREVIOUS INSTITUTE OF MEDICINE WORK ON VETERANS’ ISSUES**

Since the middle 1990s, IOM has addressed a variety of issues related to veterans’ health. A number of studies have assessed the potential association between biologic and chemical exposures and chronic health outcomes. For example, one series of studies evaluated the strength of the evidence regarding exposure to herbicides during the Vietnam War and health outcomes in
Vietnam War veterans (IOM 1994b; IOM 1996b; IOM 1999b; IOM 2001b; IOM 2003b; IOM 2005b). Another series assessed health outcomes of exposures to various chemicals (for example, sarin, pesticides, solvents, fuels, and combustion products from oil-well fires), biologics (for example, infectious diseases and vaccines), and physical agents (depleted uranium) to which military personnel might have been exposed during the Gulf War (IOM 2000b; IOM 2003a; IOM 2004; IOM 2005a; IOM 2006a; IOM 2006b). Such studies have been used by VA to assist it in developing disability compensation polices for specific groups of veterans (Vietnam War veterans and Gulf War veterans).

IOM has conducted several studies on the health of Gulf War veterans and treatment for their symptoms and syndromes (IOM 1996a; IOM 1999a; IOM 2001a). IOM committees also have reviewed and evaluated several VA programs, including the VA Persian Gulf registry and uniform case-assessment protocol and the comprehensive clinical evaluation program (IOM 1997; IOM 1998).

THE COMMITTEE’S APPROACH TO ITS CHARGE

The committee that wrote this report based its conclusion primarily on peer-reviewed, published literature. Non-peer-reviewed publications provided additional information for the committee and raised issues that were researched further in the peer-reviewed literature. The committee did not collect original data, nor did it perform any secondary data analysis.

Although the process of peer review by fellow professionals ensures high standards of quality, it does not guarantee the validity of a study or the ability to generalize results. Accordingly, committee members read each study critically and considered its relevance and quality.

The committee began its work by identifying the medical and scientific literature necessary to complete its task. The process began with a search using PubMed, a database created and managed by the National Library of Medicine that includes more than 15 million citations of biomedical publications from the 1950s to the present. The following types of studies were identified:

- Studies of ALS in the veteran population.
• Studies of ALS in nonveteran populations.
• Review articles, including reviews of animal studies.

The committee obtained full-text copies of the relevant studies and assessed them for methodologic rigor and for evidence of positive or negative associations between military service and later development of ALS.

CATEGORIES OF ASSOCIATION

The committee’s goal was to use the evidence in the medical and scientific literature to determine the relationship between ALS and military service. The committee ranked strength of association qualitatively with a five-tier system, presented below in full.

Origin and Evolution of the Categories

The International Agency for Research on Cancer (IARC), part of the World Health Organization, established criteria in 1971 to evaluate the human carcinogenic risk posed by chemicals (IARC 1998). First published in 1972, IARC’s evaluations are scientific, qualitative judgments of ad hoc working groups about the evidence for or against carcinogenicity provided by the available data. The working groups express their qualitative judgments by choosing one of five categories to describe the relative strength of the evidence that a substance or exposure is carcinogenic (IARC 1999a). That agencies in 57 countries use IARC’s published evaluations reflects the wide acceptance of the categorization scheme as it has been updated and applied to about 900 agents, mixtures, and exposures (IARC 1999b; IARC 2005).

In the early 1990s, an IOM committee adopted IARC’s categories for its evaluation of the adverse health effects of pertussis and rubella vaccines (IOM 1991). Later committees used the categories, with some modifications, in their evaluations of the safety of childhood vaccines (IOM 1994a), the health effects of herbicides used in the Vietnam War (IOM 1994b; IOM 1996b; IOM 1999b; IOM 2001b; IOM 2003b), and the relationship between indoor pollutants and asthma (IOM 2000a). The categories also were adapted and used by the present committee’s predecessors, which evaluated the health effects of vaccines given