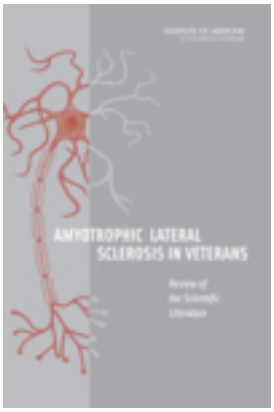

Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature

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

ISBN: 0-309-66258-3, 62 pages, 6 x 9, (2006)

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

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

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

This study was supported by Contract V101(93)P-1637, Task Order 25 and Task Order 30, between the National Academy of Sciences and the Department of Veterans Affairs**.** Any opinions, findings, or conclusions expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-10: 0-309-10254-5
International Standard Book Number-13: 978-0-309-10254-4

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu.**

Printed in the United States of America.

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

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

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

.

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
DEEPALI 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.

CONTENTS

SUMMARY

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 studies[1] evaluated veterans of the 1991 Persian Gulf War; the fourth[2] evaluated veterans who served in the military in the period 1910-1982. Because of the findings of

[1] Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756; Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749; Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

[2] Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-37.

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.

---

[3] Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-37.

[4] Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749; Coffman CJ, Horner RD, Grambow SC, Lindquist J. 2005. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) veterans using capture-recapture methods. *Neuroepidemiology* 24(3):141-150.

[5] Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756; Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

[6] Kang HK, Bullman TA. 2001. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. *American Journal of Epidemiology* 154(5):399-405.

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.

BOX S-1 Categories of Strength of Association

Sufficient Evidence of a Causal Relationship

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.

Sufficient Evidence of an Association

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.

Limited and Suggestive Evidence of an Association

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.

Inadequate or Insufficient Evidence to Determine Whether an Association Exists

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.

Limited and Suggestive Evidence of No Association

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.

1

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

to US troops and of chemical, biologic, and physical exposures that may have occurred during the Gulf War (IOM 2000b; IOM 2003a; IOM 2004; IOM 2005a; IOM 2006b). The categories are described below.

Sufficient Evidence of a Causal Relationship

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.

Sufficient Evidence of an Association

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.

Limited and Suggestive Evidence of an Association

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.

Inadequate or Insufficient Evidence to Determine Whether an Association Exists

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.

Limited and Suggestive Evidence of No Association

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.

ORGANIZATION OF THE REPORT

This report is composed of three chapters, including this introduction. Chapter 2 presents a detailed description and evaluation of studies assessing the association between ALS and military service. It also contains the committee's conclusion. Chapter 3 contains the committee's recommendations for further studies related to ALS and military service. The report has two appendixes—Appendix A summarizes a number of scientific studies on putative risk factors for the development of ALS related to military service, and Appendix B presents three possible conceptual models linking military service and other risk factors to ALS.

REFERENCES

Annegers JF, Appel SH, Perkins P, Lee J. 1991. Amyotrophic lateral sclerosis mortality rates in Harris County, Texas. *Advances in Neurology* 56:239-243.

Armon C. 2003. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. *Neuroepidemiology* 22(4):217-228.

Armon C. 2004. Amyotrophic lateral sclerosis. In: Nelson LM, Tanner CM, Van Den Eeden SK, McGuire VM, Editors. *Neuroepidemiology: From Principles to Practice*. New York: Oxford University Press. Pp. 162-187.

Banack SA, Cox PA. 2003. Biomagnification of cycad neurotoxins in flying foxes: implications for ALS-PDC in Guam. *Neurology* 61(3):387-389.

Banack SA, Murch SJ, Cox PA. 2006. Neurotoxic flying foxes as dietary items for the Chamorro people, Marianas Islands. *Journal of Ethnopharmacology* 106(1):97-104.

Brown M. 2005. *A New Study Recently Published in the Scientific Journal Neurology Suggests That Essentially All Veterans Are at Higher Risk for ALS Compared to Those Who Never Served in the Military*. Department of Veterans Affairs.

Chio A, Benzi G, Dossena M, Mutani R, Mora G. 2005. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 128(Pt 3):472-476.

Coffman CJ, Horner RD, Grambow SC, Lindquist J. 2005. Estimating the Occurrence of Amyotrophic Lateral Sclerosis among Gulf War (1990-1991) Veterans Using Capture-Recapture Methods. *Neuroepidemiology* 24(3):141-150.

Cox PA, Sacks OW. 2002. Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam. *Neurology* 58(6):956-959.

Cox PA, Banack SA, Murch SJ. 2003. Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. *Proceedings of the National Academy of Sciences of the United States of America* 100(23):13380-13383.

Cox PA, Banack SA, Murch SJ, Rasmussen U, Tien G, Bidigare RR, Metcalf JS, Morrison LF, Codd GA, Bergman B. 2005. Diverse taxa of cyanobacteria produce beta-N-methylamino-L-alanine, a neurotoxic amino acid. *Proceedings of the National Academy of Sciences of the United States of America* 102(14):5074-5078.

Department of Veterans Affairs. 2001. *Desert Shield, Desert Storm Vets Have Higher Rate of ALS*. Washington, DC: Office of Public Affairs Media Relations.

Department of Veterans Affairs. 2003. *Gulf War Service-ALS Link Confirme*d. Washington, DC: Office of Public Affairs Media Relations.

Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756.

Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749.

IARC (International Agency for Research on Cancer). 1998. *Preamble to the IARC Monographs*. [Online]. Available: http://www-cie.iarc.fr/monoeval/background.html [accessed July 19, 2005].

IARC. 1999a. *Evaluation. Preamble to the IARC Monographs.* [Online]. Available: http://www-cie.iarc.fr/monoeval/eval.html [accessed August 3, 2005].

IARC. 1999b. *Objective and Scope. Preamble to the IARC Monographs*. [Online]. Available: http://www-cie.iarc.fr/monoeval/objectives.html [accessed August 3, 2005].

IARC. 2005. *Monographs on the Evaluation of Carcinogenic Risks to Humans*. [Online]. Available: http://www-cie.iarc.fr/ [accessed August 3, 2005].

IOM (Institute of Medicine). 1991. *Adverse Effects of Pertussis and Rubella Vaccines*. Washington, DC: National Academy Press.

IOM. 1994a. *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality*. Washington, DC: National Academy Press.

IOM. 1994b. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. Washington, DC: National Academy Press.

IOM. 1996a. *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems*. Washington, DC: National Academy Press.

IOM. 1996b. *Veterans and Agent Orange: Update 1996*. Washington, DC: National Academy Press.

IOM. 1997. *Adequacy of the Comprehensive Clinical Evaluation Program: A Focused Assessment*. Washington, DC: National Academy Press.

IOM. 1998. *Adequacy of the VA Persian Gulf Registry and Uniform Case Assessment Protocol*. Washington, DC: National Academy Press.

IOM. 1999a. *Gulf War Veterans: Measuring Health.* Washington, DC: National Academy Press.

IOM. 1999b. *Veterans and Agent Orange: Update 1998*. Washington, DC: National Academy Press.

IOM. 2000a. *Clearing the Air: Asthma and Indoor Air Exposures*. Washington, DC: National Academy Press.

IOM. 2000b. *Gulf War and Health, Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, Vaccines*. Washington, DC: National Academy Press.

IOM. 2001a. *Gulf War Veterans: Treating Symptoms and Syndromes*. Washington, DC: National Academy Press.

IOM. 2001b. *Veterans and Agent Orange: Update 2000*. Washington, DC: National Academy Press.

IOM. 2003a. *Gulf War and Health, Volume 2. Insecticides and Solvents*. Washington, DC: The National Academies Press.

IOM. 2003b. *Veterans and Agent Orange: Update 2002*. Washington, DC: The National Academies Press.

IOM. 2004. *Gulf War and Health: Updated Literature Review of Sarin*. Washington, DC: The National Academies Press.

IOM. 2005a. *Gulf War and Health, Volume 3. Fuels, Combustion Products, and Propellants.* Washington, DC: The National Academies Press.

IOM. 2005b. *Veterans and Agent Orange: Update 2004*. Washington, DC: The National Academies Press.

IOM. 2006a. *Gulf War and Health, Volume 4. Health Effects of Serving in the Gulf War*. Washington, DC: The National Academies Press.

IOM. 2006b. *Gulf War and Health, Volume 5. Infectious Diseases.* Washington, DC: The National Academies Press.

Mandrioli J, Faglioni P, Merelli E, Sola P. 2003. The epidemiology of ALS in Modena, Italy. *Neurology* 60(4):683-689.

McGuire V, Longstreth WT Jr, Koepsell TD, van Belle G. 1996. Incidence of amyotrophic lateral sclerosis in three counties in western Washington state. *Neurology* 47(2):571-573.

Murch SJ, Cox PA, Banack SA. 2004a. A mechanism for slow release of biomagnified cyanobacterial neurotoxins and neurodegenerative disease in Guam. *Proceedings of the National Academy of Sciences of the United States of America* 101(33):12228-12231.

Murch SJ, Cox PA, Banack SA, Steele JC, Sacks OW. 2004b. Occurrence of beta-methylamino-l-alanine (BMAA) in ALS/PDC patients from Guam. *Acta Neurologica Scandinavica* 110(4):267-269.

Rowland LP. 2000. Hereditary and Acquired Motor Neuron Diseases. In: Rowland LP, Editor. *Merritt's Neurology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins. Pp. 708-714.

Siddique T, Deng HX. 1996. Genetics of amyotrophic lateral sclerosis. *Human Molecular Genetics* 5 Spec No:1465-1470.

Siddique T, Nijhawan D, Hentati A. 1997. Familial amyotrophic lateral sclerosis. *Journal of Neural Transmission. Supplementum* 49:219-233.

Siddique N, Sufit R, Siddique T. 1999. Degenerative motor, sensory, and autonomic disorders. In: Goetz CG, Pappert EJ, Editors. *Textbook of Clinical Neurology*. 1st ed. Philadelphia, PA: W.B. Saunders Company. Pp. 695-717.

Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. 2002. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. *Neurology* 59(2):280-282.

Valenti M, Pontieri FE, Conti F, Altobelli E, Manzoni T, Frati L. 2005. Amyotrophic lateral sclerosis and sports: a case-control study. *European Journal of Neurology* 12(3):223-225.

Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-37.

2

EVIDENCE REGARDING AMYOTROPHIC LATERAL SCLEROSIS IN VETERANS

As described in Chapter 1, the committee conducted a literature search to identify studies relevant to amyotrophic lateral sclerosis (ALS) in veterans. The committee reviewed and evaluated all peer-reviewed, published studies on ALS in the veteran population. Those studies served as the basis of the committee's conclusion, and they are critiqued in this chapter.

STUDIES ON AMYOTROPHIC LATERAL SCLEROSIS IN THE VETERAN POPULATION

In this section, the committee evaluates the studies on ALS in the veteran population that it considered to be the primary studies on which it based its conclusion. The studies are presented chronologically by year of publication. They are summarized in Table 2.1, and complete results are presented in Table 2.2.

TABLE 2.1 Design of Epidemiology Studies of ALS in US Veterans

Reference	Study Population	Comparison Population	At Risk N (ALS cases) Reference N (ALS cases)	Study Design	Case-Ascertainment Methods	Analysis	Risk Ratios (95% Confidence Intervals)
Smith et al. 2000	All active, gulf-deployed military personnel who served during the Gulf War (August 8, 1990-July 31, 1991)	Non-gulf-deployed Gulf War-era veterans	551,841 (6) 1,478,704 (12)	Cohort followup, August 1991-July 1997	DOD hospitalization records	Cox proportional - hazards analysis	1.66 (0.62-4.44); adjusted for age
Kang and Bullman 2001	Active, gulf-deployed military personnel who served during the Gulf War (August 8, 1990-March 1, 1991)	Non-gulf-deployed Gulf War-era veterans	621,902 (NA) 746,248 (NA)	Cohort followup, May 1991-December 1997	Database records of VA and Social Security Administration	Cox proportional-hazards analysis	0.59 (0.21-1.66); adjusted for age, race, sex, marital status, brach of service, unit component

Reference	Study Population	Comparison Population	At Risk N (ALS cases) Reference N (ALS cases)	Study Design	Case-Ascertainment Methods	Analysis	Risk Ratios (95% Confidence Intervals)
Haley 2003	All active, gulf-deployed military personnel who served during the Gulf War (August 1990-April 1991) and were less than 45 years old	Age-specific mortality rates from the total US population	About 695,000 (17)	Cohort followup, 1991-1998	VA data; personal contact and diagnosis	SMR; Poisson trend test	1991-1994: 0.94 (0.26-2.41); 1995-1998: 2.27 (1.27-3.88); adjusted for age
Horner et al. 2003	All active, gulf-deployed military personnel who served during the Gulf War (August 2, 1990-July 31, 1991),	Non-gulf-deployed Gulf War-era veterans	696,118 (40) 1,786,215 (67)	Cohort followup, August 1990-August 2000	Screening of VA and DOD medical databases and benefit files by ICD-9 code for ALS or riluzole use; toll-free	Age-adjusted average annual incidence; attributable risk	1.92 (1.29-2.84); adjusted for age

Reference	Study Population	Comparison Population	At Risk N (ALS cases) Reference N (ALS cases)	Study Design	Case-Ascertainment Methods	Analysis	Risk Ratios (95% Confidence Intervals)
	including mobilized reserves and National Guard				telephone enrollment; internet notices; mass mailings to neurologists, VA centers, and veteran service organizations		

Reference	Study Population	Comparison Population	At Risk N (ALS cases) Reference N (ALS cases)	Study Design	Case-Ascertainment Methods	Analysis	Risk Ratios (95% Confidence Intervals)
Weisskopf et al. 2005	Male participants in the ACS Cancer Prevention Study II cohort who had self-reported military service	Male participants with self-report of no military service at enrollment	281,874 (217) 126,414 (63)	Cohort followup, 1989-1998	Automated linkage with National Death Index	Cox proportional-hazards analysis	1.53 (1.12-2.09); adjusted for age, smoking, education, alcohol intake, self-reported exposure to pesticides and herbicides, and main occupation as farmer, electrical or welding work, or food preparation

NOTE: ACS = American Cancer Society; DOD = Department of Defense; ICD-9 = International Classification of Diseases, ninth revision; NA = not available; SMR = standardized mortality ratio; VA = Department of Veterans Affairs.

TABLE 2.2 ALS and Military Service—Cohort Studies

Reference	Study Population	Cases	Estimated Relative Risk (95% Confidence Intervals)
Smith et al. 2000	Non-gulf-deployed Gulf War-era veterans	12	1.0 (ref)
	Gulf War-deployed military personnel (1990-1991)	6	1.66 (0.62-4.44)
Kang and Bullman 2001	Non-gulf-deployed Gulf War-era veterans	NA	1.0 (ref)
	Gulf War-deployed military personnel (1990-1991)	NA	0.59 (0.21-1.66)
Haley 2003	Gulf War-deployed military personnel (1990-1991), less than 45 years old		
	Year of diagnosis:		
	1991-1994	4	0.94 (0.26-2.41)[a]
	1995-1998	13	2.27 (1.27-3.88)[a]
Horner et al. 2003	Non-gulf-deployed Gulf War-era veterans	67	1.0 (ref)
	Gulf War-deployed military personnel (1990-1991)	40	1.92 (1.29-2.84)
	Unit		
	Nondeployed active duty	61	1.0 (ref)
	Deployed active duty	31	2.15 (1.38-3.36)
	Nondeployed reserves and National Guard	6	1.0 (ref)
	Deployed reserves and National Guard	9	2.50 (0.88-7.07)
	Service branch		
	Nondeployed Air Force	24	1.0 (ref)

Reference	Study Population	Cases	Estimated Relative Risk (95% Confidence Intervals)
	Deployed Air Force	9	2.68 (1.24-5.78)
	Nondeployed Army	20	1.0 (ref)
	Deployed Army	21	2.04 (1.10-3.77)
	Nondeployed Marine Corps	5	1.0 (ref)
	Deployed Marine Corps	3	1.13 (0.27-4.79)
	Nondeployed Navy	18	1.0 (ref)
	Deployed Navy	7	1.48 (0.62-3.57)
Weisskopf et al. 2005	Self-reported no military service	63	1.0 (ref)
	Self-reported military service	217	1.53 (1.12-2.09)
	Service branch		
	No military service	63	1.0 (ref)
	Army and National Guard	97	1.54 (1.09-2.17)
	Navy	65	1.87 (1.28-2.74)
	Air Force	34	1.54 (0.99-2.39)
	Marine Corpes	4	0.64 (0.23-1.78)
	Coast Guard	3	2.24 (0.70-7.18)
	Not given	14	1.08 (0.60-1.94)
	Years of military service (median years)		
	No military service	63	1.0 (ref)
	1st quintile (2)	21	1.60 (0.95-2.70)

Reference	Study Population	Cases	Estimated Relative Risk (95% Confidence Intervals)
	2nd quintile (3)	65	1.80 (1.23-2.63)
	3rd quintile (4)	54	1.49 (1.01-2.21)
	4th quintile (5)	37	1.47 (0.95-2.25)
	5th quintile (9)	36	1.47 (0.95-2.27) p trend = 0.26
	Number of wars during service		
	No military service	63	1.0 (ref)
	0 (no wartime service)	36	1.34 (0.87-2.06)
	1	156	1.57 (1.14-2.17)
	2	15	1.74 (0.97-3.14)
	> 2	6	1.97 (0.83-4.70) p trend = 0.004
	Service during only one war		
	No military service	63	1.0 (ref)
	World War II	116	1.60 (1.12-2.30)
	Korean War	36	1.54 (0.92-2.60)
	Vietnam War	4	1.44 (0.47-4.47)

[a] Reported as standardized mortality ratios.
NOTE: ACS = American Cancer Society; CPS = Cancer Prevention Study; NA = not available, ref = reference.

Smith et al. 2000

Smith et al. (2000) relied on hospitalization records and reported an imprecisely estimated increase in relative risk of ALS

in deployed Gulf War veterans compared with non-gulf-deployed Gulf War-era veterans (relative risk [RR], 1.66; 95% confidence interval [CI], 0.62-4.44). The study population was defined as regular active-duty military personnel deployed to the Persian Gulf War theater for one or more days from August 8, 1990-July 31, 1991. The authors obtained information on deployment dates from the Defense Manpower Data Center, Seaside, CA. The study included only 18 cases of ALS in total (six among deployed veterans) and was also limited by its exclusive use of Department of Defense (DOD) hospitalization records, inclusion of only active-duty military personnel, and no more than 6 years of followup (through July 1997). The mean duration of active service during the followup period was only 3.4 years for Gulf War veterans and 3.8 years for nondeployed veterans. This study has been superseded by others with more inclusive populations and longer periods of followup.

Kang and Bullman 2001

Kang and Bullman (2001) performed a study to investigate causes of death of Gulf War veterans compared with concurrently serving veterans who were not deployed. Vital status and cause of death were determined from a variety of databases for 621,902 veterans who served in the Persian Gulf before the termination of hostilities and for 746,248 non-gulf-deployed Gulf War-era veterans, stratified by branch of service. The Gulf War veterans included in the study arrived in the Persian Gulf prior to March 1, 1991. That date was chosen in order to exclude those who arrived in the Persian Gulf theater after hostilities had ended and, therefore, might not have received "exposures of concern" (for example, chemical and biologic warfare agents, certain vaccines, and pyridostigmine bromide). The authors obtained information on deployment dates from the Defense Manpower Data Center. For disease-specific death determination, cause of death was obtained from death certificates. Followup terminated at death or on December 31, 1997, providing a maximum followup of slightly less than 7 years. The investigators found no specific cause of death that occurred with greater frequency in the veteran group that actively served in the Gulf War Theater. With respect to ALS, no excess risk was observed in the Gulf War veterans; an imprecisely

estimated risk ratio of 0.59 (95% CI, 0.21-1.66) adjusted for age (in years), race, sex, branch of service, unit component, and marital status was reported. The authors did not provide the number of cases of ALS that they identified. It could be argued that the risk reduction (the point estimate was less than 1) is of the same order of magnitude as the increases in relative risk reported in other studies described in this chapter. However, this study was uninformative because of its wide confidence limits and the short followup period (it encompassed only about 7 years after the war).

Haley 2003

Haley (2003) found an excess incidence of ALS among deployed Gulf War veterans in comparison with the expected incidence based on US vital statistics. The study population was defined as the approximately 695,000 members of the Army, Navy, Air Force, Marines, and Coast Guard who served in the Southwest Asia Theater of Operations from August 1990-April 1991. The analysis spanned 1991-1998. In the first half of that period, the increase in incidence was not apparent (standardized mortality ratio [SMR], 0.94; 95% CI, 0.26-2.41), but from 1995 to 1998 the increase was more than double (SMR, 2.27; 95% CI, 1.27-3.88). Incidence peaked in the final year of analysis (1998: SMR, 3.19; 95% CI, 1.03-7.43) and increased markedly from 1991 to 1998 ($p = 0.05$). Although the study used passive and active means of case ascertainment similar to those of Horner et al. (2003) (described below), it differed in several key respects: it restricted cases to those below the age of 45 years (instead of all ages); accepted only clinically definite cases of ALS (instead of clinically definite, probable, and suspect cases); used 8 years of followup (instead of 10); and used as a comparison population the age-adjusted rates from US mortality statistics (instead of age-adjusted rates in non-gulf-deployed Gulf War-era veterans). The major criticism of this study is its use of mortality statistics from the general population to estimate the "expected" incidence (Armon 2004c). Mortality may underestimate incidence of ALS (Armon 2004a). In addition, age at onset of ALS was defined as age at death minus 2 years. The calculations for the expected number of cases were age-adjusted but were not sex-adjusted. Because the majority of the deployed Gulf War veterans were men

and mortality from ALS is higher in men (Armon 2004a), those calculations may have resulted in an overestimation of the SMR. In summary, Haley's analyses may have underestimated the expected rates in the comparison population, thereby making SMRs appear higher. Because of the limitations discussed above, the meaning of Haley's study results remains uncertain.

Horner et al. 2003 and Coffman et al. 2005

Horner and colleagues conducted a nationwide epidemiologic study with the goal of identifying all new occurrences of ALS among deployed and nondeployed veterans in the 10 years after the end of the Gulf War (Horner et al. 2003). All active-duty and mobilized Reserves and National Guard personnel were eligible if they had served for at least 1 month at any time during the period August 2, 1990-July 31, 1991 (defined as the Gulf War period). Military personnel were considered deployed if they were in the gulf region or received hazardous duty pay during the Gulf War. All other individuals in the study population were defined as nondeployed, although they may have been stationed outside of the US. Information on deployment status and dates was obtained from the Defense Manpower Data Center. The authors used active and passive methods of case ascertainment; active methods included screening of inpatient, outpatient, and pharmacy medical databases of the Department of Veterans Affairs (VA) and DOD. For the passive methods, they established a toll-free telephone number and conducted solicitations through relevant Internet sites and mass mailings of study brochures to practicing VA neurologists and to members of the American Academy of Neurology. For all cases originally identified, they determined eligibility; and for all cases included in the analyses presented, the diagnosis of ALS was verified with medical-record or mortality-record review.

Among nearly 2.5 million eligible military personnel, they identified and confirmed 107 cases of ALS, which yielded an age-adjusted average annual incidence of 0.43 per 100,000 persons. Most of the cases (about 86%) were found through active ascertainment methods. Nearly 700,000 of the 2.5 million military personnel had been deployed to the gulf region and are referred to as deployed military personnel hereafter. Comparing deployed

with nondeployed personnel, Horner et al. observed an almost doubled age-adjusted risk of ALS (RR, 1.92; 95% CI, 1.29-2.84). The risk of ALS was increased among deployed active-duty veterans (RR, 2.15; 95% CI, 1.38-3.36). There was also an increase in the risk of ALS among deployed veterans who served in the reserves or National Guard (RR, 2.50; 95% CI, 0.88-7.07), although the estimate for this smaller group was less precise. Further subgroup analyses by service branch confirmed increased risks for Air Force personnel (RR, 2.68; 95% CI, 1.24-5.78) and Army personnel (RR, 2.04; 95% CI, 1.10-3.77); for other service branches, the numbers of ALS cases observed were small and rendered the comparison of deployed with nondeployed personnel less informative. Overall, the authors estimated the excess risk attributable to deployment to be 18% (95% CI 4.9%-29.4%), and the risk difference to be 0.32 per 100,000 persons per year.

The foremost limitation of this study lies in the potential for underascertainment of cases, which, if different between deployed and nondeployed groups, may have resulted in overestimation or underestimation of the risk. For example, underascertainment might occur if nondeployed veterans with ALS were less likely to be listed in the record systems used for active case identification or had less incentive to participate in the study than deployed personnel. Because of the rarity of ALS, differential underascertainment of even a small number of cases might exaggerate differences between groups considerably. The concern that ALS would more likely be underascertained in nondeployed than in deployed personnel, thus creating the impression that nondeployed veterans suffered a lower rate of the disease, was raised in a letter to the editor of Neurology by Carmel Armon, an ALS researcher (Armon 2004b). In a followup of the study of Horner et al., Coffman and colleagues (2005) formally assessed the potential impact of such a bias by using three statistical modeling methods known as capture-recapture methods: log-linear modeling, the sample coverage approach, and ecologic modeling. On the basis of the three modeling approaches, the investigators concluded that a modest underascertainment of cases among nondeployed military personnel might have occurred, whereas little or no underascertainment was apparent in deployed personnel. However, even after correcting the ALS rates among

the nondeployed for underascertainment, the investigators still estimated an increased age-adjusted risk of ALS in the deployed military personnel (RR, 1.77; lower bound, 1.21 with the log-linear model). Those results confirmed the original findings of Horner et al. (2003). However, their validity relies on the assumption that the number of underascertained cases in nondeployed military personnel derived from the models is a correct approximation of the number of cases missed. Armon (2004b) pointed out that the Horner et al. estimated rates for nondeployed personnel were lower than the age-adjusted rates reported in a high-quality population-based study of ALS conducted in Washington state by McGuire et al. (1996). Armon presented a table with ALS incidence rates standardized to the 1990 US population for deployed and nondeployed personnel (3.6 and 1.4 per 100,000 people per year, respectively; reported by Horner et. al.) and for the population from McGuire et al. (2.1 per 100,000 people per year; calculated by Armon). However, dividing the incidence rates in deployed personnel by the incidence rates in the McGuire et al. population (serving as the comparison group), the RR is 1.7. This result is similar to the RR estimates using the capture-recapture analyses (Coffman et al. 2005). Using the McGuire et al. rates lends further support to the Horner et al. results because even if there was underascertainment of ALS among the nondeployed military personnel (resulting in lower rates in that comparison group), the rates among deployed personnel were still higher than those reported by McGuire et al.

The committee discussed the implications of the decision by Horner et al. to use persons rather than person-time to calculate risk ratios. In order for that approach not to have resulted in bias, the investigators had to make the following assumptions: (1) that the disease is rare, and removing cases from the denominator will affect followup time minimally at worst, and (2) that the cohort is young and healthy enough not to experience competing risks or loss, which would remove subjects from the person-time denominator during followup (that is, that loss to followup or right censoring is minimal). The committee believes that those assumptions are reasonable for this cohort and the 10-year followup time after the Gulf War.

Weisskopf et al. 2005

Weisskopf et al. (2005) published the results of an analysis of a cohort study in which they examined the relationship between self-report of military service and death from ALS. The study subjects were drawn from male participants in an ongoing cohort, the American Cancer Society's Cancer Prevention Study II (CPS II) cohort. The CPS II cohort, assembled in 1982, included a total of 508,334 men who completed a four-page questionnaire at baseline. The CPS II cohort was originally designed as a prospective cohort study to examine environmental and lifestyle risk factors in the etiology of cancer. The information collected also included data on military service. In the self-administered questionnaire, military service was determined by the question "Were you in the US armed services?" For those who reported military service, followup questions were included to collect information on the branch, the location, and the years of service. At baseline, persons who did not respond to the military-service questions were excluded (N = 6,854). Because monitoring for the occurrence of ALS during followup was not included as part of the CPS II, the authors used ALS mortality as the outcome. To ascertain ALS mortality, the CPS II cohort records were linked to the National Death Index and death certificates were obtained. The CPS II cohort was established in 1982, but ALS deaths were not coded separately on death certificates before 1989. Therefore, the statistical analysis included followup (from 1989 to 1998) of only the cohort members alive in 1989 (N = 408,288).

During the followup period, 280 deaths of which ALS was the underlying or contributory cause were identified in the cohort of more than 400,000 participants. Of the 280 deaths, 217 were among 281,874 men who reported military service, and 63 were among 126,414 men who reported no military service. Cox proportional-hazards analysis with adjustment for differences in age, smoking history, education, alcohol consumption, self-reported exposure to pesticides and herbicides, and several main lifetime occupations (farming, jobs involving electrical work or welding, and food preparation) showed that persons who reported any military service were 1.5 times more likely to have died with a notation of ALS on their death certificates as those who reported no military service. For different branches of the military, risk

appeared higher among those who reported serving in the Army and National Guard (RR, 1.54; 95% CI, 1.09-2.17) and in the Navy (RR, 1.87; 95% CI, 1.28-2.74). Increases in risk (although not reaching conventional levels of significance) were also found in those who served in the Air Force and Coast Guard. There was no evidence of an increased risk for those people who served in the Marine Corps. The authors also examined ALS mortality according to the number of years of military service; there was an increase in risk regardless of the number of years of service. Finally, they examined the risk in relation to service during periods of war (that is, World War II, Korea, or Vietnam) as well as the number of wars during the period of service. Increase in ALS mortality was found to be similar across the three wars, with the RR reaching conventional levels of statistical significance only for service during World War II, the subgroup with the largest sample size. There was some evidence of a trend toward increasing risk as the number of wars during the service period increased from zero to more than two.

Although the study was large, the interpretation of the results is limited by the use of self-report of military service and the use of ALS mortality as a proxy for ALS incidence. The first limitation is mitigated somewhat because most people who have been in the military are likely to remember their service, and the report of military service took place some time prior to the onset of disease and is thus independent of subsequent ALS status. However, the use of mortality data rather than incidence data is a weakness. Nevertheless, the fact that the median survival in ALS is 3 years means that mortality data for ALS can be a good proxy for incidence data. The use of death certificates to ascertain death from ALS, however, is a potential problem because of inaccuracy of death certificate reporting of ALS. However, given the inevitable progression of ALS, it is unlikely that a large number of cases would be miscoded on death certificates. Even if some miscoding occurred, it probably was not related to military service inasmuch as the data were recorded before the putative link between service in the Gulf War and ALS had been widely reported. Weisskopf et al. have reported on the first study of ALS and military service in which sufficient data to adjust for lifestyle factors and occupation

were available. Such adjustments did not materially change the effect estimates.

A letter to the editor of the journal *Neurology* after publication of the Weisskopf et al. study raised a concern about the use of a cohort of subjects originally recruited for a cancer study. The authors of the letter suggested that the volunteer cohort might have been healthier than nonparticipants and the occurrence of ALS might have been underestimated (Horner et al. 2005). Weisskopf et al. replied that they were not concerned that the association that they found between military service and ALS mortality could have been due to the self-selection of healthy volunteers. They supported their view by showing that the age-specific death rates from ALS in the cohort were similar to those in the US population.

The study by Weisskopf et al. is the first to suggest a relationship between military service before the Gulf War and ALS mortality. While the study does have limitations inherent in an analysis of a cohort assembled for other purposes, the findings are intriguing. The implication is that military service in general—not confined to exposures specific to the Gulf War—is related to the development of ALS. The findings, if validated in other studies, suggest that exposures during military service, even among those with no wartime service, might be responsible.

CONCLUSION

The committee identified one high-quality cohort study that examined the relationship between serving in the military and development of ALS (Weisskopf et al. 2005). The study authors reported an increased risk of ALS among men who served in the military in the period 1910-1982, regardless of which war or wars the men served in. Risk was also increased among men who served in the military during nonwartime periods. Although the study has some limitations (such as lack of confirmation of ALS diagnosis because the data came from death certificates), overall it was a well-designed and well-conducted study. It adequately controlled for confounding factors (age, cigarette use, alcohol consumption, education, self-reported exposure to pesticides and herbicides, and several main lifetime occupations).

Three other studies corroborate the findings of the Weisskopf et al. study regarding service in the military and development of ALS. Horner et al. (2003), Haley (2003), and Smith et al. (2000) reported associations between deployment to the Gulf War and ALS. Although the Horner et al. study was well conducted and provides some evidence regarding military service and development of ALS, it is limited by the potential for underascertainment of cases in the comparison group. The Haley study had additional methodologic limitations. Mortality statistics from the general population were used to estimate the expected incidence, and the calculation of expected incidence was age-adjusted but not sex-adjusted. Both limitations may have underestimated the expected incidence of ALS. A study using hospitalization records of Gulf War veterans still on active duty suggested an increased risk of ALS (Smith et al. 2000). Several problems are related to the design of the study, and the committee found it to be of little value in its assessment.

Finally, a mortality study of Gulf War veterans did not report an increase in the risk of ALS (Kang and Bullman 2001); again, multiple methodologic problems limit its value in the committee's assessment.

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.

REFERENCES

Armon C. 2004a. Amyotrophic lateral sclerosis. In: Nelson LM, Tanner CM, Van Den Eeden SK, McGuire VM, Editors. *Neuroepidemiology: From Principles to Practice*. New York: Oxford University Press. Pp. 162-187.

Armon C. 2004b. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 62(6):1027.

Armon C. 2004c. Excess incidence of ALS in young Gulf War veterans. *Neurology* 63(10):1986-1987.

Coffman CJ, Horner RD, Grambow SC, Lindquist J. 2005. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) veterans using capture-pecapture methods. *Neuroepidemiology* 24(3):141-150.

Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756.

Horner RD, Feussner JR, Kasarskis EJ. 2005. Prospective study of military service and mortality from ALS. *Neurology* 65(1):180-181.

Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749.

Kang HK, Bullman TA. 2001. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. *American Journal of Epidemiology* 154(5):399-405.

McGuire V, Longstreth WT Jr, Koepsell TD, van Belle G. 1996. Incidence of amyotrophic lateral sclerosis in three counties in western Washington state. *Neurology* 47(2):571-573.

Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1): 32-37.

3

RECOMMENDATIONS

In Chapter 2, the committee critically evaluated the available literature on the potential association between service in the military and development of amyotrophic lateral sclerosis (ALS). The committee then presented its conclusion based on the evidence derived from the published studies. The committee concluded that there is limited and suggestive evidence of an association between military service and development of ALS. In this chapter, the committee lays out specific recommendations to assist the Department of Veterans Affairs (VA) in gathering more information on ALS in the veteran population so that VA might be able to determine more definitively whether there is an association. The committee also provides guidance for studying ALS risk factors that are potentially relevant to military service.

RECOMMENDATION 1: USE DATA FROM OTHER EPIDEMIOLOGIC STUDIES

Despite the importance of clarifying the relationship between military service and the subsequent risk of ALS, and the challenges faced in drawing a conclusion about it, it is unlikely that prospective cohort studies will be designed de novo to examine this question. For this reason, the committee recommends that existing cohort studies designed for other outcomes be explored for their suitability to assess the relationship between ALS and military service. The study by Weisskopf et al. (2005), which used a cohort assembled for purposes other than studying ALS, provided evidence of an association despite limitations inherent in the conduct of secondary analyses (for example, the lack of information on some important variables related to ALS, the use of self-report of military service, and the identification of ALS through death certificates as a proxy for ALS incidence). Cohorts assembled outside the United States (for example, in Canada and

the United Kingdom and other European countries) should also be considered.

Cohort studies of sufficient size and length of follow-up in which information on military service was collected for all subjects, or can be collected retrospectively in a valid manner from records or from the subjects themselves, may prove useful in examining the relationship between ALS and military service. In some studies, it may be convenient to design a case-control study nested within the cohort to reduce the cost of additional data collection about military exposures. The advantage of traditional cohort studies or nested case-control studies is that they provide a well-defined base population (although not necessarily representative of the general population), and information for a number of potential confounding variables has been collected prior to disease occurrence, thus avoiding recall bias. A cohort would be especially valuable if subjects had provided extensive details about their military experience. Ideally, "exposure" information should include

- Whether a person served in the military.
- Location of military service.
- Years of military service.
- Deployment status.
- Jobs and duties during military service.
- Rank.

The opportunity to validate military service using historical documents would further add to the methodologic rigor of such a study. Linkage with death certificates or other mechanisms for monitoring the occurrence of ALS would be necessary. Prospective monitoring of the cohort for ALS incidence that allows for application of the modified El Escorial diagnostic criteria would be ideal because it would reduce underascertainment and misclassification of disease. However, that may not be feasible. Alternatively, if death certificates are the only source of information on ALS, the investigators should consider validating a subset of diagnoses to estimate the frequency of false positives and false negatives.

High quality case-control studies could also be used to assess the relationship between ALS and military service.

Ongoing or completed rigorous case-control studies of ALS that pay close attention to reducing sources of bias and that collected details about military service as outlined above would be suitable. Case-control studies may permit a tighter control for putative confounding variables, such as lifetime occupational history and trauma, which are not regularly collected in cohort studies designed to assess other outcomes. In addition, in case-control studies, it is easier to attain a more rigorous case definition applying modified El Escorial diagnostic criteria and to ensure the exclusion of motor neuron disease other than ALS (such as primary lateral sclerosis).

In summary, for any secondary analysis of military service and ALS, in even the most rigorously designed and conducted epidemiological study, it is important to carefully assess the quality of the exposure and outcome data that have been collected and the adequacy of the sample size for drawing conclusions.

The National Registry of Veterans with ALS (Kasarkis et al. 2004), although important, is inappropriate to serve as the basis for a cohort study or a case-control study because it is limited to cases of ALS, and the selection of an appropriate comparison (control) group would be difficult because the base population from which cases were identified is not clearly defined.

RECOMMENDATION 2: IN-DEPTH ANALYSIS OF EXISTING RISK-FACTOR STUDIES

In addition to reviewing the literature on military service and the development of ALS, the committee reviewed selected published studies that examined the role of a number of putative risk factors in the etiology of ALS and identified several factors that may be important in relation to military service (see Box 3.1). Those risk factors might be confounding variables in the relationship between military service and ALS, and military service itself might be a proxy for any of those variables. Appendix A contains brief summaries of the putative risk factors listed in Box 3.1; its purpose is to highlight key studies on the risk factors, but it is not a comprehensive review or critique. Appendix B illustrates three possible conceptual models for linking military service and other risk factors with ALS; the models are provided as

aids for visualizing the complexity of the possible mechanisms and are not intended to be exhaustive.

It is beyond the scope of the committee's work to conduct in-depth systematic reviews of the literature to gauge the potential importance of risk factors, and the committee does not suggest that the risk factors reviewed in Appendix A constitute a complete list of military-service-associated potential risk factors for ALS. The committee recommends that VA identify putative risk factors relevant to military service, particularly risk factors common to military service since the 1940s, and conduct in-depth systematic literature reviews on them.

BOX 3.1 Putative ALS Risk Factors Relevant to Military Service

- Intensive physical activity
- Life-style factors
  - Cigarette-smoking
  - Alcohol consumption
- Trauma
- Transmissible agents
- Occupational toxicants
  - Lead
  - Pesticides
- Environmental toxicants

RECOMMENDATION 3: CONDUCT ADDITIONAL EPIDEMIOLOGIC STUDIES OF THE ASSOCIATION BETWEEN MILITARY SERVICE AND AMYOTROPHIC LATERAL SCLEROSIS

In reaching the conclusion of limited and suggestive evidence of an association between military service and later development of ALS, the committee was hampered by the paucity of well-conducted epidemiologic studies that are sufficiently free of bias. In particular, few studies were designed to be able to consider the possible confounding effects of other risk factors for ALS. The committee therefore recommends that further corroborative and exploratory studies be designed and conducted to elucidate the relationship between military service and ALS. Particular attention should be paid to the inclusion of risk factors

that might be related to the development of ALS and to their adequate measurement (or methods of accounting for them in study design). The results of the systematic literature reviews described in Recommendation 2 should provide information to help researchers to design the further studies.

REFERENCES

Kasarkis EJ, Dominic K, Oddone EZ. 2004. The National Registry of Veterans with Amyotrophic Lateral Sclerosis: Department of Veterans Affairs Cooperative Studies Program (CSP) #500a. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 5(Suppl 1):129-132.

Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1): 32-37.

A

EXAMPLES OF RISK FACTORS POSSIBLY RELEVANT TO MILITARY SERVICE

The committee summarizes below several studies of putative risk factors for amyotrophic lateral sclerosis (ALS) relevant to military personnel. This section is not a comprehensive review or critique; rather it highlights selected studies thought to be of relevance.

PHYSICAL ACTIVITY

A number of studies have examined the association between workplace and leisure-time physical activity and ALS. The most methodologically sound is a population-based case-control study conducted in western Washington state with 174 incident cases and 348 sex-matched and age-matched (within 5 years) controls (Longstreth et al. 1998). Using in-person interviews, the authors obtained information on a variety of measures of predisease physical activity. Workplace and leisure-time physical activity generally were not found to be associated with ALS. One exception was an increased risk associated with participation in organized high-school sports (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.03-2.25). All analyses were adjusted for age, sex, and education. More recently, a case-control study in the Netherlands reported on the physical activity of 219 ALS patients and 254 acquaintance controls (Veldink et al. 2005). Information on physical activity was obtained from mailed questionnaires, and cases were responsible for finding controls for the study. There was a weak and imprecisely estimated increase in risk among positive respondents to "engaged in sports as adult" (OR, 1.3; 95% CI, 0.8-2.1) and "ever extreme physical activity" (OR, 1.2; 95% CI, 0.6-2.3) but not those "engaged in sports as youngster" (OR, 1.0; 95% CI, 0.6-1.5). Results were adjusted for age, education, body mass index, alcohol use, and smoking. The

authors of both studies conclude that physical activity is unlikely to be a major contributor to ALS risk (Veldink et al. 2005; Longstreth et al. 1998). Veldink et al. also reported on a systematic review of 24 studies published from 1966 to 2003. They found that most studies were methodologically weak and that all studies that had reported a relationship between physical activity and ALS had less than rigorous designs.

A recent study of 7,325 male Italian professional football (soccer) players over the period 1970-2003 revealed an increased incidence of ALS relative to what would have been expected given ALS incidence in the general population in Italy (Chio et al. 2005). Five cases were identified among the players compared with 0.77 expected from age- and sex-specific rates in the general population (standardized mortality ratio, 6.5; 95% CI, 2.1-15.1). The authors also reported an increased risk associated with number of years as a professional soccer player (≤ 5 years: standardized incidence ratio [SIR], 3.5; 95% CI, 0.4-12.7; > 5 years: SIR, 15.2; 95% CI, 3.1-44.4).

CIGARETTE-SMOKING AND ALCOHOL CONSUMPTION

A case-control study of 110 newly diagnosed ALS patients from two centers in New England and 210 population-based controls examined demographic characteristics, family history of ALS, and histories of smoking and alcohol consumption (Kamel et al. 1999). With adjustment for age, sex, region, and education, "ever smoking" was associated with a 70% increase in ALS risk (OR, 1.7; 95% CI, 1.0-2.8). "Current smoking" was not found to be associated with ALS (OR, 0.9; 95% CI, 0.4-1.8), but risk was increased among those who reported having stopped smoking more than 5 years before the time of the interview (OR, 1.9; 95% CI, 1.1-3.3) and even more among those who had quit within the last 5 years (OR, 4.2; 95% CI, 1.7-10.7). Increases in risk were reported for every stratum of "cigarettes per day," "years smoked," and "pack-years"; a statistically significant trend ($p = 0.046$) was observed in connection with "cigarettes per day." In contrast, ever having used alcohol was not associated with increased ALS risk (OR, 1.1; 95% CI, 0.4-3.2). A weak and imprecisely estimated increase was noted among those who reported more than 31 drinks

per month 5 years before onset of ALS (OR, 1.4; 95% CI, 0.7-3.0), but the increase disappeared when smoking was taken into account in the analysis. Excluding two cases with a family history of ALS did not notably affect any of the results.

The Washington state study also provided results on cigarette-smoking and alcohol consumption (Nelson et al. 2000). Smoking showed consistently positive relationships with ALS (for example, "ever smoked": OR, 2.0; 95% CI, 1.3-3.2). Current smokers experienced a higher risk (OR, 3.5; 95% CI, 1.9-6.4) than smokers who had quit (OR, 1.5; 95% CI, 0.9-2.4). Risk increased linearly with smoking duration and with cumulative pack-years (p trend, 0.001 for both duration and cumulative pack-years).

A case-control study of 219 ALS patients in the Netherlands reported an inverse association between "ever/current alcohol use" and ALS (OR, 0.6; 95% CI, 0.3-0.9), and a positive relationship between current smoking and ALS (OR, 1.8; 95% CI, 1.0-3.0; $p = 0.03$) (Veldink et al. 2005).

TRAUMA

In 1980, Kurtzke and Beebe published one of the first studies of ALS in veterans (Kurtzke and Beebe 1980). On the basis of 504 ALS deaths in male veterans from 1963 to1967, they conducted a case-control study, selecting military controls matched on sex, age, date of entry into military service, and branch of service. They reported a greater frequency of self-reported injury before service among cases (7.5% in cases vs 3.2% in controls; matched OR, 2.6; $p < 0.01$). In addition, when they considered diagnoses responsible for hospitalizations or confinement to quarters during service, more of the ALS cases (163 of 504) than of the controls (115 of 504) had diagnoses related to accidents, poisonings, and violence. Given the number of hypotheses examined and the scarcity of some of the data, the authors themselves considered the study to be a "fishing expedition." Nevertheless, the findings were intriguing and have led others to study the question of trauma and, in particular, fractures, in the etiology of ALS.

A population-based case-control study of 103 patients in the Scottish Motor Neuron Disease Registry reported similar

findings (lifetime history of fracture: OR, 1.3; 95% CI, 0.7-2.5), although there was a more pronounced increase in the 5 years before diagnosis in matched analysis (OR, 15; 95% CI, 2.3-654) (Chancellor et al. 1993). Controls were nearest age- and sex-appropriate persons from the general practitioners' files. In this study, however, risk-factor information was obtained from the cases and controls through in-person interviews conducted by the primary author of the paper.

In a more recent case-control study of high methodologic quality conducted in Washington state, the authors found no consistently increased ORs for prior fractures or electric shock (Cruz et al. 1999). On the basis of in-person interviews and adjustment of all results for age, sex, education, and smoking, the authors reported a weak and imprecisely estimated increase in the odds of fractures in the interval 5 years before diagnosis in cases compared with controls (OR, 1.3; 95% CI, 0.7-2.3); they suggested that fractures may be consequences of subclinical ALS onset rather than potential risk factors.

TRANSMISSIBLE AGENTS

A few studies have examined the possible role of infection in the etiology of ALS, but these seroepidemiologic studies have generated inconsistent findings. One case-control study of 20 incident ALS cases and age-, sex-, and residence-matched population controls in Italy examined seropositivity of human herpesvirus-6 and -8 and echovirus-7 (Cermelli et al. 2003). Despite the small sample, strong but imprecisely estimated increases in ORs for the presence of antibodies to HHV-6 (OR, 3.2; 95% CI, 0.8-12.9), HHV-8(OR, 8.4; 95% CI, 0.9-79.4), and echovirus-7 (OR 3.0, 95% CI, 0.8-18.1) were reported. One limitation of this study is the difficulty in establishing whether infection occurred before ALS onset or was a consequence or correlate of the disease itself.

Nicolson and colleagues (2002), studying eight Gulf War veterans with ALS and two comparison populations, reported that the Gulf War veterans all had serologic evidence of systemic myocoplasmal infection, as did the majority of nonveteran ALS patients. Seven of the eight veterans with ALS were positive for a

specific species (M. fermentans), compared with 13 of 22 positive (of 28 total) civilians with ALS and two of 70 total control patients without ALS. The authors suggest a link between a specific myocoplasmal infection and ALS; however, comparison subjects were not adequately described to support a judgment of the quality of the study. In addition, the ALS subjects were atypical in their clinical presentation. For these reasons, the data presented do not clearly support a relationship between mycoplasmal infection in Gulf War veterans and ALS.

LEAD

In a case-control study conducted in New England, 109 newly diagnosed ALS patients from two centers (the Neuromuscular Research Unit at New England Medical Center and the Neurophysiology Laboratory at Brigham and Women's Hospital) and population controls were interviewed about lead exposure (Kamel et al. 2002). Self-reported occupational exposure to lead was associated with an increase in ALS risk (OR, 1.9; 95% CI, 1.1-3.3) and a dose-response relationship was observed with respect to lifetime days of exposure. No association with residential or recreational exposure to lead was found.

In the case-control study conducted in Washington state (described above), lead exposure was also examined. McGuire et al. (1997) assessed 174 cases of ALS from three counties in Washington for various occupational exposures. Determination of exposure was obtained from self-reports and from an assessment by a panel of four industrial hygienists that reviewed self-reported job titles, tasks, durations, and exposures to specific agents. Self-reported exposure was found to be linked to ALS (OR, 1.9; 95% CI, 1.0-3.6), but the association was lost when the panel assessment was used as the basis of assigning exposure (OR, 1.1; 95% CI, 0.6-2.1). According to self-reports, there were four more cases and seven fewer controls reporting exposure than were classified by the panel as exposed.

A small case-control study of 74 ALS patients from the Mayo Clinic in Rochester, Minnesota, and up to four controls per case, for a total of 201 controls, reported a strong association (OR,

5.5; 95% CI, 1.44-21.0) with total lifetime exposure to lead in excess of 200 hours (Armon et al. 1991).

PESTICIDES

The case-control study of occupational exposures in Washington state reported that exposure to agricultural chemicals was associated with ALS (OR, 2.0; 95% CI, 1.1-3.5) on the basis of panel assessment of exposure (McGuire et al. 1997). The association was attenuated when analysis was based strictly on self-reported exposure (OR, 1.6; 95% CI, 1.0-2.7). Agricultural chemicals were defined as fertilizers and pesticides, which consisted of herbicides, fungicides, insecticides, and other pesticides. Separate analyses showed increases in risk associated with each of those components except "other pesticides," which had only one exposed case.

ENVIRONMENTAL TOXICANTS

In the early 1950s, a much higher than expected incidence of ALS was reported in Guam (Rowland 2000; Siddique et al. 1999). Several environmental factors were proposed, including cycad flour (a part of the Guamanian diet) and exposure to low concentrations of calcium and magnesium in the local environment. Recent evidence indicates that a substituted amino acid, BMAA, produced by cyanobacteria and bioconcentrated through fruit bats, may be responsible for the ALS-parkinsonism-dementia complex of Guam (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).

REFERENCES

Armon C, Kurland LT, Daube JR, O'Brien PC. 1991. Epidemiologic correlates of sporadic amyotrophic lateral sclerosis. *Neurology* 41(7):1077-1084.

Banack SA, Cox PA. 2003. Biomagnification of cycad neurotoxins in flying foxes: implications for ALS-PDC in Guam. *Neurology* 61(3):387-389.

Banack SA, Murch SJ, Cox PA. 2006. Neurotoxic flying foxes as dietary items for the Chamorro people, Marianas Islands. *Journal of Ethnopharmacology* 106(1):97-104.

Cermelli C, Vinceti M, Beretti F, Pietrini V, Nacci G, Pietrosemoli P, Bartoletti A, Guidetti D, Sola P, Bergomi M, Vivoli G, Portolani M. 2003. Risk of sporadic amyotrophic lateral sclerosis associated with seropositivity for herpesviruses and echovirus-7. *European Journal of Epidemiology* 18(2):123-127.

Chancellor AM, Slattery JM, Fraser H, Warlow CP. 1993. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. *Journal of Neurology, Neurosurgery and Psychiatry* 56(11):1200-1206.

Chio A, Benzi G, Dossena M, Mutani R, Mora G. 2005. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 128(Pt 3):472-476.

Cox PA, Sacks OW. 2002. Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam. *Neurology* 58(6):956-959.

Cox PA, Banack SA, Murch SJ. 2003. Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. *Proceedings of the National Academy of Sciences of the United States of America* 100(23):13380-13383.

Cox PA, Banack SA, Murch SJ, Rasmussen U, Tien G, Bidigare RR, Metcalf JS, Morrison LF, Codd GA, Bergman B. 2005. Diverse taxa of cyanobacteria produce beta-N-methylamino-L-alanine, a neurotoxic amino acid. *Proceedings of the National Academy of Sciences of the United States of America* 102(14):5074-5078.

Cruz DC, Nelson LM, McGuire V, Longstreth WT Jr. 1999. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. *Neuroepidemiology* 18(2):101-110.

Kamel F, Umbach DM, Munsat TL, Shefner JM, Sandler DP. 1999. Association of cigarette smoking with amyotrophic lateral sclerosis. *Neuroepidemiology* 18(4):194-202.

Kamel F, Umbach DM, Munsat TL, Shefner JM, Hu H, Sandler DP. 2002. Lead exposure and amyotrophic lateral sclerosis. *Epidemiology* 13(3):311-319.

Kurtzke JF, Beebe GW. 1980. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. *Neurology* 30(5):453-462.

Longstreth WT, McGuire V, Koepsell TD, Wang Y, van Belle G. 1998. Risk of amyotrophic lateral sclerosis and history of physical activity: a population-based case-control study. *Archives of Neurology* 55(2):201-206.

McGuire V, Longstreth WT Jr., Nelson LM, Koepsell TD, Checkoway H, Morgan MS, van Belle G. 1997. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. *American Journal of Epidemiology* 145(12):1076-1088.

Murch SJ, Cox PA, Banack SA. 2004a. A mechanism for slow release of biomagnified cyanobacterial neurotoxins and neurodegenerative disease in Guam. *Proceedings of the National Academy of Sciences of the United States of America* 101(33):12228-12231.

Murch SJ, Cox PA, Banack SA, Steele JC, Sacks OW. 2004b. Occurrence of beta-methylamino-l-alanine (BMAA) in ALS/PDC patients from Guam. *Acta Neurologica Scandinavica* 110(4):267-269.

Nelson LM, McGuire V, Longstreth WT Jr, Matkin C. 2000. Population-based case-control study of amyotrophic lateral sclerosis in western Washington State. I. Cigarette smoking and alcohol consumption. *American Journal of Epidemiology* 151(2):156-163.

Nicolson GL, Nasralla MY, Haier J, Pomfret J. 2002. High frequency of systemic mycoplasmal infections in Gulf War veterans and civilians with Amyotrophic Lateral Sclerosis (ALS). *Journal of Clinical Neuroscience* 9(5):525-529.

Rowland LP. 2000. Hereditary and acquired motor neuron diseases. In: Rowland LP, Editor. *Merritt's Neurology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins. Pp. 708-714.

Siddique N, Sufit R, Siddique T. 1999. Degenerative motor, sensory, and autonomic disorders. In: Goetz CG, Pappert EJ, Editors. *Textbook of Clinical Neurology*. 1st ed. Philadelphia, PA: W.B. Saunders Company. Pp. 695-717.

Veldink JH, Kalmijn S, Groeneveld GJ, Titulaer MJ, Wokke JH, van den Berg LH. 2005. Physical activity and the association with sporadic ALS. *Neurology* 64(2):241-245.

B

POSSIBLE CONCEPTUAL MODELS LINKING MILITARY SERVICE AND AMYOTROPHIC LATERAL SCLEROSIS

Figure B.1 illustrates three possible conceptual models linking military service or other risk factors that might be related to military service with amyotrophic lateral sclerosis (ALS). The models are provided as aids in visualizing the complexity of the possible mechanisms; they are not intended to be exhaustive.

Model A represents a chain of events involving specific environmental exposures. Involvement in military service in any war, some sports, and some occupations may expose people to specific environmental agents. The environmental exposures are the common step in the chain of events. These not-yet-identified exposures (chemical; biologic, including infectious; or physical) might trigger one of several possible mechanisms of neuronal damage leading to the development of ALS.

Model B represents a chain of events involving strenuous physical activity. Involvement in military service in any war, some sports, and some occupations may expose people to strenuous physical activity. Strenuous physical activity is the common step in the chain of events. Strenuous physical activity might trigger one of several possible mechanisms of neuronal damage leading to ALS.

Model C takes into account the possibility of gene-environment interactions. Involvement in military service, some sports, and some occupations may expose people to specific environmental exposures or to strenuous physical activity. These factors might act in conjunction with a genetic susceptibility inherited by some people from their parents. The joint occurrence of those two factors—one genetic and one environmental—is necessary to trigger one of several possible mechanisms of neuronal damage leading to ALS.

FIGURE B.1 Possible Conceptual Models