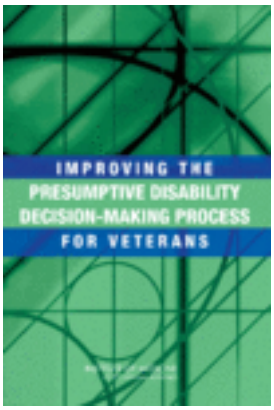

Improving the Presumptive Disability Decision-Making Process for Veterans

Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans, Jonathan M. Samet and Catherine C. Bodurow, Editors

ISBN: 0-309-10731-8, 440 pages, 6 x 9, (2008)

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Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans

Board on Military and Veterans Health

Jonathan M. Samet and Catherine C. Bodurow, *Editors*

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

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This study was supported by Contract No. V101 (93) P-2136 between the National Academy of Sciences and United States Department of Veterans Affairs. Any opinions, findings, conclusions, or recommendations 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-13: 978-0-309-10730-3
International Standard Book Number-10: 0-309-10730-X

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.

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Suggested citation: IOM (Institute of Medicine). 2008. *Improving the presumptive disability decision-making process for veterans*. Washington, DC: The National Academies Press.

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

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Reviewers

This report has been reviewed in draft form by individuals 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 for 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 individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Gilbert S. Omenn,** University of Michigan Medical School, and **Willard G. Manning,** University of Chicago. Appointed by the National Research Council and Institute of Medicine, respectively, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

This committee, the Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (Committee), was charged with describing the current process for how presumptive decisions are made for veterans who have health conditions arising from military service and with proposing a scientific framework for making such presumptive decisions in the future. Although an individual veteran can establish a direct service connection for an illness, the needed information on the responsible exposure received during military service may be unavailable or incomplete. Additionally, there may be scientific uncertainty as to whether the exposure is known to cause the health condition. To ensure that veterans are compensated when information for direct service connection is needed but unavailable, Congress or the Secretary of the Department of Veterans Affairs (VA) can decide to service connect entire groups of veterans for specific health conditions due to exposures received during service. This decision to compensate particular groups of veterans is called a presumptive disability service-connection decision or, simply, a presumption. A presumption may address unavailable or incomplete information on exposure or gaps in the evidence as to whether the exposure increases risk for the health condition.

Each veteran identified as eligible for coverage under a presumptive decision will have a separate, individual disability rating conducted by the VA and will be eligible for disability compensation based on the nature and severity of the health condition. That is, the presumptive disability service-connection decision is separate from the rating evaluation and compensation process.

The Committee took on the task of addressing presumptions while the United States was involved in conflict in Iraq and Afghanistan and veterans from prior conflicts were developing health conditions linked to service in Vietnam and the 1990 Persian Gulf War. The Committee's charge involved examination of the processes used by all participants in the presumptive disability decision-making process for veterans—Congress, VA, the National Academies (National Research Council [NRC] and Institute of Medicine [IOM]), veterans service organizations, and veterans. The Committee examined the processes used by the NRC and IOM to evaluate scientific evidence in support of presumptive disability decision-making by the VA and how the VA used the syntheses and scientific classifications of the NRC and IOM, along with other information, to establish presumptive decisions. The Committee was asked to describe the current process. The Committee's approach involved a series of case studies, intended to draw out "lessons learned" that would inform the development of a new approach. The case studies are not intended as criticisms about the work of past NRC or IOM committees or previously established presumptive decisions by Congress and VA. Rather the case studies serve as an appropriate and informative foundation for proposing an approach for the future.

The Committee concluded that the presumptive disability decision-making process should be based on evidence about veterans' health and how their health had been affected by military service. The Committee proposes a framework for the future that will be based on findings about the health of veterans that come from careful charting of Service member exposures during military service and tracking of their health at entry into, during, at separation from and after military service. The proposed framework may be applied to all types of exposures (e.g., chemical, biological, infectious, physical, and psychological); however, we recognize that characterizing psychological stressors, particularly under combat circumstances, is particularly difficult, although highly relevant to the chronic neuropsychiatric disorders faced by veterans. The Committee offers its framework for evaluation of the resulting evidence and for considering the evidence from studies of veterans in the context of all other relevant lines of scientific evidence. The Committee recommends a two-step approach for evaluation of scientific evidence on exposures of military personnel and risks to health. The first step is to determine the strength of evidence in support of causation and to classify the strength of the causal classification. The second step is to describe the magnitude of the disease burden caused by the exposure in a specific group of veterans.

Presumptive decisions, while based in evidence on risks to health status, are also affected by other considerations. The report acknowledges these considerations. The Committee recognizes that its proposed framework for the future will be applied in a context set by many considerations beyond

the scope of scientific evidence and its classification with regard to the strength of evidence for causality. Nonetheless, the Committee respectfully hopes that the Veterans' Disability Benefits Commission will recommend and that Congress and the VA will adhere to an evidence-based approach for the future presumptive disability decision-making process for veterans.

I am highly appreciative of the dedication and work of the members of the Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans. They willingly took on this important effort at a time when every American is aware of the great sacrifices that military service men and women and our veterans have and do make each day. The Committee addressed its charge with great dedication and worked tirelessly to consider all of the relevant information, to deliberate at length in committee meetings and conference calls. Of course, each committee member invested substantial time in this effort, reflective of its importance and of its challenging nature. The proposed scientific framework, levels for strength of evidence, and other recommendations in this report reflect the thoughtful and carefully considered conclusions of the Committee. The Committee wishes to express its appreciation for the valuable support of its dedicated staff directed by Catherine Bodurow. This report would not have been possible without their contributions.

Veterans have sacrificed a great deal for our nation. We owe them the best possible process for ensuring that those having service-related health conditions are properly identified, treated, and compensated.

Jonathan M. Samet, M.D., M.S.
Chair, Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans

Acknowledgments

The Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (Committee) and Institute of Medicine (IOM) staff would like to thank many individuals for providing information, data, discussions, and comments throughout this study. The Committee and IOM staff are indebted to these individuals for their assistance and contributions.

The Committee and IOM staff would like to acknowledge and thank members of the Veterans' Disability Benefits Commission (VDBC) for taking time to attend and participate at the Committee's open session meetings. The commissioners include: James T. Scott (VDBC's Chairman), John Grady, Rick Surratt, and Joe Wynn. We would also like to recognize the VDBC Staff for their attendance and participation at the Committee's open session meetings as well as any needed technical assistance throughout the study. These individuals include: Ray Wilburn (VDBC's Executive Director), Jacqueline Garrick, Kathleen Greve, Steve Riddle, Jim Wear, and Donald Zeglin. IOM staff is appreciative of the assistance provided by Marcelle Habibion (Department of Veterans Affairs' [VA] Director of Program Evaluation Service in the Office of Policy and Planning) during the course of the study. Many others from VA also provided information, presented at Committee meetings or participated in meetings with the Committee Chair and IOM staff. They are recognized, as follows, in alphabetical order: David Barrans, Mark Brown, Douglas Dembling, Lawrence Deyton, Patrick Dunne (VA's Assistant Secretary for Policy and Planning), George Fitzelle, Duane Fleming, Bradley Flohr, Paul Hutter (VA's Acting General

Counsel), P. Craig Hyams, Patrick Joyce, Gordon Mansfield (VA's Deputy Secretary), David McLenachen, Thomas Pamperin, and Joseph Salvatore.

The Committee benefited greatly from the knowledge, information, and views of presenters and panelists at its three open session meetings. The Committee would like to recognize the following individuals from its open session meeting on May 31, 2006 (listed in order of their presentation): John Grady (VDBC), Rick Surratt (VDBC), Joe Wynn (VDBC), Ray Wilburn (VDBC), Thomas Pamperin (VA), David Barrans (VA), Mark Brown (VA), Patrick Joyce (VA), and Bradley Flohr (VA). The Committee would like to recognize the following individuals who presented at its second open session meeting on July 27, 2006 (listed in order of their presentation): Rose Marie Martinez (IOM), Han Kang (VA), Lawrence Deyton (VA), R. Craig Postlewaite (DoD), Jack M. Heller (DoD), John Seibert (DoD), Cathy Wiblemo (The American Legion), Leonard Selfon (United Spinal Association), Quentin Kinderman (Veterans of Foreign Wars of the United States), and Rick Weidman (Vietnam Veterans of America). Finally, the Committee would like to recognize the following individuals who presented at its third open session meeting on October 4, 2006 (listed in order of their presentation): Laura Petrou, Patrick Ryan, Edward Scott, Chris Yoder, Nhan Do (DoD), Cliff Freeman (VA), and James T. Scott (VDBC's Chairman). In addition, several congressional staffers joined a panel discussion in person or by phone. They are recognized in alphabetical order, as follows: William Brew, Kelly Craven, Mary Ellen McCarthy, Paige McManus, Dahlia Melendrez, Kingston Smith, Jon Towers, and Lupe Wissel.

Representatives of the Department of Defense (DoD) contributed to the Committee's efforts by attending and presenting at open session meetings, participating in conference calls, and providing written responses to Committee questions. The Committee and IOM staff would like to thank Ellen Embrey (DoD's Deputy Assistant Secretary of Defense for Force Health Protection and Readiness), along with Michael Kilpatrick and George Johnson of her office, for making the assistance and expertise of many in DoD available to the Committee and IOM staff. IOM staff would like to acknowledge Craig Postlewaite who facilitated and participated in each of the DoD, Committee, and IOM staff interactions. The following individuals (listed in alphabetical order) contributed substantial time and effort to providing the Committee documents, answers to questions and participating at panel discussions during open session meetings: Kenneth Cox, Donna Doganiero, Jack Heller, Brad Hutchens, Jack Jeter, Bill Monk, Christine Moser, John Seibert, Becky Sobel, and Hew Wolf.

Throughout the course of the study, the Committee received written comments from veterans service organizations, individual veterans, and the public. These comments served to heighten awareness of important issues

that the Committee considered during its deliberations of the proposed levels for strength of evidence, proposed framework for the presumptive disability decision-making process, and recommendations. The Committee and IOM staff are grateful for the level of interest demonstrated and information that was shared.

IOM staff assembled an extensive electronic library of public laws, *Federal Register* notices, and all related presumptive disability decision documents with the assistance of librarians and experts at the Library of Congress. These individuals provided assistance in assembling an enormous knowledge base—from microfiche to electronic files—for the Committee, which was extensively researched and used throughout the study process. IOM staff is greatly indebted to the staff at the Library of Congress for these efforts.

The Committee was provided invaluable background information and expertise from IOM staff, including Rose Marie Martinez, David Butler, Jennifer Cohen, Carolyn Fulco, Abigail Mitchell, and Mary Paxton, during the course of the study. The Committee would like to thank these individuals for their contributions.

The Committee was fortunate to have the assistance of two knowledgeable consultants throughout the study. Melissa McDiarmid provided invaluable scientific input to the Committee's efforts. Robert Epley provided guidance on VA processes and background. The Committee is indebted to both of these individuals for the time and efforts they contributed.

Finally, the Committee would like to acknowledge the support of the IOM staff. The Committee would like to recognize, in particular, the efforts of Catherine Bodurow (Study Director) who worked tirelessly over the course of the study. The Committee is also particularly appreciative of the efforts of Morgan Ford (Program Officer), Alice Vorosmarti (Research Associate), and Reine Homawoo (Senior Program Assistant) who supported the study at its conclusion and delivered this report. The Committee would also like to recognize Frederick Erdtmann (Board Director) who attended each of the Committee meetings and provided assistance throughout the study. There were many who provided part-time staff support to the committee's efforts over the course of the study. These additional staff included: Leslie Sim (Program Officer), Cara James (Research Associate), Anisha Dharshi (Research Associate), Kristen Butler (Research Assistant), Kristen Gilbertson (Research Assistant), Jon Sanders (Program Associate), and Vera Diaz (Intern). Additional staff support included assistance from: Andrea Cohen (Financial Associate), Pamela Ramey-McCray (Administrative Assistant), Lara Andersen (Office of Reports and Communication), and Mark Goodin (Copyeditor). The staff would also like to acknowledge William McLeod (Senior Librarian, The National Academies) who provided invaluable support throughout the study.

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[1]Appendixes D-M can be found on a CD attached to the back of the report cover.

Tables, Figures, and Boxes

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BOXES

Acronyms and Abbreviations

ACB	Army Classification Battery
ACES-EM	Automated Civil Engineering System-Environmental Management
ACHRE	Advisory Committee on Human Radiation Experiments
ADA	American Diabetes Association
AEC	Atomic Energy Commission
AF	Attributable fraction
AF-EMIS	Air Force Environmental Management Information System
AFCESA	Air Force Civil Engineer Support Agency
AFHLTA	Armed Forces Health Longitudinal Technology Application
AFHS	Air Force Health Study
AFHSC	Armed Forces Health Surveillance Center
AHA	American Heart Association
AHLTA	Armed Forces Health Longitudinal Technology Application
AhR	Aryl hydrocarbon receptor
AIDS	Acquired immunodeficiency syndrome
AIS	Automated information systems
ALS	Amyotrophic lateral sclerosis (Lou Gehrig's disease)
AML	Acute myelogenous leukemia
ANG	Air National Guard
ANLL	Acute non-lymphocytic leukemia

APIMS	Air Program Information Management System
AS	Assigned share
ASTM	American Society for Testing and Materials
ATSDR	Agency for Toxic Substances and Disease Registry
BEIR	Biological Effects of Ionizing Radiation
BMI	Body mass index
C&P Service	Compensation and Pension Service
CCB	Configuration Control Board
CCS	Command Core System (Air Force)
CDC	Centers for Disease Control and Prevention
CDVA	Commonwealth Department of Veterans' Affairs
CERHR	Center for the Evaluation of Risks to Human Reproduction
CES-D	Centers for Epidemiological Studies-Depression Scale
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CHF	Congestive heart failure
CHPPM	Center for Health Promotion and Preventive Medicine (Army)
CI	Confidence interval
CIA	Central Intelligence Agency
CIRRPC	Committee on Interagency Radiation Research and Policy Coordination
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRDP	Concurrent Retirement and Disability Payments
CRS	Congressional Research Service
CRSC	Combat-Related Special Compensation
CSM	Cerebrospinal malformation
CSP	Cooperative Studies Program
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DCI SCI	Director of Central Intelligence Sensitive Compartmented Information Programs
DECC-D	Defense Enterprise Computing Center-Detachment
DHHS	Department of Health and Human Services
DISA	Defense Information Systems Agency
DMDC	Defense Manpower Data Center

DMSS	Defense Medical Surveillance System
DNBI	Disease and nonbattle injury
DoA	Department of the Army
DoD	Department of Defense
DoDI	Department of Defense Instruction
DOE	Department of Energy
DOEHRS	Defense Occupational and Environmental Health Readiness System
DoL	Department of Labor
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DTAS	Defense Theater Accountability Software
EA	Exposure Assessment
EAR	Excess absolute risk
EEOICPA	Energy Employees Occupational Illness Compensation Program Act
EESOH-MIS	Enterprise Environmental Safety and Occupational Health-Management Information System
EO	Executive Order
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ERIC	Epidemiologic Research and Information Center
ERR	Excess relative risk
FECA	Federal Employees' Compensation Act
FERS	Federal Employees Retirement System
FHIE	Federal Health Information Exchange
FHP	Force Health Protection
fMRI	Functional magnetic resonance imaging
FN	False negative
FNR	False negative rate
FOUO	For official use only
FP	False positive
FPR	False positive rate
FR	Federal Register
FY	Fiscal Year
GAF	Global Assessment of Functioning
GAO	Government Accountability Office
GBD	General birth defect
GBS	Guillain-Barre syndrome

GPS	Global Positioning System
GT test	General Technical test
GW	Gulf War
Gy	Gray (measure of dose of irradiation)
HART	Health Assessment Review Tool
HCFA	Health Care Financing Administration
HEW	U.S. Department of Health, Education, and Welfare
HHIM	Health Hazard Information Module
HIV	Human immunodeficiency virus
HMMS	Hazardous Materials Management System
HUS	Hemolytic-uremic syndrome
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IH	Industrial hygiene
IHIMS	Industrial Hygiene Information Management System (Navy)
IOM	Institute of Medicine
IQ	Intelligence quotient
IREP	Interactive RadioEpidemiological Program
IU	Individual unemployability
LIMDIS	Limited Dissemination
LMF	Lovelace Medical Foundation
MDS	Myelodysplastic syndrome
MFUA	Medical Follow-up Agency
MMPI	Minnesota Multiphasic Personality Inventory
MOA	Memorandum of Agreement
MOS	Military occupational specialty
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTF	Military Treatment Facility
NAS	National Academy of Sciences
NCEH	National Center for Environmental Health
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NEHC	Navy Environmental Health Center
NESHAP	National Emission Standards for Hazardous Air Pollutants
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphoma

NHLBI	National Heart, Lung, and Blood Institute
NHS	Nurses Health Study
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOCONTRACT	Not releasable to contractors
NOED	Navy Occupational Exposure Database
NOFORN	Not releasable to foreign nationals
NPV	Negative predictive value
NRC	National Research Council
NTP	National Toxicology Program
NTS	Nevada Test Site
OEF	Operation Enduring Freedom
OEH	Occupational and environmental health
OEHHA	Office of Environmental Health Hazard Assessment
OEHS	Occupational environmental health and safety
OEL	Occupational exposure limit
OGC	Office of the General Counsel
OH	Occupational health
OHMIS	Occupational Health Management Information System
OIF	Operation Iraqi Freedom
OMB	Office of Management and Budget
OPHEH	Office of Public Health and Environmental Hazards
OPM	Office of Personnel Management
OR	Odds ratio
ORCON	Originator controlled dissemination and extraction of information
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy
PAF	Population attributable fraction
PAR	Population attributable risk
PC	Probability of causation
PCB	Polychlorinated biphenyl
PDDM	Presumptive disability decision making
PHA	Periodic health assessment
PKDL	Post-kala-azar dermal leishmaniasis
PL	Public Law
POM	Program Objectives Memorandum
POW	Prisoner of War
PPB	Parts per billion
PPG	Pacific Proving Grounds

PPM	Parts per million
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSG II	Professional Staffing Group II
PTF	Presidential Task Force
PTSD	Posttraumatic stress disorder
PY	Person-year
RADS	Reactive airways dysfunction syndrome
RCT	Randomized controlled/clinical trial
RD	Restricted data
ReA	Reactive arthritis
RECA	Radiation Exposure Compensation Act of 1990
RECAC	Radiation Exposure Compensation Act Committee
REVCA	Radiation-Exposed Veterans Compensation Act
RO	Rey-Osterreith Test
ROC	Receiver Operator Characteristics curve
RR	Relative risk/risk ratio
RTI	Research Triangle Institute
SAD	Service-attributable disease
SAF	Service-attributable fraction
SANG	Saudi Arabian National Guard
SAP	Special Access Program
SCI	Sensitive Compartmented Information
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders
SCL	Symptoms Checklist
SEER	Surveillance Epidemiology and End Results
SEG	Similar exposure group
SES	Socioeconomic status
SF	Standard Form
SFFWG	Shared Functions Focus Working Group
SHAD	Project Shipboard Hazard and Defense
SMITREC	Serious Mental Illness Treatment Research and Evaluation Center
SMR	Standardized mortality ratio
SSA	Social Security Administration
SSDI	Social Security Disability Insurance
SSI	Supplemental Security Income
TBI	Traumatic brain injury
TCDD	Tetrachlorodibenzo-*p*-dioxin

TN	True negative
TNR	True negative rate
TP	True positive
TPR	True positive rate
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
USC	United States Code
USPSTF	U.S. Preventive Health Services Task Force
VA	Department of Veterans Affairs
VAO	Veterans and Agent Orange
VASRD	Veterans Administration Schedule for Rating Disabilities
VBA	Veterans Benefits Administration
VDBC	Veterans' Disability Benefits Commission
VDRECSA	Veterans' Dioxin and Radiation Exposure Compensation Standards Act
VES	Vietnam Experience Study
VET (registry)	Vietnam Era Twin (registry)
VHA	Veterans Health Administration
VHI	Veterans Health Initiative
VISTA	Veterans Health Information Systems and Technology Architecture
VOC	Volatile organic compound
VSO	Veterans Service Organization
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WNINTEL	Warning notice, intelligence sources, and methods involved
WRIISC	War-Related Illness and Injury Study Centers
WWI	World War I
WWII	World War II
YLD	Years of life lived with disability
YLL	Years of life lost

General Summary

The United States has long recognized and honored the service and sacrifices of its military and veterans. Veterans who have been injured by their service (whether their injury appears during service or afterwards) are owed appropriate health care and disability compensation. For some medical conditions that develop after military service, the scientific information needed to connect the health conditions to the circumstances of service may be incomplete. When information is incomplete, Congress or the Department of Veterans Affairs (VA) may need to make a "presumption" of service connection so that a group of veterans can be appropriately compensated. The missing information may be about the specific exposures of the veterans, or there may be incomplete scientific evidence as to whether an exposure during service causes the health condition of concern. For example, when the exposures of military personnel in Vietnam to Agent Orange could not be clearly documented, a presumption was established that all those who set foot on Vietnam soil were exposed to Agent Orange.

The Institute of Medicine (IOM) Committee was charged with reviewing and describing how presumptions have been made in the past and, if needed, to make recommendations for an improved scientific framework that could be used in the future for determining if a presumption should be made. The Committee was asked to consider and describe the processes of all participants in the current presumptive disability decision-making process for veterans. The Committee was not asked to offer an opinion about past presumptive decisions or to suggest specific future presumptions. The Committee heard from a range of groups that figure into this decision-making process, including past and present staffers from Congress,

the VA, the IOM, veterans service organizations, and individual veterans. The Department of Defense (DoD) briefed the Committee about its current activities and plans to better track the exposures and health conditions of military personnel. The Committee further documented the current process by developing case studies around exposures and health conditions for which presumptions had been made. The Committee also reviewed general methods by which scientists, as well as government and other organizations, evaluate scientific evidence in order to determine if a specific exposure causes a health condition.

The history of presumptions is a fascinating and complex story. In 1921 Congress empowered the VA Administrator (now Secretary) to establish presumptions of service connection for veterans. Only Congress and VA have the authority to establish presumptions for veterans. Since 1921, nearly 150 health outcomes have been service-connected on a presumptive basis by Congress and VA. This process has evolved over the years. The current process for making presumptions can be traced to the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 2d Sess.), an act that established a model for decision making by VA that still stands today. In the 1991 Act, Congress asked VA to contract with an independent organization to review the scientific evidence on Agent Orange. VA turned to the IOM of the National Academy of Sciences to carry out these reviews. Subsequently, VA turned to IOM for issues arising from the 1990 Gulf War. Based on the work of a committee, IOM provides VA with reports that describe the strength of evidence that links agents of concern with specific health conditions. VA uses IOM reports and other information in an internal decision-making process to decide whether a presumption will be made.

The Committee carefully studied the current approach to presumptive disability decision making and examined a number of specific case examples. This assessment led to a number of recommendations to improve the process:

- As the case studies demonstrated, Congress could provide a clearer and more consistent charge on how much evidence is needed to make a presumption. There should be clarity as to whether the finding of an association in one or more studies is sufficient or the evidence should support causation.
- Due to lack of clarity and consistency in congressional language and VA's charges to the committees, IOM committees have taken somewhat varying approaches since 1991 in reviewing the scientific evidence and in forming their opinions on the possibility that exposures during military service contributed to causing a health condition. Future committees could improve their review and classification of scientific evidence if they were given clear and consistent charges and followed uniform evaluation procedures.

- The internal processes by which the VA makes its presumptive decisions following receipt of an IOM report have been unclear. VA should adopt transparent and consistent approaches for making these decisions.
- Complete exposure data and health condition information for military personnel (both individuals and groups) usually have not been available from DoD in the past. Such information is one of the most critical pieces of evidence for improving the determination of links between exposures and health conditions.

All of these improvements are feasible over the longer term and are needed to ensure that the presumptive disability decision-making process for veterans is based on the best possible scientific evidence. Decisions about disability compensation and related benefits (e.g., medical care) for veterans should be based on the best possible documentation and evidence of their military exposures as well as on the best possible information on any health conditions caused by these exposures. While it is impossible to provide certainty in every case, a fresh approach could do much to improve the current process. The Committee's recommended approach (Figure GS-1) has several parts:

- An open process for nominating exposures and health conditions for review; involving all stakeholders in this process is critical
- A revised process for evaluating scientific information on whether a given exposure causes a health condition in veterans; this includes a new set of categories to assess the strength of the evidence for causation, and an estimate of the numbers of exposed veterans whose health condition can be attributed to their military exposure
- A consistent and transparent decision-making process by VA
- A system for tracking the exposures of military personnel (including chemical, biological, infectious, physical, and psychological stressors), and for monitoring the health conditions of all military personnel while in service and after separation
- An organizational structure to support this process

To support the Committee's recommendations, we suggest the creation of two panels. One is an Advisory Committee (advisory to VA), that would assemble, consider, and give priority to the exposures and health conditions proposed for possible presumptive evaluation. Nominations for presumptions could come from veterans and other stakeholders as well as from health tracking, surveillance, and research. The second panel would be a Science Review Board, an independent body, which would evaluate the strength of the evidence (based on causation) that links a health condition to a military exposure and then estimates the fraction of exposed veterans

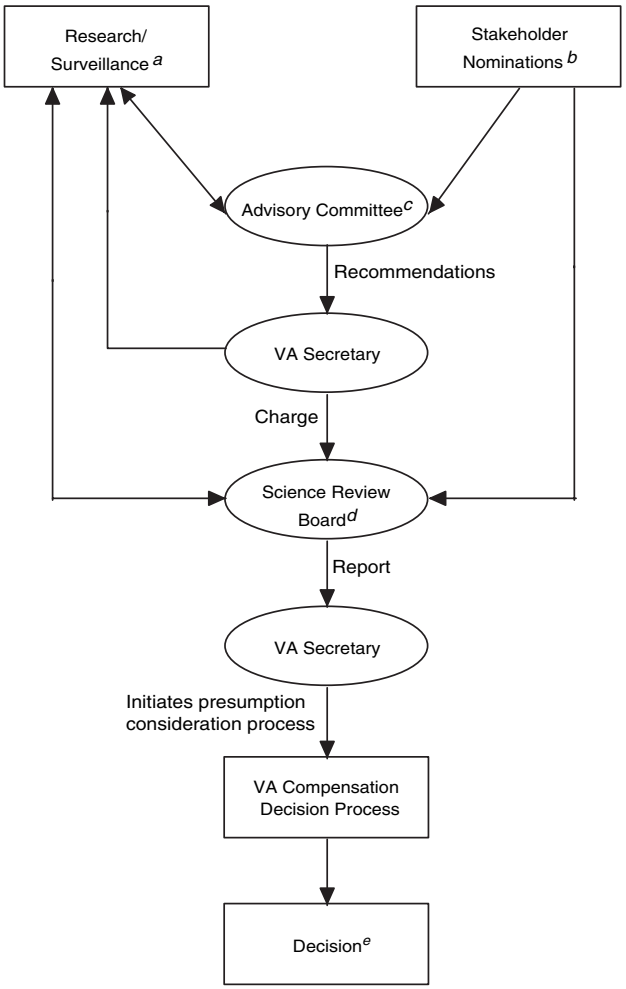

FIGURE GS-1 Proposed framework for future presumptive disability decision-making process for veterans.

[a] Includes research for classified or secret activities, exposures, etc.

[b] Includes veterans, Veterans Service Organizations, federal agencies, scientists, general public, etc.

[c] This committee screens stakeholders' proposals and research in support of evaluating evidence for presumptions and makes recommendations to the VA Secretary when full evidence review or additional research is appropriate.

[d] The board conducts a two-step evidence review process (see report text for further detail).

[e] Final presumptive disability compensation decisions are made by the Secretary, Department of Veterans Affairs, unless legislated by Congress.

whose health condition could be attributed to their military exposure. The Science Review Board's report and recommendations would go to VA for its consideration. VA would use explicit criteria to render a decision by the VA Secretary with regard to whether a presumption would be established. In addition, the Science Review Board would monitor information on the health of veterans as it accumulates over time in the DoD and VA tracking systems, and nominate new exposures or health conditions for evaluation as appropriate.

This Committee recommends that the following principles be adopted in establishing this new approach:

1. Stakeholder inclusiveness
2. Evidence-based decisions
3. Transparent process
4. Flexibility
5. Consistency
6. Causation, not just association, as the target for decision making

The Committee suggests that its framework be considered as the model to guide the evolution of the current approach. While some aspects of the approach may appear challenging or infeasible at present, feasibility would be improved with the full implementation of the Committee's recommendations, provision of appropriate resources to all of the participants in the presumptive disability decision-making process for veterans, and future methodological developments. DoD and VA have already been discussing various aspects of improving exposure and health tracking and how the two agencies can share data and information with each other. Veterans deserve to have these improvements accomplished as soon as possible.

Summary

INTRODUCTION

The United States has long recognized and honored military veterans' service and sacrifices. Veterans injured by their service, becoming ill while in service, or having an illness after discharge as a long-term consequence of their service have been given healthcare coverage and disability compensation. As the complexity of exposures during combat has increased, the list of service-connected illnesses has grown. The Department of Veterans Affairs (VA) now provides disability compensation to approximately 2.6 million veterans for 7.7 million disabilities annually, expending approximately $24 billion for this purpose (VBA, 2006, pp. 19, 24, 27).

Disability compensation for military veterans requires that there be a service connection. A medical illness or injury that occurred while a member was in military service is considered service connected whether caused by or aggravated by an exposure or event during service *or simply occurring coincidentally* with military service. However, if a medical condition appears after the period of military service and it is presumed to be caused by or aggravated by an exposure or an event that occurred during military service, then veterans may receive compensation based on that presumption (Pamperin, 2006).

In making a decision to provide compensation, VA needs to determine whether the illness of concern can generally be caused by exposures received during service and whether the illness in a specific claimant was caused by the exposure. The answer to the general question of causality comes from a careful review of all available scientific information, while the answer

to the question of causation in a specific person hinges on knowledge of the exposure received by that individual and of other factors that may be relevant. If the scientific evidence is incomplete, there may be uncertainty on the question of causation generally; if there is limited or no information on exposure of individual claimants or if other factors also contribute to disease causation, there may be uncertainty on the question of individual causation.

To provide benefits to veterans in the face of these two broad types of uncertainty, Congress and VA make presumptive decisions that bridge gaps in the evidence related to causation and to exposure. Presumptions may relieve the veteran of persuading VA that the exposure produced the adverse health outcome and of proving that an exposure occurred during military service (Pamperin, 2006). Once a medical condition is service connected through presumptions, and the veteran can document military service consistent with having received the given exposure, the veteran only has to show the basic fact that he or she suffers from the condition in order to receive a disability payment and eligibility for medical care (Zeglin, 2006).

In 2004, Congress established the Veterans' Disability Benefits Commission (the Commission), which was charged with "studying the benefits provided to compensate and assist veterans for disabilities attributable to military service" (VDBC, 2006, p. 1; as found in Appendix A). The Commission identified the presumptive disability decision-making process as a topic needing assessment and asked the Institute of Medicine (IOM) to establish a committee for this purpose that would be funded by VA. The resulting committee, the Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (the Committee), was given the following charge by VA:

- Describe and evaluate the current model used to recognize diseases that are subject to service connection on a presumptive basis.
- If appropriate, propose a scientific framework that would justify recognizing or not recognizing conditions as presumptive.

The Commission further elaborated the charge, asking the Committee to "help ensure that future veterans are granted service connection under a presumptive basis based on the best scientific evidence available" (VDBC, 2006, p. 4; as found in Appendix A). The Commission asked the Committee to "evaluate the current model used to determine diseases that qualify for service connection on a presumptive basis, and if appropriate, propose improvements in the model" (VDBC, 2006, p. 1; as found in Appendix A). The Commission emphasized that "having a method of granting service connection quickly and fairly based on a presumption is

of critical importance to our disabled veterans and their surviving spouses" and that "ensuring that future presumption processes reflect the then current medical knowledge about the causal relationship would benefit the entire veteran community" (VDBC, 2006, p. 4; as found in Appendix A). The Commission's summary statement further commented that "[t]o the extent possible, suggestions that will avoid the necessity for many future presumptions by ensuring that exposure of service members is documented and scientific evidence is made available would be important" (VDBC, 2006, p. 4; as found in Appendix A).

IOM appointed a 14-member committee that covered the broad scientific and medical areas of general, occupational, and psychiatric medicine; biostatistics; epidemiology; toxicology; industrial hygiene; and exposure and risk assessment. The Committee's members also brought expertise in law, philosophy, causal decision making, and policy as well as knowledge of the Department of Defense (DoD) and VA's approach to disability compensation.

THE COMMITTEE'S APPROACH TO ITS CHARGE

In fulfilling its charge, the Committee first investigated and attempted to characterize Congress' and VA's recent approach to presumptive disability decision making, and then developed a conceptual framework for a new, more evidence-based process. It then constructed a way to move forward that builds on the framework and addresses deficiencies of the current process.

The Committee held three open meetings to gather information on the current presumptive disability decision-making process. The Committee heard from past and present congressional staff members, representatives of VA, DoD, IOM, various stakeholder groups (e.g., veteran service organizations [VSOs]) and the general public. Committee members also participated in conference calls with DoD experts on medical surveillance and exposure data collection and exposure assessment systems.

The Committee reviewed extensive background information including: documents provided by the Commission, public laws and supporting House and Senate reports, *Federal Register* notices, VA documents (e.g., cost estimates, a white paper on VA's decision-making processes [found in Appendix G], and responses by VA to written questions from the Committee), DoD documents, and past IOM reports commissioned by DoD and VA. The Committee conducted 10 case study reviews—Mental Disorders' Presumptions, Multiple Sclerosis Presumption, Prisoners of War Presumptions, Amputees and Cardiovascular Disease Presumption, Radiation Presumptions, Mustard Gas and Lewisite Presumptions, Gulf War Presumptions, Agent Orange and Prostate Cancer Presumption, Agent Orange and Type 2

Diabetes Presumption, and Spina Bifida Program (not a presumption but a VA program area)—that cover a wide variety of circumstances for which presumptions have been established by Congress and VA since 1921. The case studies were a foundation for the Committee's efforts in understanding past practices of all participants in the presumptive disability decision-making process (see Appendix I).

The Committee also researched and considered capabilities and limitations of the exposure data and health outcome information available to DoD and VA for exposure assessment, surveillance, and research purposes. The Committee examined whether DoD and VA have a strategic research plan and vision for the necessary interface between the agencies, as well as with other, relevant research organizations.

The Committee considered the use of scientific evidence in guiding the process for making presumptive decisions that affect the compensation of veterans. Drawing upon the Committee members' expertise in epidemiology, medicine, toxicology, biostatistics, and causal decision making, the Committee covered the evaluation of evidence for inferring association and causation as well as methods for quantifying the contribution of an agent to disease causation in populations and extending this quantification to individuals. Using this framework, the Committee developed an evidence-based approach for making future decisions with regard to presumptions.

THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS FOR VETERANS

In 1921 Congress empowered the VA Administrator (now Secretary) to establish presumptions of service connection for veterans. Only Congress and the VA Secretary have the authority to establish presumptions. Over time, presumptions have been made to relieve veterans of the burden to prove that disability or illness was caused by a specific exposure that occurred during military service (e.g., Prisoners of War). Since 1921, nearly 150 health outcomes have been service connected on a presumptive basis (see Appendix F). In February 2006, Congress codified all regulatory presumptions that VA had put in place to that time.

The current presumptive disability decision-making process for veterans involves several steps and several organizations. The process involves input from many parties—Congress, VA, the National Academies, and stakeholders (e.g., VSOs, advisory committees, and individual veterans) (Figure S-1). Congress has made presumptions itself. In the current model, Congress or stakeholders acting through Congress may call on VA to assess whether a presumption is needed. The VA turns to IOM for completion of a review of the scientific evidence. The findings of that evaluation are consid-

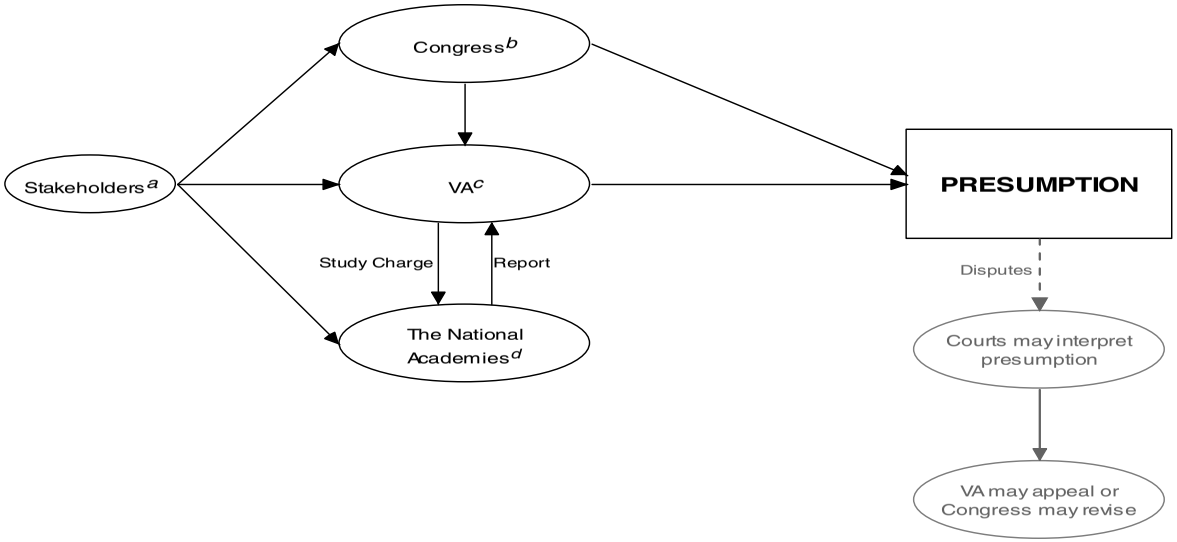

FIGURE S-1 Roles of the participants involved in the presumptive disability decision-making process for veterans.
[a] Stakeholders include (but are not limited to) veterans service organizations (VSOs), veterans, advisory groups, federal agencies, and the general public; these stakeholders provide input into the presumptive process by communicating with Congress, VA, and independent organizations (e.g., the National Academies).
[b] Congress has created many presumptions itself; in 1921, Congress also empowered the VA Secretary to create regulatory presumptions; on several occasions in the past, Congress has directed VA to contract with an independent organization (e.g., the National Academies) to conduct studies and then use the organization's report in its deliberations of granting or not granting regulatory presumptions.
[c] VA can establish regulatory presumptions; VA sometimes contracts with the National Academies to conduct studies and uses the organization's report in its deliberations of granting or not granting regulatory presumptions.
[d] The National Academies (Institute of Medicine and National Research Council) submit reports to VA based on requests and study charges from VA.

ered by VA in its presumptive disability decision-making process. Decisions made in the courts have also influenced the current presumptive process.

Three major legislative actions by Congress have influenced the recent presumptive decisions—the Radiation Exposed Veterans Compensation Act of 1988 (Public Law 100-321. 100th Cong., 2d Sess.), the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.), and the Persian Gulf War Acts of 1995 (Veterans' Benefits Improvement Act of 1994. Public Law 103-446. 103rd Cong., 2d Sess.) and 1998 (Making Omnibus Consolidated and Emergency Appropriations for the Fiscal Year Ending September 30, 1999, and for Other Purposes. Public Law 105-277. 105th Cong., 2d Sess.). The concept of "at least as likely as not" with regard to exposure potential was introduced for radiation exposures and its use has since been continued. The Agent Orange Act (Public Law 102-4. 102d Cong., 1st Sess.) grew out of events following the Vietnam War, and its language expresses substantial and significant elements of the presumptive story. The presumptions put in place by Congress for Gulf War illnesses represent the first time that Congress produced a list of health outcomes that it defined as "undiagnosed illnesses" (Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.).

When Congress enacted the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.), it started a model for a decision-making process that is still in place. Congress asked VA to contract with an independent organization—VA contracted with IOM—to review the scientific evidence for Agent Orange. Since 1994, IOM has produced biennial reports on Agent Orange for VA to use as it considers making presumptive decisions (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b). IOM has also delivered five volumes on the Gulf War (IOM, 2000a, 2003a, 2005a, 2006, 2007). Congress requires VA to respond after receiving an IOM report with a determination as to whether VA will make a service connection for particular health outcomes on a presumptive basis. VA has described its internal decision-making processes to the Committee in a general fashion, and the Committee has reviewed VA's *Federal Register* notices and documents (see Chapter 3). However, it remains unclear to the Committee how VA makes particular determinations with regard to weighing strength of evidence for causation and exposure potential in making its presumptive decisions.

Analysis of the Agent Orange and Gulf War case studies (see Appendix I) shows important similarities and differences relevant to the overall presumptive process. One difference is that Agent Orange is a single product (actually a mixture of compounds that contains the contaminant dioxin), extensively researched for associated health outcomes, whereas the health consequences of the Gulf War are unlikely to be the result of any single agent. Military service men and women may have received a number of health-relevant exposures during service in the Persian Gulf, complicating the development of evidence reviews. For Agent Orange, there is one

exposure of concern and a more constrained set of health indicators. There have been some differences in approaches of Agent Orange and Gulf War committees. The IOM Agent Orange reports (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) did not explicitly include a causal category in their evaluations whereas recent Gulf War reports (IOM, 2000a, 2003a, 2005a, 2006, 2007) did include a category for evidence sufficient to infer causation when characterizing the strength of evidence for agents evaluated. For neither set of reports does VA describe in its *Federal Register* notices how it accounted for exposure potential or magnitude in making its presumptive decisions.

FINDINGS OF CASE STUDIES

The case studies offered a diverse set of lessons learned and indicated elements of the current process that need to be addressed. In carrying out the case studies, this Committee had the opportunity to retrospectively examine the work of IOM committees as they grappled with the challenge of using uncertain evidence and of VA staff as they used the findings of IOM committees to make decisions about presumptions. The case studies demonstrate that the process has acted to serve the interests of veterans in many instances. Congress and VA have repeatedly acted to maximize the sensitivity of presumptive decisions so as to assure that no veteran who might have been affected is denied compensation. On the other hand, in maximizing sensitivity of presumptive disability decision making, substantial numbers of veterans whose illnesses may or may not have been actually service related are nonetheless compensated. There are both financial and nonfinancial costs to such decisions.

The case studies illustrate the use of presumptions to cover gaps in evidence, gaps that exist in part because of lack of information on exposures received by military personnel and inadequate surveillance of veterans for service-related illnesses. Secrecy is a particularly troubling source of incomplete information, as illustrated by the veterans who participated in studies of mustard gas and lewisite. Research carried out directly on the health of veterans has proved useful in some instances, leading to a decision, for example, on granting disability compensation for cardiovascular disease in amputees. But the research has not been systematic, and in the example of cardiovascular disease in amputees no further evidence relevant to a presumption made in 1979 has been collected. Research on radiation risks in veterans has been severely constrained by a lack of dose information, and the studies on radiation-exposed veterans have not been highly informative.

Across the case studies, the Committee found variable approaches to synthesizing evidence on the health consequences of military service. The inferential target of scientific evidence reviews has not been consistent

and varied between causation (e.g., mustard gas and lewisite, Gulf War) and association alone (e.g., Agent Orange). The more recent IOM Agent Orange reports have emphasized findings of observational studies on association and interpretation that might have been enhanced by placing the findings within a biological framework strengthened by greater attention to other lines of evidence. In the Agent Orange case studies, the category "limited/suggestive" for classifying evidence for association has been used for a broad range of evidence from indicating the mere possibility of an association to showing that an association is possibly causal. The "limited/suggestive" evidence of association—on which the VA's presumptive decisions to compensate type 2 diabetes and prostate cancer were made—may be below the level of certainty needed to support causation absent strong mechanistic understanding or to meet the congressional language of "if the credible evidence for the association is equal to or outweighs the credible evidence against the association," which the Committee refers to "at least as likely as not."

Both prostate cancer and type 2 diabetes illustrate situations in which the contribution of military exposures should be assessed against a background of disease risk that has other strong determinants: age in the case of prostate cancer and family history and obesity in the case of type 2 diabetes, as indicated by the IOM committee in its report (IOM, 2000b). For both type 2 diabetes and prostate cancer, the magnitude of the relative risks observed for pesticide exposure implies that the contribution of military exposures is likely to be small in comparison to those of the other contributing factors. In such circumstances, an estimation of the proportion of cases attributable to military exposures could be helpful to the VA in considering whether or not to presumptively service-connect disabilities. The Committee recognizes that development of such estimations is a complicated process dependent on acquiring better exposure data, which may not be available for some period of time.

In the case studies, the Committee's analyses were based on the very general information provided by VA about its internal decision-making processes. The case studies and VA's decision to withhold documents related to specific decisions from the Committee did make clear, however, that these processes are not fully transparent. VA believes that access to predecisional documents by outside sources could stifle candid staff discussions on issues. Once IOM carries out its reviews and provides VA with reports documenting the extent of evidence available on associations, the internal processes of VA that follow are not fully open to scrutiny. This closed process could reduce trust of veterans in the presumptive disability decision-making process and may hinder efforts to optimize the use of scientific evidence. The Committee also found inconsistency in the decision-making process.

SCIENTIFIC FOUNDATION FOR PRESUMPTIVE DISABILITY DECISION MAKING

In developing a future approach for presumptive disability decision making, the Committee first gave extensive consideration to causal inference and the processes used to make causal judgments. In other words, the Committee considered how scientific evidence is used to determine *if* exposure causes some disease. These determinations are generally made by expert committees that examine all relevant evidence for strengths and weaknesses and then synthesize the evidence to make a summary judgment. The Committee defines "exposure" in a broad manner to include chemical, biological, infectious, physical, and psychological stressors. The Committee recognizes that psychological stressors may be particularly difficult to describe, let alone measure and quantify.

The Committee then considered the quantification of the contribution of a particular exposure to disease causation. This second issue addresses the question of *how much* of the observed disease in a group, in both absolute and relative terms, is caused by the exposure.

Provision of compensation to veterans on a presumptive basis, or to any other group that has been injured, requires a *general* decision as to whether the agent or exposure of concern has the potential to cause the condition or disease for which compensation is to be provided in at least some individuals, and a *specific* decision as to whether the agent or exposure has caused the condition or disease in a particular individual. The determination of causation in general is based in a review and evaluation of all relevant evidence including (1) data on exposures of military personnel during service; (2) evidence on risks for disease coming from observational (epidemiologic) studies of military personnel; (3) other relevant epidemiologic evidence, including findings from studies of nonmilitary populations exposed to the agent of interest or similar agents; and (4) findings relevant to plausibility from experimental and laboratory research. The determination of causation in a particular case is based first on the general determination as to whether the exposure can cause disease, then on information about the exposures of the individual being evaluated for compensation, and on any other relevant information about the individual.

The Committee considered the properties of a decision-making process, recognizing the possibility of two types of systematic errors: making a decision to compensate when the exposure has not caused the illness (false positive) and to not compensate when the exposure has actually caused the illness (false negative). The Committee recommends that any decision process consider the trade-off between these two errors and attempt to optimize both the sensitivity (i.e., minimize the false negatives) and the specificity (i.e., minimize the false positives). Generally, higher sensitivity

cannot be achieved without lower specificity. These errors have costs. False positive errors result in the expenditure of funds for cases of disease not caused by military service while false negative errors leave deserving veterans uncompensated. The appropriate balancing of these costs also needs consideration.

The Committee considered ways to classify evidence, reaching the conclusion that a broader and more inclusive evidence review process is needed. It found that IOM reviews could be enhanced if a broader array of epidemiologic and other evidence (e.g., animal and mechanistic data) was considered. The Committee also found that the target of inference had varied from causation (e.g., mustard gas and lewisite, Gulf War) to association (e.g., Agent Orange). Consequently, the Committee recommends that categories of evidence for reviews be established to make clear those relationships that are at least as likely as not to be causal. The Committee has concluded that a categorization of evidence is needed that gives a scientifically coherent rendering of the language employed by Congress in calling for review of available scientific evidence. The Committee proposes a four-level hierarchy that classifies the strength of evidence for *causation, not just association,* and that incorporates the concept of equipoise: that is, whether the weight of scientific evidence makes causation at least as likely as not in the judgment of the reviewing group.

The Committee also gave consideration to the quantification of the burden of disease attributable to an exposure. This quantification would be made to provide an evaluation of the numbers of veterans to be compensated, but it would not be a component of the evidence evaluation for causation. For the purpose of quantification, the attributable risk, termed the *service-attributable fraction*, can be calculated if the needed information is available on the relative risk of disease among exposed individuals. For those exposures meeting the necessary level of evidence for compensation, the Committee recommends that the service-attributable fraction should be estimated overall and for subgroups of veterans, perhaps grouped by level of exposure, if the requisite data are available. Until more complete exposure information becomes available in the future, such calculations may not be possible for all conditions for which presumptions are made.

COMMITTEE'S RECOMMENDED APPROACH FOR THE FUTURE

Overview

The Committee's recommended approach for the future (Figure S-2) has multiple new elements: a process for proposing exposures and illnesses for review; a systematic evidence review process incorporating a new evidence classification scheme and quantification of the extent of disease

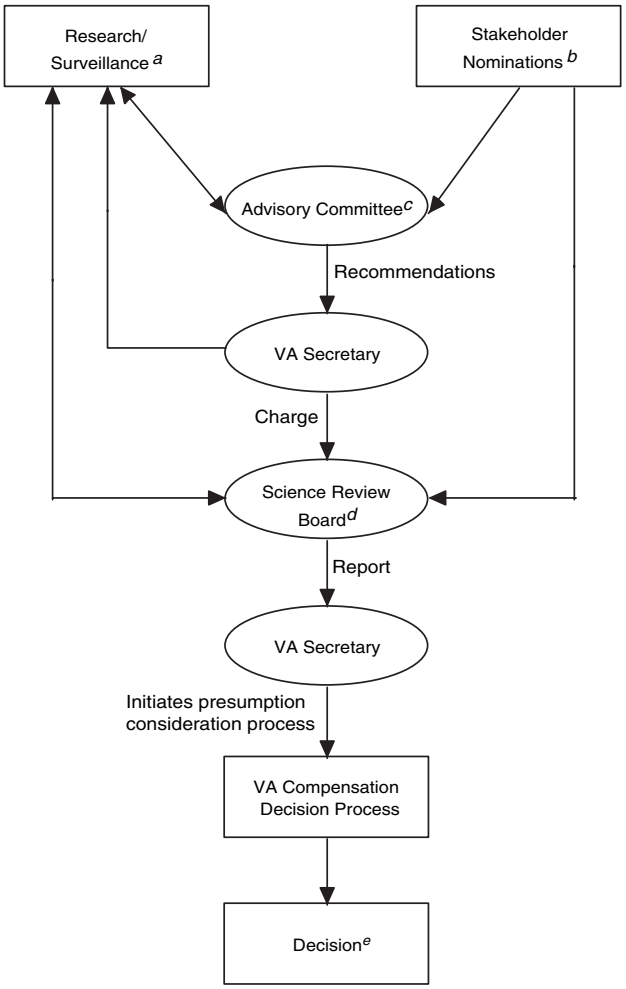

FIGURE S-2 Proposed framework for future presumptive disability decision-making process for veterans.

[a] Includes research for classified or secret activities, exposures, etc.

[b] Includes veterans, Veterans Service Organizations, federal agencies, scientists, general public, etc.

[c] This committee screens stakeholders' proposals and research in support of evaluating evidence for presumptions and makes recommendations to the VA Secretary when full evidence review or additional research is appropriate.

[d] The board conducts a two-step evidence review process (see report text for further detail).

[e] Final presumptive disability compensation decisions are made by the Secretary, Department of Veterans Affairs, unless legislated by Congress.

attributable to an exposure; a transparent decision-making process by VA; and an organizational structure to support the process. The Committee also calls for comprehensive tracking of exposures of military personnel and monitoring of their health while in service and subsequently.

Organizational Structure

The Committee recommends the creation by Congress of two new permanent boards: the Advisory Committee, serving in an advisory capacity to VA, and the Science Review Board (independent from VA). The Advisory Committee would consider the exposures and illnesses that might be a basis for presumptions and recommend to the VA Secretary exposures and illnesses needing further consideration. It would also consider research needs and assist VA with strategic research planning. The Science Review Board would evaluate the evidence for causation and, if warranted, estimate the service-attributable fraction of disease in veterans. One critical element in the deliberations of the Science Review Board would be evidence from monitoring the exposures and health of the veterans. The Science Review Board would provide VA with input for its presumptive decisions, including a summary report of the available scientific evidence in a standardized classification scheme.

Congress and VA may find alternative processes to achieve the overall objective of the Committee's recommendations: an evidence-based approach to making presumptive disability decisions. The Committee recognizes that specific elements of its proposal (e.g., the call for carrying out exposure assessments and making exposure estimates) are not yet fully practicable and would take time to develop and implement. However, future methodologic developments should enhance the feasibility of some of the challenging elements of this proposal. The Committee believes that this proposal can significantly improve the presumptive disability decision-making process for veterans and, therefore, the process for implementing it should begin without delay.

Underlying Principles

VA's decision to make a presumption may involve weighing difficult and incomplete scientific evidence, in the context of veterans' concerns and society's obligations to the affected veterans, and potential costs. Although the potential complexity of the decision-making process may make a complete codification difficult, the underlying principles can be clearly expressed. The Committee suggests the following six principles as a foundation for its proposed framework: (1) stakeholder inclusiveness; (2) evidence-based decisions; (3) transparent process; (4) flexibility; (5) consistency; and (6) using

causation, not just association, as the basis for decision making. Flexibility and consistency are not contradictory constructs here. Flexibility refers to the ability to be adaptable through time in evaluating scientific evidence, and consistency refers to being consistent in the process of evaluating evidence and making consistent decisions based on a comparable level of certainty based on the scientific evidence.

Proposals to Review for Potential Presumption

In this process, conditions and causative agents or circumstances would be proposed for review based on evidence of a connection between the condition and military service and evidence that a sizable or well-defined group of veterans is likely to be affected. The possibility of a need for a presumption might arise from surveillance of veterans or active military personnel, laboratory research discoveries, or findings from studies of exposed workers. The process would be open, with proposals accepted from any source (e.g., veterans, veterans' families, VSOs, VA, DoD, other governmental bodies, researchers, the general public). Proposals accepted by the VA Secretary would be sent to the Science Review Board for full, comprehensive scientific evaluation.

Science Review Board

The Committee recommends a two-step process for scientific evaluation by the Science Review Board. The first step would involve a systematic review of all relevant data to decide the strength of evidence for causation, using one of four categories:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

If the evidence for causation were categorized as *Sufficient* or at *Equipoise and Above*, then we anticipate that VA would consider a presumptive service connection based upon causal evidence categorization and its consideration of the service-attributable fraction if available (to be estimated in the second step of the process, described below). As is current VA policy,

if the evidence is at *Equipoise*, the benefit of the doubt would be given to the veteran. If the evidence were categorized as *Against*, then we anticipate that VA would not consider a presumptive service-connection. If, however, the evidence were categorized as *Below Equipoise*, then we anticipate that VA would, after carefully considering the prospects and recommendations for future research, decide on an appropriate time frame for the subsequent scientific review of the evidence, with the expectation that the evidence would then be sufficient to resolve matters either for or against the causal claim at that time. Such information would be considered by the Advisory Committee serving in its capacity as overseer of the overall process and advisor to the VA Secretary.

If the VA Secretary were to decide that a presumption would not be established for evidence categorized as *Below Equipoise* or, for other reasons, for evidence categorized as *Equipoise and Above*, then during the period of further evidence development and gathering and prior to the subsequent scientific review of the evidence, VA should consider providing some support to potentially affected veterans, such as providing provisional access to medical care.

As evidence accumulates, the balance might move to strengthen or to weaken the case for causality. Importantly, the Science Review Board should be free to upgrade the level of evidence, to downgrade the level of evidence, or to leave it as the same categorization. For evidence that has reached the classification of *Sufficient*, we would not anticipate a potential lowering of the classification, if the original determination was correctly made and based on sound scientific evidence.

If the strength of the evidence reaches *Sufficient* or *Equipoise and Above*, then the evaluation would move to step two, the calculation of the service-attributable fraction of disease when required data and information are available. This calculation is independent of the classification of the strength of evidence for causation, and the magnitude of the service-attributable fraction is not considered in the application of the four-level schema for categorizing evidence. Rather, the service-attributable fraction would be of value for decision making, giving an understanding of the scope of the population to be covered by a presumption.

In step two, the Science Review Board would consider the extent of exposure among veterans and subgroups of veterans, as well as dose-response relationships. When such information is available, the board would estimate the service-attributable fraction and its related uncertainty. The purpose of step two is to convey the impact of the exposure on veterans as a whole for the purpose of decision making and planning, but not to serve inappropriately as an estimate of probability of causation for individuals. Some exposures may contribute greatly to the disease burden of veterans, while other exposure (even with a known causal effect) may have

a small impact overall. This additional information would be useful to VA in its decision making as to whether a presumption should be made for the veteran population in general, for subgroups, or not at all. In the absence of service-attributable fraction data, as will likely occur for many exposures over the short term, we assume the VA would consider presumptions on the information contained in step one.

Expanding the Evidence Base

In the Committee's view, the best scientific decisions about presumptions can be made only with comprehensive exposure and health surveillance of military personnel. Data collection should begin on entry into the military and continue through discharge, and when harmful exposures are suspected surveillance should be extended indefinitely. Surveillance refers to the ongoing collection, analysis, and use of data relevant to the health of a population. Elements of a surveillance system are already in place, but fall short of what is required. A fully functioning surveillance system would track military exposures and health outcomes, during military service and after discharge, and maintain a repository of data and biological specimens so that emerging and unanticipated questions could be retrospectively addressed. The system needs to be seamless in following military personnel, including National Guard and reservists, from active duty as they transition and become civilians.

This surveillance system should also track job and deployment history for each Service member through the period of service, with exposure assessment and monitoring for a range of job categories. Information on disease risk factors more generally could also be tracked. Use of personal biological samples for individual monitoring also holds promise.

Assessing exposures relevant to the neuropsychiatric disorders that are frequent among veterans of recent and current combats is particularly problematic. Documentation of stress is requisite to the diagnosis of post-traumatic stress disorder (PTSD), but approaches for capturing exposures to such stressors and to the circumstances of combat have not yet been developed and put into place. Research is needed for this purpose that builds on existing approaches so that data become available over the long-term.

In addition to surveillance, the Committee recommends an effort to coordinate and focus research on the health effects of military exposures. Associations identified in the surveillance data might need follow-up through more focused epidemiologic studies or exposure assessments. Toxicological research might be indicated to explore the mechanistic basis for an association between an exposure and a health condition.

VA Procedures

Ultimately, the decision regarding which proposed topics for potential presumptions deserve full evaluation resides with VA. In the Committee's proposed process, VA also receives scientific input from the Science Review Board. We recommend that VA establish a uniform and transparent process for making decisions regarding presumptions following receipt of evidence reviews. VA should establish procedures with input from the many stakeholders, and a clear, evidence-based rationale should be offered for all decisions. The Committee's recommendations are aimed at providing a sound scientific framework for the presumptive disability decision-making process. The Committee clearly recognizes that there are social, economic, political, and legal factors beyond the scope of scientific evidence that may influence the presumptive disability decision-making process for veterans and the presumptive decisions that are established by Congress and VA.

Scientific evidence is not static, and it often is less than certain. Given that the scientific basis for presumptive decisions will change over time, the Committee recommends that VA should be able to adjust future decisions when such change is scientifically justified. This does not mean that the Committee recommends that benefits previously granted should be terminated. The Committee is aware that disabled veterans and their families are often dependent on such payments and that it could create a hardship to remove them, a matter that VA disability policy recognizes in other situations.

SPECIFIC RECOMMENDATIONS

Based on its evaluation of the current process for establishing presumptive disability decisions and its consideration of alternatives, the Committee has specific recommendations for an approach that would build stronger scientific evidence into the decision-making process and, at the same time, be even more responsive and open to veterans. We propose a transformation of the current presumptive disability decision-making process. We recognize that considerable time would be needed to implement some of these recommendations as would additional investment to create systems needed to track exposures and health status of currently serving military service personnel and veterans. Progress depends on greater research capacity and improvements in the evaluation and utilization of scientific evidence in making compensation decisions. We find that there are elements of the current process that could be changed quickly and we recommend that VA consider prompt action as it moves toward implementation of a new approach. The recommendations that follow are based around the Committee's proposed framework for making presumptive decisions. We list the recommendations in relation to the appropriate body.

Congress

Recommendation 1. Congress should create a formal advisory committee (Advisory Committee) to VA to consider and advise the VA Secretary on disability-related questions requiring scientific research and review to assist in the consideration of possible presumptions.

Recommendation 2. Congress should authorize a permanent independent review body (Science Review Board) operating with a well-defined process that will use evaluation criteria as outlined in this Committee's recommendations to evaluate scientific evidence for VA's use in considering future service-connected presumptions.

Department of Veterans Affairs

Recommendation 3. VA should develop and publish a formal process for consideration of disability presumptions that is uniform and transparent and clearly sets forth all evidence considered and the reasons for the decisions reached.

Science Review Board

The recommendations that follow are directed towards the proposed, future Science Review Board, the entity to be established in the Committee's proposed approach.

Recommendation 4. The Committee recommends that the goal of the presumptive disability decision-making process be to ensure compensation for veterans whose diseases are *caused by* military service and that this goal must serve as the foundation for the work of the Science Review Board. The Committee recommends that the Science Review Board implement its proposed two-step process.

Recommendation 5. The Committee recommends that the Science Review Board use the proposed four-level classification scheme, as follows, in the first step of its evaluation. The Committee recommends that a standard be adopted for "causal effect" such that if there is at least as much evidence in favor of the exposure having a causal effect on the frequency or severity of disease as there is evidence against, then a service-connected presumption will be considered.

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.

2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

Recommendation 6. The Committee recommends that a broad spectrum of evidence, including epidemiologic, animal, and mechanistic data, be considered when evaluating causation.

Recommendation 7. When the causal evidence is at Equipoise and Above or Sufficient, the Committee recommends that an estimate also be made of the size of the causal effect among those exposed.

Recommendation 8. The Committee recommends that, as the second part of the two-step evaluation, the relative risk and exposure prevalence be used to estimate an attributable fraction for the disease in the military setting (i.e., service-attributable fraction).

Department of Defense and Department of Veterans Affairs

The following recommendations are intended to improve the evidence on exposures and health status of veterans:

Recommendation 9. Inventory research related to the health of veterans, including research funded by DoD and VA, and research funded by the National Institutes of Health and other organizations.

Recommendation 10. Develop a strategic plan for research on the health of veterans, particularly those returning from conflicts in the Gulf and Afghanistan.

Recommendation 11. Develop a plan for augmenting research capability within DoD and VA to more systematically generate evidence on the health of veterans.

Recommendation 12. Assess the potential for enhancing research through record linkage using DoD and VA administrative and health record databases.

Recommendation 13. Conduct a critical evaluation of Gulf War troop tracking and environmental exposure monitoring data so that improvements can be made in this key DoD strategy for characterizing exposures during deployment.

Recommendation 14. Establish registries of Service members and veterans based on exposure, deployment, and disease histories.

Recommendation 15. Develop a plan for an overall integrated surveillance strategy for the health of Service members and veterans.

Recommendation 16. Improve the data linkage between the electronic health record data systems used by DoD and VA—including capabilities for handling individual Service member exposure information that is included as part of the individual's health record.

Recommendation 17. Ensure implementation of the DoD strategy for improved exposure assessment and exposure data collection.

Recommendation 18. Develop a data interface that allows VA to access the electronic exposure data systems used by DoD.

Recommendation 19. DoD and VA should establish and implement mechanisms to identify, monitor, track, and medically treat individuals involved in research and other activities that have been classified and are secret.

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1

Introduction

Veterans and their families have served the American people and our country in ways that cannot easily be summarized or measured. Our nation has long recognized and honored military veterans' service and sacrifices. From the very beginning, benefits have been provided to those whose illnesses were incurred or aggravated by their military service. Ascertaining whether an illness is service connected is not unduly difficult when the illness emerges while the person is engaged in military service. But when an adverse health effect becomes manifest after military service, at times many years later, determining and proving a service connection may raise complex scientific and policy questions.

Presumptions enable veterans to be granted service connection who, through no fault of their own, are unable to establish that the injury was caused by their military service. Since 1921, Congress and the Department of Veterans Affairs (VA) have created numerous presumptions to assist veterans in establishing that they have a service-connected disease entitling them to disability payments (see Appendix D for an historical overview).

Much has happened since 1921 that has made the presumptive disability decision-making process more critical and complex. Fortunately, a far greater percentage of service men and women are surviving combat injuries, and the life expectancy of all veterans has greatly increased. As a result, disability payments are made for much longer periods, and recipients may develop medical complications that were much less frequent when presumptions were first employed. In addition, warfare has changed. Service personnel are subjected to numerous new types of exposures, about some of which we know very little. On the other hand, we understand a good

deal more now about disease processes because of recent research based in epidemiology, toxicology, and genetics. This report proposes a framework for presumptive disability decision making that would employ our best scientific understanding while protecting the interests of veterans and other stakeholders by including them in the decision-making process. It provides findings from a committee convened to assess the current approach of the presumptive disability decision-making process for veterans and to provide a framework for a future approach. The committee was appointed by the Institute of Medicine (IOM) of the National Academies at the request of a special congressional commission (see below).

VETERANS' DISABILITY BENEFITS COMMISSION

The Veterans' Disability Benefits Commission (Commission) was created by the National Defense Authorization Act of 2004 (Public Law 108-136. 108th Cong., 1st Sess.). The Commission is charged with "studying the benefits provided to compensate and assist veterans for disabilities attributable to military service. The Commission was mandated to consult with the Institute of Medicine (IOM) of the National Academy of Sciences with respect to the medical aspects of contemporary disability compensation policies" (VDBC, 2006, p. 1; as found in Appendix A). The Commission was asked to evaluate and assess the following:

- The appropriateness of benefits
- The appropriateness of the level of those benefits
- The appropriate standard(s) for determining whether the disability should be compensated (VDBC, 2006, p. 1; as found in Appendix A)

To meet its goals, "the Commission produced a list of 31 research questions to be answered during its investigation" (VDBC, 2006, p. 1; as found in Appendix A). The Commission requested two studies from IOM. This report will address the issue of presumptions. Another committee, the Committee on Medical Evaluation of Veterans for Disability Compensation, issued a report entitled *A 21st Century System for Evaluating Veterans for Disability Benefits*, in June 2007. That report made recommendations to the Commission on how several components of VA's medical evaluation and disability rating process for veterans could be updated and improved.

The independent Commission "consists of 13 members who were appointed by the President and the leaders of Congress" (VDBC, 2006, p. 1; as found in Appendix A) and is funded by VA. Twelve of the commissioners have served in the military. Nine members have combat experience. "The Commission is charged to submit its report by October 1, 2007, to

the President and Congress" (VDBC, 2006, p. 1; as found in Appendix A). The Commission's website is www.vetscommission.org.

IOM COMMITTEE CHARGE AND APPROACH

In response to a request from the Veterans' Disability Benefits Commission, IOM constituted the Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans (Committee). To address the charge from the Commission, IOM assembled 14 full committee members, 1 volunteer scientific consultant, and 1 paid consultant—all with diverse backgrounds and expertise. The Committee's website is www.iom.edu/pddm.

As the independent Commission does not have its own funding source, this study was funded by VA. The task order description provided by VA is to (1) describe and evaluate the current model used to recognize diseases that are subject to service connection on a presumptive basis; and (2) if appropriate, propose a scientific framework that would justify recognizing or not recognizing conditions as presumptive.

The Committee gained many insights from a four-page statement clarifying the task order that was presented to the Committee at its first meeting by Commissioner John Grady (Grady, 2006; VDBC, 2006; as found in Appendix A). The statement emphasized that the granting of a presumptive service connection be "based on the best scientific evidence available" (VDBC, 2006, p. 4; as found in Appendix A). The Commission asked the Committee to "evaluate the current model used to determine diseases that qualify for service connection on a presumptive basis, and if appropriate, propose improvements in the model" (VDBC, 2006, p. 1; as found in Appendix A). The Commission emphasized that "having a method of granting service connection quickly and fairly based on a presumption is of critical importance to our disabled veterans and their surviving spouses," and asked the Committee to consider process improvements to address the long periods of elapsed time before presumptions are established (VDBC, 2006, pp. 3-4; as found in Appendix A).

During the first meeting, the Committee asked questions of the commissioners to further clarify the charge. In responding, the Commission indicated that it did not expect a full, exhaustive review of all presumptions established since 1921 and that a review of case studies would facilitate the Committee's understanding of the current process. The Commission also clarified the scope of the evaluation, indicating that it would like the Committee to evaluate all participants in the current process—including Congress, VA, IOM, veterans stakeholders, and any others—and to thoroughly assess the processes currently used to make presumptions, as well as in the past, since an understanding of past processes would be instructive in

considering possible future processes (as stated during Commission Panel discussion on May 31, 2006; VDBC, 2006, as found in Appendix A). The Committee approached the review of present and past processes and practice, including the roles and responsibilities of the different parties involved, through a series of case studies (see Appendix I). The Commission asked if there should "be a defined process in place at VA to review and establish presumptions" and if "the same or a different process should be used periodically to review existing presumptions" (VDBC, 2006, p. 3; as found in Appendix A). The Committee deliberated the case studies to learn the past processes of presumptive decisions and to develop its proposed framework for the future of the presumptive disability decision-making process.

At the heart of such processes are the principles used by participants for evaluating evidence on whether or not an effect was caused by military service. The Commission therefore asked about the "amount of increase in occurrence rate . . . to warrant compensation" and for "advice, from an epidemiologic and statistical standpoint, on what strength of evidence would be the appropriate requirement when the Secretary of Veterans Affairs considers whether to establish a presumption" (VDBC, 2006, p. 3; as found in Appendix A). These requests address considerations of magnitude of risk and strength of evidence in making presumptive decisions, and the methodology used in determining causal relationships. These issues became a cornerstone for future Committee discussions regarding the use of causation versus association, interpretation of population versus individual risks, and use of attributable fraction or probability of causation for compensation purposes.

An important legal definition the Committee discussed throughout the study process was that "an association is considered 'positive' if the credible evidence for the association is equal to or outweighs the credible evidence against the association" (VA, 1996, p. 41368). This legal definition was an important part of deliberations for the Committee and became the foundation for the Committee's proposed strength of evidence categories.

Finally, the Commission asked the Committee to address some specific issues. First, several presumptions have been established "because it was not possible to document exposure to biological, chemical, radiological, or other environmental agents by accurate information on the exact locations to which military [S]ervice members were assigned during precise periods of time" (VDBC, 2006, p. 2; as found in Appendix A). The Commission stated the Committee "may be able to provide substantive advice concerning how to ensure that this situation is not repeated in the future" (VDBC, 2006, p. 3; as found in Appendix A). Second, in its statement, the Commission asked if the case of Vietnam veterans with diabetes and prostate cancer was fully supported by medical evidence for these presumptions (VDBC, 2006; as found in Appendix A). When the Committee questioned

the commissioners whether the intent was for the Committee to reevaluate the body of evidence for these presumptions, it was determined that this was beyond the charge of the Committee (as stated during Commission Panel discussion on May 31, 2006; VDBC, 2006; as found in Appendix A). However, the Committee did decide to include these two presumptions as part of the case study series to learn more about the processes that put these presumptions in place.

INFORMATION GATHERING BY THE COMMITTEE

The Committee engaged in extensive information gathering while conducting its inquiries. This enabled the Committee to develop the case study series, review the work and processes of VA and of the National Academies' (IOM and National Research Council [NRC]) committees, consider congressional mandates and intent, consider future possible approaches for making presumptions, and review the underlying current and planned Service member and veteran surveillance systems at the Department of Defense (DoD) and VA that could support the presumptive decision-making process. The Committee collected and reviewed hundreds of public laws, congressional committee reports, federal government reports, National Academies' (IOM and NRC) reports, as well as other documents.

The Committee also held three open session meetings—on May 31, July 27, and October 4, 2006—for information gathering purposes. The agendas for these meetings may be found in Appendix B. The Committee heard from the key participants in the presumptive disability decision-making process for veterans during these meetings—past and present congressional staff, VA representatives, IOM representatives, DoD representatives, veterans service organizations (VSOs), veterans, and the general public. Among the VSOs the Committee heard from were the American Legion, AMVETS, NAM-POWS Corporation, Non-Commissioned Officers Association, Texas Veterans Commission, United Spinal Association, Veterans for America, Veterans of Foreign Wars of the United States, and Vietnam Veterans of America. The individuals who participated are noted in the acknowledgments.

To better and more clearly understand VA's process and how it uses the National Academies' (IOM and NRC) reports, the Committee asked VA for task force reports, working group documents, and cost estimate documents that related to specific, past presumptive decisions. VA declined the request to release these documents on the basis of the predecisional nature of the documents (Mansfield, 2006). As an alternative, VA offered to respond to questions offered by the Committee. A list of questions was prepared in writing by the Committee. VA did not respond to all of the Committee's questions and cited similar reasons for not responding as were expressed

previously with regard to release of VA's task force documents (Dunne, 2006).

Availability of VA Documents

The IOM Committee sought to review VA's decision-making documents to better understand the factors considered in making recommendations by the working group and task force. These were not made available because VA considered them to be predecisional and possibly sensitive. As an alternative, VA prepared a white paper (found in Appendix G) that provides a general description of VA's decision process following the receipt of an IOM report on Agent Orange or the Gulf War. VA also offered to respond to Committee questions regarding VA's presumptive decision-making procedures. The Committee submitted questions, and VA responded to several but not all of them (VA, 2006). In a letter to the Committee Chair, VA explained it was reluctant to respond to some of the questions for the following reasons:[1]

- The requested answers would cause VA to describe the contents of memoranda and notes of internal meetings that are pre-decisional, and reflective of internal deliberations of VA personnel who advise the Secretary of Veterans Affairs on matters of policy and law.
- In order to ensure that the Secretary receives the best possible advice, VA personnel must remain free to engage in vigorous discussion of important issues facing the Department without the constraints that necessarily would apply, if their deliberations were subject to external review.
- Statements made in the context of robust deliberations, if viewed apart from that context, may be misconstrued or misrepresented.
- The possibility of public disclosure may inhibit free discussion in future deliberations and needlessly limit the thorough and thoughtful consideration that must attend the formulation of policies affecting our Nation's veterans.
- Providing the requested answers to the Presumptions Committee may effectively waive any protections VA would have against broader public disclosure of this pre-decisional information.

It should be noted that the Committee offered to receive redacted documents in accordance with the provisions of the Freedom of Information Act, but that offer was not accepted by VA. Similar reasons were given for not providing working group and task force reports to the Committee. In a separate letter to IOM, the Deputy Secretary of Veterans Affairs, Gordon

[1]Personal communication, P. W. Dunne, Department of Veterans Affairs, December 2006.

H. Mansfield, indicated VA was "concerned that statements made in the context of robust deliberations, if viewed apart from that context, may be misconstrued or misrepresented for purposes of litigation or other ends."[2] The Committee believes that this report has been limited to some degree by lack of access to requested documents, to an extent we cannot assess without actually seeing the documents.

ORGANIZATION OF THE REPORT

This report is organized into 13 chapters with supporting appendixes. Chapters 2 through 5 address the historical and current presumptive disability decision-making process for veterans and describe how it is working. An overview of presumptive disability decisions established by Congress and VA since 1921 is found in Chapter 2. Chapter 3 describes the current presumptive disability decision-making process, and the roles of Congress, VA, and IOM. The legislative background pursuant to the more current presumptions of Radiation, Agent Orange, and Gulf War is included in Chapter 4. Chapter 5 summarizes the past and current practices found in the Committee's 10 case studies (see Appendix I):

- Mental Disorders' Presumptions
- Multiple Sclerosis Presumption
- Prisoners of War Presumptions
- Amputees and Cardiovascular Disease Presumption
- Radiation Presumptions
- Mustard Gas and Lewisite Presumptions
- Gulf War Presumptions
- Agent Orange and Prostate Cancer Presumption
- Agent Orange and Type 2 Diabetes Presumption
- Spina Bifida Program (VA program but not a presumption)

The lessons learned from these case studies provided valuable insights into past and current processes, as well as presenting opportunities for process improvements by all participants in the presumptive disability decision-making process.

The second part of the report (Chapters 6-13) focuses on methodological aspects of the process, laying the foundation for a path forward, and proposes a process for establishing presumptions in the future. Following an overview of an evidence-based framework for making presumptive decisions in Chapter 6, Chapters 7 and 8 lay the groundwork for developing

[2]Personal communication, G. H. Mansfield, Department of Veterans Affairs, December 2006.

methods to consider whether a substance or exposure may cause a specific health condition of concern. Chapter 9 then focuses on to what extent military service could be responsible for a specific health condition in veterans (in general or in a group of veterans)—taking as a given that an exposure during military service can cause the illness. Accurate evidence is critical for the process of conducting the assessments discussed in Chapters 7 through 9. Chapter 10 summarizes health and exposure data systems within DoD for collecting exposure, incidence, and health status information during service, and within VA and other organizations for following military personnel after they leave service and through the remainder of their lives. Chapter 10 offers suggestions for improved research and surveillance to better support the presumptive disability decision-making process. Secrecy leads to gaps in evidence, and Chapter 11 therefore addresses governmental classification and secrecy. These earlier chapters are preparatory to Chapter 12, which introduces "The Way Forward" with the Committee's proposed framework for the future of presumptive disability decision making for veterans. Chapter 13 presents the Committee's recommendations to Congress, VA, a Science Review Board, and DoD.

The appendixes contain information organized by the Committee and IOM staff that may assist the reader who wishes to further delve into the issues and historical background on presumptions. In addition to the appendix material introduced earlier (i.e., Commission statement, meeting agendas), the appendixes include acronyms, abbreviations, and a glossary (Appendix C), an overview of the current compensation system and its historical context (Appendix D), summary tables of the presumptive decisions established by Congress and VA since 1921 (Appendix F), VA's White Paper (Appendix G), IOM's Agent Orange and Gulf War Statements of Tasks and Conclusions (Appendix H), the complete series of case study chapters (Appendix I), additional background material on causation and statistical causal methods (Appendix J), additional background material on exposure and health data for veterans (Appendix K), and additional classification and secrecy information (Appendix L). Finally, Appendix M provides brief biographical information for Committee members, consultants, and selected staff responsible for this effort.

The Committee was not asked to and did not make judgments regarding specific cases in which individual veterans have claimed injuries and illnesses. This report neither supports nor criticizes the presumptive decisions Congress and VA have established since 1921. As well, the Committee did not make recommendations for any new, specific presumptions. These areas were beyond the Committee's charge. However, the Committee did review, analyze, and report on the available information regarding the presumptive disability decision-making process for veterans.

COMMITTEE MEMBERS' COMMITMENT TO VETERANS

All Committee members agreed to serve on this effort because of the importance of the issue and because of their deep gratitude and respect for those serving in the military and veterans who have served in the past. We submit this report with the hope that our effort will be to the benefit of those who have served in the past and who will serve in the future.

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2

A Brief History of Presumptive Disability Decisions for Veterans

INTRODUCTION

Presumptions have played an important role in both the conceptual basis for service connection and the actual administration of the Department of Veterans Affairs (VA) compensation program. Presumptions are used to bridge gaps in scientific and medical knowledge, as well as to resolve complex policy questions and simplify determinations of service connection for VA (VA, 1993a). This chapter offers a brief history of the presumptive disability decisions established for veterans since 1921. It is not intended as a comprehensive or exhaustive account of all presumptive decisions; rather, it provides background on presumptions—it explains how they operate, why they are used, and their role in making disability compensation available to veterans. The chapter focuses on presumptions for health outcomes rather than administrative presumptions. For a comprehensive review of presumptive decisions, the reader is referred to *Analysis of Presumptions of Service Connection* (VA, 1993a), *Presumptions of Service Connection* (Zeglin, 2006), *VA Disability Compensation Program: Legislative History* (Economic Systems Inc., 2004a), and *VA Disability Compensation Program: Literature Review* (Economic Systems Inc., 2004b).

What Is a Presumption?

In the law, there is general agreement about what a presumption is, although there is considerable controversy about what a presumption does. A presumption is a procedural device that dictates that once basic fact A is

established, the existence of fact B must be assumed unless the presumed fact is rebutted. A presumption therefore operates to relieve a party of the burden of establishing facts that it would otherwise be required to prove in order to prevail on its claim. A presumption that cannot be rebutted is a rule of substantive law; it does not satisfy the definition of a presumption because fact B must be assumed conclusively rather than conditionally. It does not allow for the possibility that fact B can be disproved.

A legislature has numerous choices when drafting a presumption; there is no uniform terminology that must be employed. To ensure passage, presumptions are often couched in somewhat ambiguous terms, particularly when they deal with sensitive and controversial policy issues. The result may be a deliberate fuzziness and ambiguity in the language that governs a particular presumption that will ultimately require recourse to the courts (Allen, 1980). Consequently, it is not always simple to determine precisely why a particular presumption was adopted or how it should be interpreted.

Why Are Presumptions Created?

Presumptions are created for a number of reasons. They promote fairness by simplifying proceedings and by making it less burdensome for claimants to gather evidence that is more accessible to the party against whom the claim is asserted. When the probability of the presumed fact's existence is high if the basic fact exists, presumptions eliminate the expense and time that would be required to establish the presumed fact by direct evidence. Sometimes presumptions are established for policy reasons because of a desire to make it easier for particular types of claimants to establish their claims. This may for instance be true for veterans' claims when information needed for an epidemiologic assessment, such as exposure data, is unavailable because it was not collected at the relevant time. Gratitude and sympathy for those who served their country obviously also play an important role (Reagan, 1988).

What Does a Presumption Do?

A true presumption affects the burden of proof. This can, however, mean different things as legislators, administrators, and judges do not always use consistent terminology to express their intentions. *Burden of proof* is a term used to label two different concepts: the burden of production and the burden of persuasion (*Director, Office of Workers' Compensation Programs, Department of Labor v. Greenwich Collieries et al.*, 1994. 512 U.S. Supreme Court 267, Case No. 93-744). See 512 U.S. Supreme Court 267, Case No. 93-744, for an extensive discussion of the evolution

of the term *burden of proof*. A claimant or plaintiff ordinarily begins with both burdens. For instance, a veteran who relies on direct proof to show that he has a service-connected disability must generally both (1) produce evidence on that issue, and (2) persuade VA that the service connection exists.

Types and Categories of Presumptions

There are two major types of presumptions. Type 1 presumptions shift both the burden of production and the burden of persuasion. Type 2 presumptions have a lesser effect. For type 2 presumptions, establishment of the basic fact does not shift to the other party the burden of persuading the adjudicator that the presumed fact does not exist. The other party of the presumption only has to produce evidence that is contrary to, or meets the presumption. If the other party does so, the presumption vanishes, and the party with the original burden of persuasion—the party that had to establish the basic fact—continues to have the burden of proving the presumed fact.

The difference between type 1 and 2 presumptions can be illustrated by the presumption of death after an unexplained absence of 7 years. If the presumption is a type 2 presumption, as it would be under the Federal Rules of Evidence unless Congress provides otherwise (Federal Rules of Evidence: Rule 301: Presumptions in General Civil Actions and Proceedings. 1975. Public Law 93-595. 93rd Cong., 2nd Sess.), the plaintiff would prove an absence of 7 years, the basic facts needed for the presumption to apply. Under Rule 301 if the opponent of the presumption introduces a witness to testify that she saw the absentee 1 year after his disappearance, the presumption vanishes, and the plaintiff has the burden of proving death as though there had never been a presumption. If this is a type 1 presumption, as it is in presuming death for veterans after a 7-year absence (Seven-Year Absence Presumption of Death. 2006. 38 U.S.C. § 108), the basic facts establish death unless VA has sufficient evidence to show that the veteran is alive.

Presumptions for Veterans

There are several reasons justifying the widespread use of presumptions in the adjudication of VA benefit claims. Presumptions may simplify and streamline the adjudication process by eliminating the need to obtain evidence and decide complex issues. Presumptions also promote accuracy and consistency in adjudications by requiring similar treatment in similar cases. Presumptions may relieve claimants and VA of the necessity of producing direct evidence when it is impractical or unduly burdensome to do so.

"Finally, presumptions may implement policy judgments that the burdens arising in certain cases be borne by the government rather than the veteran claimants notwithstanding the uncertainty surrounding the issue of whether the claimants' disabilities were, in fact, incurred or aggravated by service" (Zeglin, 2006, p. 3).

To establish direct service connection for a VA disability compensation claim, a veteran must demonstrate the following: (1) that a disability currently exists, (2) that an event of disease or injury occurred or was aggravated in the military, and (3) that a medical connection can be shown between the service event and the existing disability (as stated in Barrans, 2006). Presumptions lighten the burden of proof when patterns of circumstances impair veterans' abilities to establish direct service connection. A presumption relieves the veteran of proving one or more of the requirements for direct service connection. The only difference between direct and presumptive service connection is the amount of proof required. All entitlements under presumptive service connection are identical to those under direct service connection (VA, 2006c).

There are both statutory and regulatory presumptions. Some presumptions relate to particular medical health outcomes, and others are administrative in nature (Pamperin, 2006). For example, there are several well-known presumptions of an administrative nature: presumption of death, presumption of sound condition, presumption of service connection due to aggravation, and presumption of total disability. The definitions of these presumptions are as follows:

- Presumption of death: Presumption of death upon 7 years of unexplained absence (Seven-Year Absence Presumption of Death. 38 U.S.C. § 108[b])
- Presumption of sound condition: "Every veteran shall be taken to have been in sound condition when examined, accepted, and enrolled for service except as to defects, infirmities, or disorders noted at the time of the examination, acceptance, and enrollment, or where clear and unmistakable evidence demonstrates that the injury or disease existed before acceptance and enrollment and was not aggravated by such service." (Presumption of Sound Condition. 38 U.S.C. § 1111)
- Presumption of service connection—Aggravation: "A preexisting injury or disease will be considered to have been aggravated by active military, naval, or air service, where there is an increase in disability during such [active] service, unless there is a specific finding that the increase in disability is due to the natural progress of the disease." (Compensation for Service-Connected Disability or Death. Aggravation. 38 U.S.C. § 1153)
- Presumption of total disability: "A person shall be considered to be permanently and totally disabled if such person is . . . suffering from any

disability which is sufficient to render it impossible for the average person to follow a substantially gainful occupation, but only if it is reasonably certain that such disability will continue throughout the life of the person." (Veterans' Benefits. Determination with Respect to Disability. 38 U.S.C. § 1502)

Medical health outcome presumptions have generally been adopted after periods of war and have been driven by the concerns of and for returning Service members. Military service is demanding, and those serving often do not know where they will be stationed and to which agents they will be exposed. In addition, military personnel are governed by the "line of duty" clause. VA will cover disability for a veteran "resulting from personal injury suffered or disease contracted in line of duty, or for aggravation of a pre-existing injury suffered or disease contracted in line of duty, in the active military, naval, or air service," unless such injury or disease was "a result of the veteran's own willful misconduct or abuse of alcohol or drugs" (Compensation for Service-Connected Disability or Death. Basic Entitlement. 38 U.S.C. § 1110).

Presumptions established by Congress and VA have generally been defined by or linked to a location (e.g., service in Persian Gulf, Vietnam) or an activity (e.g., detonation of a nuclear device). Presumptions have also been defined by categories of disease. In general, VA categorizes medical health outcome presumptive decisions into the following categories: Chronic Diseases, Tropical Diseases, Former Prisoners of War (POWs), Radiation, Herbicide Agents, Mustard Gas/Lewisite, and Persian Gulf War (Zeglin, 2006).

Veterans are entitled to compensation for certain medical conditions that become manifest to a degree of 10 percent or more disability after they leave the military service, if there is a relationship between service and the condition being claimed (Presumptions Relating to Certain Diseases and Disabilities. 38 U.S.C. § 1112). The health outcomes for presumptions must be rated at least at a 10 percent level in order for a veteran to receive compensation for a specific presumption (Presumptions Relating to Certain Diseases and Disabilities. 38 U.S.C. § 1112). In addition, a veteran must establish the presumptive relationship within the prescribed presumptive period set by Congress or VA. The presumptive period is the allowable period after active duty period in which a veteran must develop a disease in order to be eligible for compensation. In the past, most presumptive periods were set at 1 year. Recently, the presumptive periods associated with certain diseases have been greatly lengthened to accommodate the long latency periods associated with some health outcomes (e.g., cancers), the considerable time required to resolve disability, the problems caused by government-mandated secrecy about some exposures (e.g., mustard gas during WWII)

(see Appendix F, Table 1). Personal habits (e.g., tobacco use, alcohol and substance abuse) can be used to rebut presumptions, but in practice this is infrequently done (as stated in Barrans, 2006). Only subsequent to the diagnosis of mental health disorders will VA cover a veteran's alcohol and substance abuse treatment (as stated in Pamperin, 2006).

The last extensive study of the use of presumptions was performed by the Bradley Commission in the 1950s. The Bradley Commission recommended that the existing presumptions for service connection should be withdrawn. They felt that "there is otherwise in the law sufficient protection for the veteran to establish service connection of any and all diseases" (President's Commission on Veterans' Pensions, 1956, p. 178). The Bradley Commission noted that several diseases that were presumptively service connected were probably caused by old age, not necessarily service. It also believed that some diseases that were presumptively service connected had little to do with service in the military and in fact would be developed regardless of active duty. In addition to this, the specialists believed that more thorough medical exams should be given to Service members after military service to better classify health status after active duty. Overall, they believed that the list of chronic diseases at the time needed to be completely resurveyed to more accurately reflect the most updated medical knowledge. They noted advancements in treatment and diagnosing methods to support their theory. One criticism was that the system for presumptive conditions was outdated and overly simplistic. The findings not only called for a change in methods but also demanded much stricter guidelines for rating presumptive conditions. In addition, the Bradley Commission stated that medical principles should allow direct service connection rather than having to resort to presumptions in many instances. The analysis cited changes in medical knowledge and improving technology as reasons for updating the rating system and urged VA to completely change its policy of expansive presumptive periods to reflect the current situation of the medical world (President's Commission on Veterans' Pensions, 1956). Congressional hearings on the report were held, but no favorable action was taken on these recommendations.

THE PUBLIC POLICY DEBATE SURROUNDING PRESUMPTIONS

Members of Congress, representatives of VA, veterans service organizations (VSOs), and individual veterans have long debated the basis for and application of presumptions of service connection (VA, 2006b). The general categories of arguments favoring and opposing presumptions can be found in Table 2-1. Appendix E provides quotations that support these categories of arguments favoring and opposing presumptions.

TABLE 2-1 Categories of Arguments Favoring and Opposing Presumptions

Categories of Arguments Favoring Presumptions	Categories of Arguments Opposing Presumptions
1. **Medical uncertainty.** Onset of illness vs. appearance of symptoms. Doctors disagree over relationship to service.	1. **Questions of fact.** Each case should be considered on its own merits. Service connection should be a question of fact rather than a question of law.
2. **Inadequacy of service records and examinations.**	2. **Relationship to service.** Presumptive disabilities cannot be shown to be related to circumstances of military service.
3. **Excessive burden of proof on veteran.** Unfair to veteran to require medical proof when medical science is uncertain. Unreasonable to expect veterans afflicted with mental disability to prove SC.	3. **Administrative function.** Selecting diseases for inclusion as presumptive disabilities involves detailed medical and adjudicatory determinations best addressed administratively.
4. **Incidence of disease** among veteran population.	4. **Improved military procedures/records.** Modern facilities, procedures, and record keeping allow case-by-case determinations.
5. **Difficult/delayed Diagnoses.** Only medical specialists are likely to diagnose disease (MS) in early stages. Average person is unlikely to consult for original symptoms.	5. **Advances in medical science.** Advancements in medical science (since WWI) facilitate detection and diagnosis of diseases. Accepted medical principles can reasonably and accurately establish onset of disease.
6. **Social benefits.** Treatment of disease has broad social benefits. Treatment and compensation improve health of the nation generally.	6. **Philosophy of program.** Statutory presumptions for disabilities that cannot be shown to be related to service are inconsistent with the theory of compensation.
7. **Enforce Congress's view.** Congress disagreed with findings of VA doctors.	7. **Elevates cases without merit.** Puts cases without merit (from standpoint of service connection) on a par with those proven to be service connected.
8. **Association with risk factors.** A disease associated with a known military risk factor and not associated with other risk factors.	8. **Provisions are adequate without presumptions.** Reasonable doubt to be resolved in favor of veteran eliminates need for presumption.
9. **Promote health.** Providing disability benefits relieves veterans of the need to perform work that could further compromise their health.	9. **Qualifying criteria excessively liberal.** In some cases, a bill's language is seen as overly inclusive.
10. **Conditions of service.** Long-range harm can be caused by particularly harsh conditions of service, such as those experienced by POWs.	

SOURCE: VA (Veterans Administration). 2006b (unpublished). *Presumption of service connection: The public policy debate*. Washington, DC: VA.

BRIEF CHRONOLOGICAL HISTORY OF PRESUMPTIONS

This section summarizes presumptions that were established by Congress and VA from the 1920s to present. The health outcomes covered can generally be organized into the following presumptive categories: Chronic Diseases, Tropical Diseases, Former Prisoners of War, Radiation, Herbicide Agents, Mustard Gas/Lewisite, and Persian Gulf War. Table 2-2 summarizes all of the health outcomes that have been service connected for these presumptive categories to date. The information in this table was compiled from the health outcomes found in Tables F-1 and F-2 of Appendix F, which list all of the appropriate public laws and statutory citations. There are nearly 150 health outcomes that have been presumptively connected by Congress and VA since 1921.

TABLE 2-2 Presumptive Categories and Their Designated Health Outcomes

Presumptive Categories	Health Outcomes (in alphabetical order)
Chronic Diseases	Anemia; arteriosclerosis; arthritis; atrophy; brain hemorrhage; brain thrombosis; bronchiectasis; calculi of the kidney, bladder, or gallbladder; cardiovascular-renal disease including hypertension; cirrhosis of the liver; coccidioidomycosis; diabetes mellitus; encephalitis lethargica residuals; endocarditis; endocrinopathies; epilepsies; Hansen's disease; Hodgkin's disease; leukemia; lupus erythematosus, systemic; myasthenia gravis; myelitis; myocarditis; nephritis; other organic diseases of the nervous system; osteitis deformans; osteomalacia; palsy, bulbar; paralysis agitans; psychoses; purpura idiopathic, hemorrhagic; Raynaud's disease; sarcoidosis; scleroderma; sclerosis, amyotrophic lateral; sclerosis, multiple; syringomyelia; thromboangiitis obliterans (Buerger's disease); tuberculosis, active; tumors, malignant, or of the brain or spinal cord or peripheral nerves; ulcers
Tropical Diseases	Amebiasis; blackwater fever; cholera; dracontiasis; dysentery; filariasis; leishmaniasis, including kala-azar; loiasis; malaria; onchocerciasis; Oroya fever; pinta; plague; schistosomiasis; yaws; yellow fever
Former Prisoners of War	Atherosclerotic heart disease and hypertensive vascular disease, including hypertensive heart disease; avitaminosis; beriberi; chronic dysentery; cirrhosis of the liver; dysthymic disorder (or depressive neurosis); helminthiasis; irritable bowel syndrome; malnutrition; organic residuals of frostbite; pellagra; peptic ulcer disease; peripheral neuropathy; posttraumatic osteoarthritis; psychosis; stroke; any other nutritional deficiency; any of the anxiety states

continued

TABLE 2-2 Continued

Presumptive Categories	Health Outcomes (in alphabetical order)
Radiation	Bronchiolo-alveolar carcinoma; cancer of the bile ducts, bone, brain, breast, colon, esophagus, gall bladder, lung, ovary, pancreas, pharynx, salivary gland, small intestine, stomach, thyroid, and urinary tract; leukemia; lymphomas; multiple myeloma; primary liver cancer
Herbicide Agents	Acute and subacute peripheral neuropathy; chloracne; chronic lymphocytic leukemia; Hodgkin's disease; multiple myeloma; non-Hodgkin's lymphoma; porphyria cutanea tarda; prostate cancer; respiratory cancers; soft-tissue sarcoma, including: adult fibrosarcoma, dermatofibrosarcoma protuberans, malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, epithelioid leiomyosarcoma, rhabdomyosarcoma, ectomesenchymoma, angiosarcoma, proliferating angioendotheliomatosis, malignant glomus tumor, malignant hemangiopericytoma, synovial sarcoma, malignant giant cell tumor of tendon sheath, malignant schwannoma, malignant mesenchymoma, malignant granular cell tumor, alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma of tendons and aponeuroses, extraskeletal Ewing's sarcoma, congenital and infantile fibrosarcoma, malignant ganglioneuroma; type 2 diabetes
Mustard Gas and Lewisite	Acute nonlymphocytic leukemia; cancers (nasopharyngeal, laryngeal, lung [except mesothelioma], squamous cell carcinoma of the skin); chronic conjunctivitis; chronic form of laryngitis, bronchitis, emphysema, and asthma; chronic obstructive pulmonary disease; corneal opacities; keratitis; scar formation
Persian Gulf War	An undiagnosed illness, which may be associated with the following chronic symptoms: fatigue; symptoms involving skin, headache, muscle pain, joint pain, neurological symptoms, neuropsychological symptoms; symptoms involving the respiratory system, sleep disturbances, gastrointestinal symptoms, cardiovascular symptoms, abnormal weight loss, or menstrual symptoms. Also included are the following medically unexplained chronic multisymptom illnesses that are defined by a cluster of signs or symptoms: Chronic Fatigue Syndrome, Fibromyalgia, and Irritable Bowel Syndrome

SOURCE: Appendix F, Tables F-1 and F-2.

1920s

The first presumptions were established in 1921: "In my opinion, that provision of the law which places the burden upon the disabled veteran of connecting his disease with his service has been responsible for more complaints, dissatisfaction and disappointment . . . than any other single provision. . . . Consequently, I propose to offer an amendment to section 18 which will shift the burden of proof in the case of two classes of disease

only—tubercular and neuropsychiatric. I propose that when it is proved by an incapacitated soldier that he has either of these two types of disease he shall immediately be entitled to compensation unless the Government proves—the burden thus being shifted to the Government—that he has contracted the disease since the time of his discharge and it is not traceable to service in line of duty" (Senator Walsh, 61 Cong. Rec. 4105, 1921, as referenced in VA, 1993a, p. 7, and as found in Appendix E).

Neuropsychiatric disease (later called *psychoses*) and active pulmonary tuberculosis were the first two presumptions established on August 9, 1921 (Veterans' Bureau. Public Law 67-47. 1921. 67th Cong., 1st Sess.). These health outcomes must have manifested to 10 percent or more within 2 years of separation from active military service and must have been contracted during military service. On November 12, 1921, the first list of chronic constitutional diseases (later referred to as Chronic Diseases) was established (VA, 1921). These must have manifested within 1 year after the date of separation from service. The list included anemia (primary), arteriosclerosis, beriberi, diabetes insipidus, diabetes mellitus, endocrinopathies, gout, hemochromatosis, hemoglobinuria (paroxysmal), hemophilia, Hodgkin's disease, leukemia (all types), ochronosis, pellagra, polycythemia (erythremia), purpura, rickets, and scurvy. The category of Chronic Diseases was expanded in 1924 (World War Veterans' Act, 1924. Public Law 68-242. 68th Cong., 1st Sess.), 1925 (VA, 1925), and 1928 (VA, 1928).

1930s

In 1933, epilepsies and organic diseases of the nervous system were added to the Chronic Diseases category, and requirements for the manifestation of tuberculosis were more specifically characterized (Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933). Osteitis deformans (Paget's disease) was added in 1935 (Executive Order 6089. Instruction No. 2-A, Implementing Vet. Reg. No. 1. August 14, 1935).

1940s

The 1940s saw the growth in the number of presumptions and the addition of one new presumptive category—Tropical Diseases. The first tropical disease for which a presumption was made was malaria in 1945 (VA, 1945). Malaria must have been contracted during active service with a presumptive period of 1 year after separation from active military service. The Tropical Diseases category was greatly expanded in 1946 (VA, 1947) and 1948 (Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess.) with clarifications appearing in 1949 (VA, 1949a). As well, the number

of presumptions in the category of Chronic Diseases increased greatly in 1948 (Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess.) and 1949 (VA, 1949a,b). The increase in the number of presumptions during this decade was related to the high incidence of such diseases observed in returning veterans from WWII.

1950s

The 1950s were not very active in establishing new presumptions. Sarcoidosis was added to the Chronic Diseases category, and amebiasis was added to the Tropical Diseases category in 1950 (VA, 1950). Clarifications on the dates of service, locations, and presumptive periods occurred in 1957 (Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess.). It should be noted that the Bradley Commission, which reviewed the presumptive process and decisions, issued its report in 1956 (President's Commission on Veterans' Pensions, 1956).

1960s

In 1961, criteria for the presumptions in the Chronic Diseases and Tropical Diseases categories appeared (VA, 1961). No new presumptions were created during this decade.

1970s

A new presumptive category was established in the 1970s—Former Prisoners of War (POWs). POWs from WWII, the Korean War, and the Vietnam era were specifically connected for various physical and mental health outcomes in 1970 (Public Law 91-376. Sec. 3. 91st Cong., 2d Sess., 1970). "Problems with nutrition, forced labor, and other inhumane treatment were deemed to be strong reasons to presume that the conditions were the direct result of captivity" (Economic Systems Inc., 2004a, p. 20). Clarification for the presumptive periods of Hansen's disease (leprosy) and tuberculosis to 3 years as well as multiple sclerosis to 7 years from date of separation occurred in 1970 (VA, 1970). In 1979, ischemic heart disease (or other cardiovascular disease) was presumptively associated with service amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles (VA, 1979).

1980s

The decade demonstrated an expansion of presumptions with in the categories of POWs, Herbicide Agents, and Radiation. In 1981, the POW

imprisonment requirement of 90 days or more was reduced to 30 days or more (Former Prisoner of War Benefits Act of 1981. Public Law 97-37. 97th Cong., 1st Sess.). In 1985, chloracne was presumptively connected with dioxin exposure (VA, 1985). In that same year, presumptions for exposure to ionizing radiation in Hiroshima or Nagasaki, Japan (September 1945 until July 1946) and all forms of leukemia (except chronic lymphatic leukemia), many cancers, and multiple myeloma were made (VA, 1985). For POWs, organic residuals of frostbite and posttraumatic osteoarthritis were added in 1986 (Veterans' Benefits Improvements and Health-Care Authorization Act of 1986. Public Law 99-576. 99th Cong., 2d Sess.). In 1988, the scope of presumptive service connection law expanded dramatically when Congress passed a law providing a 40-year presumptive period for a long list of cancers associated with nuclear testing during the 1940s (Veterans' Benefits and Services Act of 1988. Public Law 100-322. 100th Cong., 2d Sess.). This law introduced the phrases "radiation-exposed veteran" and "radiation-risk activity," and added to the list POWs who were being held in Japan at the time of the nuclear detonations.

1990s

The generation of presumptions accelerated in the decade of the 1990s. Each year of this decade new presumptions or clarifications of presumptive periods were established by Congress or VA. The Radiation Exposure Compensation Act of 1990 (Public Law 101-426. 101st Cong., 2d Sess.) added presumptions for downwinders to the Radiation category, but it did not cover veterans. Also in 1990, non-Hodgkin's lymphoma was presumptively connected for Vietnam service (VA, 1990). In 1991, Congress passed the Agent Orange Act (Public Law 102-4. 102d Cong., 1st Sess.). This act added non-Hodgkin's lymphoma, soft-tissue sarcomas, and chloracne (or other acneform disease) in the presumptive category of Herbicide Agents. Presumptions for the Mustard Gas/Lewisite category, stemming from WWII full-body, field, or chamber experiments, were established in 1992 (VA, 1992a). Also in 1992, peripheral neuropathy was presumptively connected to the Herbicide Agents category (VA, 1992b), and cancer of the salivary gland and urinary tract were added to the Radiation category (Veterans' Radiation Exposure Amendments of 1992. Public Law 102-578. 102d Cong., 2d Sess.). Both ovarian cancer and parathyroid cancer were presumptively connected to the Radiation category in 1993 (VA, 1993b). During that same year, posttraumatic stress disorder was presumptively connected for military service and former POWs (VA, 1993c). Finally, several additional diseases associated with service in Vietnam were added in 1993 (VA, 1993d).

In 1994, numerous additions occurred in the presumptive categories of Mustard Gas/Lewisite (VA, 1994a), Herbicide Agents (VA, 1994d,e;

Veterans' Benefits Improvements Act of 1994. Public Law 103-446. 103d Cong., 2d. Sess.), and Radiation (VA, 1994b). Also in 1994, the Persian Gulf War undiagnosed illnesses were proposed (VA, 1994c). The Persian Gulf War undiagnosed illnesses were finalized in the 1995 Compensation for Certain Undiagnosed Illnesses rule, the first time that Congress had made a presumption for a list of medical terms (VA, 1995b). Additional presumptions in the Radiation category were added for cancer of the rectum and lymphomas (other than Hodgkin's disease) later that year (VA, 1995a). In 1996, prostate cancer as well as acute and subacute peripheral neuropathy were presumptively connected under the category of Herbicide Agents (VA, 1996). The presumptive period for undiagnosed illnesses to manifest within 2 years after service was extended to December 31, 2001, in 1997 (VA, 1997). Prostate cancer and any other cancer were presumptively connected for the Radiation category in 1998 (VA, 1998). The Persian Gulf War Veterans Act of 1998 (Public Law 105-277. 105th Cong., 2d Sess.) established service connection for diseases associated with exposure to biological, chemical, or toxic agents; environmental or wartime hazards; or preventive medicines or vaccines associated with service in the southwest Asia theater of operations during the Persian Gulf War. Finally, the Veterans Millennium Health Care and Benefits Act of 1999 (Public Law 106-117. 106th Cong., 1st Sess.) established a presumption for bronchiolo-alveolar carcinoma and radiation exposure.

2000 to Present

The final Veterans Millennium Health Care and Benefits Act presumptively connected bronchiolo-alveolar carcinoma to radiation exposure in 2000 (VA, 2000). In April 2001, VA published a final rule stating that veterans' use of tobacco products and associated adverse health outcomes would not be considered service connected (VA, 2001a). In May 2001, VA presumptively connected type 2 diabetes with herbicide exposure (VA, 2001b). In the same year, additional presumptions for the Radiation category were established (VA, 2001c) and clarifications for presumptive periods relating to Persian Gulf War and Vietnam service were published (VA, 2001d; Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.). Additional cancer presumptions were added for radiation-risk activities in 2002 (VA, 2002). Cirrhosis of the liver was presumptively connected in 2003 for former POWs (VA, 2003b), and chronic lymphocytic leukemia was presumptively connected the same year for herbicide exposures (VA, 2003a). The list of diseases presumptively connected for POWs was expanded in 2003 (Veterans Benefits Act of 2003. Public Law 108-183. 108th Cong., 1st Sess.), and additional

diseases were presumptively connected for POWs in 2004 (VA, 2004). The definition of radiation-risk activity was clarified in 2004 to include service in a capacity if performed as an employee of the Department of Energy (Veterans Benefits Improvement Act of 2004. Public Law 108-454. 108th Cong., 2d Sess.). Once again, additional health outcomes were presumptively connected for POWs in 2005 (VA, 2005). In early 2006, Congress codified all presumptions established to date (Veterans' Benefits. Title 38 U.S.C.). In 2006, VA published an interim final rule that the presumptive period for undiagnosed illnesses to manifest within 2 years after service would be extended to December 31, 2011 (VA, 2006a).

SUMMARY

Many presumptive decisions have been made since the first presumptions were established in 1921. These decisions reflect the complexity of exposures during service. The increased longevity of veterans means that there are many more diseases from which veterans may suffer and which may have originated in military service. In the 50 years since the Bradley Commission's report was released (President's Commission on Veterans' Pensions, 1956), there have been substantial changes in medical care and in the evidence relevant to making presumptions. However, a need for presumptions has persisted, and the creation of new presumptions has increased rapidly in the last two decades.

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VA. 1994b. Claims based on exposure to ionizing radiation. Final rule. *Federal Register* 59(171):45975.
VA. 1994c. Compensation for certain undiagnosed illnesses. Proposed rule. *Federal Register* 59(235):63283-63285.
VA. 1994d. Disease associated with exposure to certain herbicide agents. Final rule. *Federal Register* 59(23):5106-5107.
VA. 1994e. Disease associated with exposure to certain herbicide agents (multiple myeloma and respiratory cancers). Final rule. *Federal Register* 59(110):29723-29724.
VA. 1995a. Claims based on exposure to ionizing radiation (lymphomas other than Hodgkin's disease and cancer of the rectum). Final rule. *Federal Register* 60(198):53276-53277.
VA. 1995b. Compensation for certain undiagnosed illnesses. Final rule. *Federal Register* 60(23):6660-6666.
VA. 1996. Diseases associated with exposure to certain herbicide agents (prostate cancer and acute and subacute peripheral neuropathy). Final rule. *Federal Register* 61(217):57586-57589.
VA. 1997. Compensation for certain undiagnosed illnesses. Interim rule with request for comments. *Federal Register* 62(82):23138-23139.

VA. 1998. Claims based on exposure to ionizing radiation (prostate cancer and any other cancer). Final rule. *Federal Register* 63(185):50993-50995.

VA. 2000. Veterans Millennium Health Care and Benefits Act. Final rule. *Federal Register* 65(136):43699-43700.

VA. 2001a. Claims based on the effects of tobacco products. Final rule. *Federal Register* 66(67):18195-18198.

VA. 2001b. Disease associated with exposure to certain herbicide agents: Type 2 diabetes. Final rule. *Federal Register* 66(89):23166-23169.

VA. 2001c. Diseases specific to radiation-exposed veterans. Proposed rule. *Federal Register* 66(153):41483-41485.

VA. 2001d. Extension of the presumptive period for compensation for Gulf War veterans' undiagnosed illnesses. Interim final rule with request for comments. *Federal Register* 66(218):56614-56615.

VA. 2002. Diseases specific to radiation-exposed veterans. Final rule. *Federal Register* 67(17):3612-3616.

VA. 2003a. Disease associated with exposure to certain herbicide agents: Chronic lymphocytic leukemia. Final rule. *Federal Register* 68(200):59540-59542.

VA. 2003b. Presumption of service connection for cirrhosis of the liver in former prisoners of war. Final rule. *Federal Register* 68(138):42602-42603.

VA. 2004. Presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. Interim final rule. *Federal Register* 69(194):60083-60090.

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VA. 2006a. Extension of the presumptive period for compensation for Gulf War veterans. Interim final rule. *Federal Register* 7(242):75669-75672.

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3

The Presumptive Disability Decision-Making Process

This chapter describes the current presumptive disability decision-making process for veterans and outlines the roles of various participants in the process. The description is based on presentations at the Committee's open sessions, public documents, documents provided by the Department of Veterans Affairs (VA), the Institute of Medicine (IOM) reports, and other relevant materials.

SUMMARY OF THE PROCESS

The current presumptive disability decision-making process for veterans involves multiple parties and is not controlled by any single entity or organization. The process involves input from Congress, VA, the National Academies (IOM and National Research Council [NRC]) and the veteran community. Decisions made in the courts have also influenced the current presumptive process. Figure 3-1 depicts roles of participants in the current process. Although the number and extent of presumptions have varied over the last 80 years, it appears that the presumptive decisions established since the early 1990s have led to growing concerns and questions about the presumptive process itself.

When Congress enacted the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.), it started a model for a decision-making process that is still in place today. Congress asked VA to contract with an independent organization—VA contracted with IOM—to review the scientific evidence related to Agent Orange and disease. The process begins with VA supplying a study charge to the IOM committee carrying out the review,

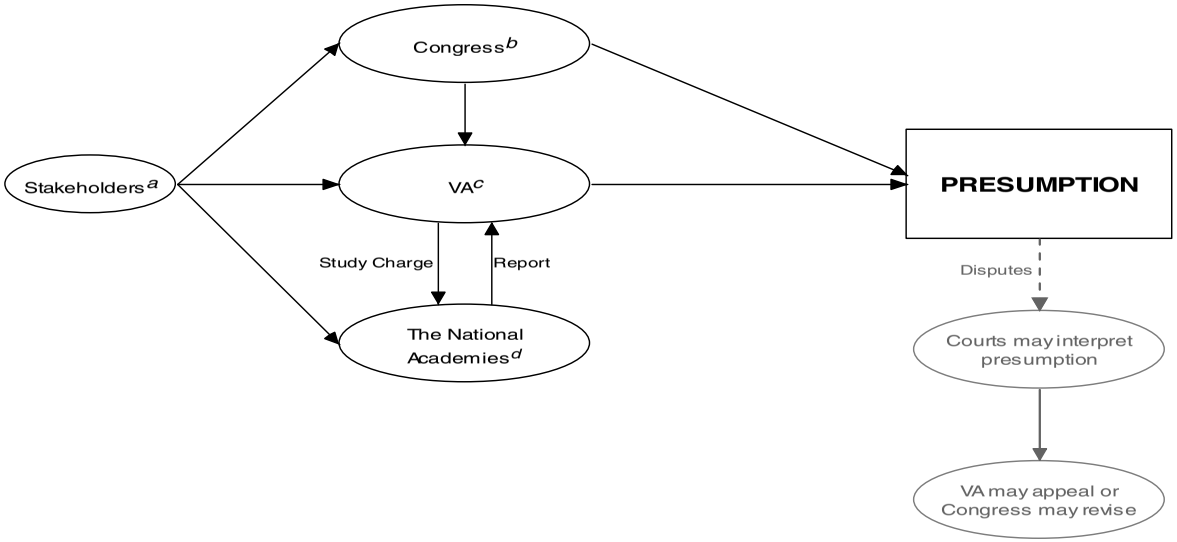

FIGURE 3-1 Roles of the participants involved in the presumptive disability decision-making process for veterans.
[a] Stakeholders include (but are not limited to) veterans service organizations (VSOs), veterans, advisory groups, federal agencies, and the general public; these stakeholders provide input into the presumptive process by communicating with Congress, VA, and independent organizations (e.g., the National Academies).
[b] Congress has created many presumptions itself; in 1921, Congress also empowered the VA Secretary to create regulatory presumptions; on several occasions in the past, Congress has directed VA to contract with an independent organization (e.g., the National Academies) to conduct studies and then use the organization's report in its deliberations of granting or not granting regulatory presumptions.
[c] VA can establish regulatory presumptions; VA sometimes contracts with the National Academies to conduct studies and uses the organization's report in its deliberations of granting or not granting regulatory presumptions.
[d] The National Academies (Institute of Medicine and National Research Council) submit reports to VA based on requests and study charges from VA.

and it ends with the IOM committee responding with a report, based on a comprehensive review, that addresses the charge. Since 1994, IOM has produced six biennial reports on Agent Orange (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) and five volumes on the Gulf War (IOM, 2000a, 2003a, 2005a, 2006b, 2007a) for VA to use in its deliberations when making presumptive decisions.

Through this process, health outcomes, such as prostate cancer and type 2 diabetes, have been presumptively service connected to Agent Orange exposure in Vietnam. The process for establishing presumptions continued to evolve in recent years to respond to veterans who were deployed to the Persian Gulf during or shortly following the Gulf War in 1990. Although the focus for presumptions among Vietnam veterans centered on their exposure and health outcomes relating to the dioxin-contaminated herbicide Agent Orange, the Gulf War has added new challenges caused by the multiple and various agents to which Service members were exposed. The IOM report process has responded to the multiplicity of agents of concern by developing reports on large groups of similar agents, such as combustion products (IOM, 2000a, 2003a, 2005a).This chapter reviews the roles of each major participant in the presumptive disability decision-making process for veterans.

DESCRIPTION OF ROLES FOR SPECIFIC PARTICIPANTS (IN ALPHABETICAL ORDER)

Role of Congress

The power to compensate veterans for their service-connected adverse health effects resides in Congress. Consequently, Congress has the power to create presumptions that make it easier for a veteran to establish service connection (see Chapter 2). Congress has sometimes exercised its power through legislation; at other times Congress has delegated its authority to the VA Secretary to prescribe "all rules and regulations . . . with respect to *the nature and extent of proof and evidence* and the method of taking and furnishing them in order to establish the right to benefits under such laws" (Rules and Regulations. 2003. 38 U.S.C. § 501(a); emphasis added). This general authority has been used sparingly by VA over the years to establish presumptions.

The vast majority of presumptions have resulted from public laws that specifically identify a disability or disease and set forth the conditions under which a presumption of service connection attaches (see Appendix F). Subsequent legislative enactments often modify the conditions under which these specific presumptions apply. As a matter of law, most presumptions can be rebutted by competent evidence (see Chapter 2) although this rarely occurs in practice.

Beginning in the 1980s, Congress has also legislated procedures to be employed in responding to service-related claims initially concerning herbicide and radiation exposures and later with respect to various exposures encountered during the Gulf War (see Appendix F). The procedures that Congress has established essentially involve review by a committee from the National Academies (e.g., IOM and NRC) of medical and scientific evidence concerning the relationship of disabilities or diseases to certain exposure agents. On a periodic basis, IOM furnishes findings for Agent Orange and Gulf War to the VA Secretary who must then decide whether or not to grant a presumption within a specified number of days of receipt of a report (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.; Veterans Programs Enhancement Act of 1998. Public Law 105-368. 105th Cong., 2d Sess.).

The formal role of Congress in establishing these presumptions follows a comparatively transparent process. Issues are brought to the attention of Congress by individual constituents seeking assistance from members in securing veteran benefits for which they claim entitlement, and by veteran service organizations (VSOs) that represent their interests. Media attention concerning veteran issues can also engage the interest of Congress. Finally, legislation concerning presumptions can also be initiated at the request of the executive branch, although this has been a rare occurrence.

A bill to establish a presumption is introduced in one or both houses of Congress, and it is usually accompanied by the sponsors' floor statements setting forth the reasons why it should be enacted. Public hearings are held by one or both of the veterans affairs committees and testimony is received from a variety of witnesses including VSOs and individual veterans who are often constituents of various committee members. VA's position on the legislation along with cost estimates prepared by the Director of the Congressional Budget Office, where applicable, are also received and considered by Congress (Johnson, 2003).

The Veterans Affairs Committee considering the legislation next moves to consider the legislation and amendments thereto in executive session. At one time these meetings were closed to the public, but they have been conducted in open session for approximately the past 30 years. After consideration of any amendments, the measure, if approved by the committee, is ordered to the floor for consideration by the entire Senate or House. The bill as amended is accompanied by a report prepared by the committee's majority staff that sets forth the rationale for the legislation. The report also includes a summary of testimony received and information considered together with the administration's position and cost estimates (Johnson, 2003). The report may also include separate and minority views, although this has been infrequent with veterans legislation that is more often than not reported unanimously.

Floor debate on the pending bill is televised and transcribed in the *Congressional Record*. Procedures for considering legislation on the floor, however, differ substantially between the House and the Senate. The amount of debate and the ability to consider amendments to the measure on the floor of the House is for the most part limited, which enhances the authority of the House Committee on Veterans Affairs. In the Senate the ability to attach amendments and to have extensive debate is rarely constricted (Johnson, 2003). Because of the frequent need to keep the "trains moving on time," an individual Senator need not be a member of the Veterans Affairs Committee to exercise considerable influence in shaping veterans legislation.

It should be observed parenthetically that historically the House Veterans Affairs Committee has been the initiator of most veterans legislation. This resulted from the fact that until 1971 only the House had a full standing committee on veterans affairs. The Committee enjoyed a stable, "tenured" leadership and staff for long periods of time that enabled it to develop considerable expertise in veterans' matters. Given House floor procedures, committee views were rarely challenged and invariably prevailed (Carr, 2001). In the Senate, by contrast, veterans legislation—depending on its content—was handled either by the Committee on Finance or the Committee on Labor and Public Welfare (SOURCE: http://veterans.senate.gov/index.cfm?FuseAction=About.CommitteeHistory), both of which had numerous other issues that engaged the committee members' time and interest. As a result, the Senate frequently deferred to the position of the House in veterans' matters prior to 1971.

The creation of the Senate Committee on Veterans Affairs in 1971 amid concern generated about treatment of returning Vietnam veterans altered the status quo as the Senate developed a larger voice in veterans' matters (SOURCE: http://veterans.senate.gov/index.cfm?FuseAction=About.CommitteeHistory). This contributed to changes in how presumptions were created as the issue of Agent Orange exposure grew in intensity.

In situations where the two houses have not adopted identical measures, the differences need to be resolved often through a formal House-Senate conference committee. The veterans affairs committees, however, rarely resort to the formal conference committee process. Instead they negotiate their differences in informal, nonpublic meetings that frequently involve committee staff acting as surrogates for the members. Once agreement is reached, an amended version is reported to the floor of either the House or the Senate where it is passed and sent to the other body, which accepts the measure as amended causing it to be transmitted to the President for action. Both committees insert an identical joint explanatory statement in the *Congressional Record* that sets forth the changes made and the parties' understanding and rationale of the compromise measure (Johnson, 2003).

As this description of the congressional process indicates, an extensive public record is developed with respect to the consideration and adoption of presumptions. Whether this record is a complete and accurate description of why a presumption was or was not adopted or why processes or standards were crafted in the manner they were is another matter. The politics of an issue often are not openly acknowledged in the public record. The personal views of key individual members can often have enormous weight. "Horse trading" on other matters often affects the shape and outcome of a particular bill. Moreover, substantive differences are sometimes papered over with ambiguous language to gain approval of the legislation, which presents a variety of problems to those who are charged with implementing their provisions. All of this suggests that the science justifying a presumption is but one factor considered by Congress in the enactment of the legislation. For additional information and analysis of the role of Congress in the development of presumptions, the reader is directed to the case studies, in particular the discussion of Agent Orange and Gulf War presumptions, found in Appendix I.

Congressional Perspective

The Committee received views from a panel of former congressional staff members, most of whom had served on either the Senate or the House Veterans Affairs committees in the 1980s and 1990s at a time when there were intense concern and questions about the effect of service exposures on the subsequent health of veterans (presentations made to the Committee on October 5, 2006). Among the factors arguably affecting the enactment of presumption legislation were (1) increasing concern about federal budget problems, (2) the perceived strength of key members of Congress considering the legislation, and (3) the continuing reminder of American Service members who had been recently killed or wounded and the debt our society owed them (Petrou, 2006; Ryan, 2006; Scott, 2006; Yoder, 2006).

It was observed that "scientific integrity is critical" in the presumptive disability compensation process and that if it was "lacking, the quality of the decisions [would] suffer, and veterans and the American people [would] lose faith in the decision-making process" (Petrou, 2006, p. 8). At the same time, faced with the claims of veterans with many real disabilities and diseases, it was acknowledged that presumptive decisions were shaped by the perceived "need to make 'yes or no' decisions in the face of pervasive uncertainty" with regards to the level, if any, of exposure and the likely health effects resulting therefrom (Yoder, 2006, p. 1). Panel members were critical of insufficient efforts to monitor the health of Service members. They noted the absence of predeployment health assessments and inadequate surveillance of environmental exposures that troops may have encountered

during the Gulf War notwithstanding lessons that should have been learned from Agent Orange and Vietnam (Petrou, 2006; Ryan, 2006; Scott, 2006; Yoder, 2006). Although there was disagreement as to its wisdom, there was uniform agreement that if a connection between exposure and disease were established, Congress has a strong bias in favor of compensating *all* veterans even if the attributable risk was small and large numbers of false positives would result (Petrou, 2006; Ryan, 2006; Scott, 2006; Yoder, 2006).

Role of Department of Veterans Affairs (VA)

The Committee's description of the VA process is based on presentations to the Committee as well as a general description provided by VA (see Appendix G). The Committee requested internal documents related to specific presumptions, but these were not provided (see Chapter 1). Based on the information available, the Committee found that VA has developed an ad hoc process for establishing presumptions that relies upon National Academies (e.g., IOM and NRC) reports, recommendations of advisory committees, and VA research findings (Barrans, 2006; Pamperin, 2006a). Currently, VA follows the process that began with the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.). Upon receipt of an IOM Veterans and Agent Orange (VAO) or Gulf War (GW) report, the VA Secretary is required to determine whether a presumption of service connection is warranted for any diseases discussed in the report.

VA has not adopted formal procedures governing its internal review and utilization of findings of IOM reports. However, a general practice has developed that VA usually follows in conducting its internal review. The general practice involves a three-tiered review with a working group (tier 1), a task force group (tier 2), and the VA Secretary (tier 3). Working group members include internal VA staff and outside experts as needed, with the option of seeking input from VSOs, Congress, and veterans (Deyton, 2006). Representatives at each tier are shown in Box 3-1.

The Working Group convenes after receiving the briefing from the IOM VAO or GW committee. "Prior to the meeting, VHA personnel usually will seek to identify, based on the IOM report and the committee briefing, the diseases that may warrant special consideration because IOM's findings with respect to those diseases appear to be potentially significant. The . . . VHA generally provides the working group members with additional information concerning those diseases, including copies of any significant scientific studies identified in the IOM report and other information. . ." (VA, 2006, p. 3; as found in Appendix G).

"At the initial working group meeting, the OGC [Office of the General Counsel] representative briefs the working group on the legal standard governing the VA Secretary's decision. . . . The working group will try to

BOX 3-1
Representatives at Each Tier of VA's Internal Review of NAS Reports

Tier 1: Working Group Representatives*
- Veterans Health Administration (VHA) Office of Public Health and Environmental Hazards (OPHEH)
- Veterans Benefits Administration (VBA)—Compensation and Pension Service (C&P Service)
- Office of the General Counsel (OGC)—Professional Staff Group II
- VHA personnel with specialized medical training or experience
- Outside technical experts such as National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and Environmental Protection Agency (EPA), as needed

Tier 2: Task Force Representatives**
- Under Secretary for Health
- Under Secretary for Benefits
- General Counsel
- Assistant Secretary for Policy and Planning
- Other experts (CDC, EPA, as appropriate)

Tier 3: The VA Secretary

SOURCE: Deyton, 2006; VA, 2006; as found in Appendix G.
*The members generally are assigned to the working group by supervisory personnel within VHA, VBA, and OGC. The working group may receive input from outside content experts as well as veterans, VSOs, and Congress.
**Appointed by the VA Secretary.

reach consensus as to whether the scientific evidence appears to warrant a presumption of service connection for any diseases under the applicable legal standard" (VA, 2006, p. 3; as found in Appendix G).

"If the Working Group concludes that the scientific evidence and legal standard do not provide a clear basis for recommending for or against establishing a presumption . . . the Working Group generally will agree to set forth a range of options for a decision by VA policy-making officials. In those circumstances, the Working Group will discuss the factors that preclude a clear recommendation, which may include ambiguity in the governing statutory standard as applied to certain IOM findings. . . . The Working Group will discuss the options available to the VA Secretary and may also

discuss the factors that may be relevant to the VA Secretary's decision among those options" (VA, 2006, pp. 3-4; as found in Appendix G). The Working Group prepares a written report that typically includes the following:

- A summary of the issues to be decided under applicable law and the IOM report
- A summary of the findings contained in the IOM report
- A summary of the legal standard governing VA's decision
- A summary of the Working Group's analysis of the medical evidence in relation to the legal standard, particularly with respect to any potentially significant findings in the IOM report
- A statement of the Working Group's recommendations or of the options identified by the Working Group

In arriving at such recommendations, the Working Group generally does not prepare or obtain a cost estimate for the options. However, it may provide general information, for example, the prevalence rates of certain diseases under consideration. If the Working Group report lists a range of options available to the VA Secretary, it ordinarily would identify the scientific and legal considerations relevant to the VA Secretary's choice among those options, and may also identify policy implications associated with various options" (VA, 2006, p. 4; as found in Appendix G).

The VA task force receives this report and reviews its recommendations. "The Task Force often, though not always, provides a separate report to the VA Secretary that is . . . usually similar to the Working Group's report in format and content. . . . [O]nce the report is drafted, it is circulated to the Task Force members for signature and is then transmitted to the VA Secretary" (VA, 2006, p. 4; as found in Appendix G).

"Based on the Task Force's report, the VA Secretary determines whether to establish presumptions for any diseases discussed in the IOM report and directs appropriate action to implement the decision. . . . [I]f the VA Secretary determines that a presumption of service connection is warranted for any disease, VBA (through the C&P Service staff) will prepare proposed rules to establish such presumptions" and "an estimate of the costs associated with the rule. . . . VA will transmit the proposed rule and cost estimate to OMB [Office of Management and Budget] for review. If OMB approves the proposed rule, it will be transmitted to the VA Secretary for signature. VA will then transmit the rule to the *Federal Register* for publication. Once the period for providing public comments on the rule has ended, VBA will prepare a final rule. VA will submit the final rule to the *Federal Register* for publication" (VA, 2006, p. 5; as found in Appendix G).

"If the VA Secretary determines that a presumption of service connection is not warranted for certain diseases, VBA will prepare a notice

explaining the scientific basis for that decision with respect to each such disease prior to publication" (VA, 2006, p. 5; as found in Appendix G). VA then publishes this notice in the *Federal Register*.

Presentations made at Committee open session meetings brought out several issues of importance to VA. The scientific, independent review process, as well as the breadth and thoroughness of IOM reports, provide credibility to the presumptive disability decision-making process. However, interpretation of the IOM reports can be problematic for VA. The difficulty lies not only in determining the effects of exposure but in separating the effects of a specific exposure of concern from the effects of other potential exposures. Past IOM committees have not been charged to provide guidance on this issue. VA is also hindered by not having exposure data for individuals. VA noted that some exposures known to contribute to conditions of concern are common in nonmilitary settings, complicating interpretation of studies of risks of military exposures for these outcomes.

VA, under statutes outlining the presumptive process for Agent Orange and Gulf War (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.; Veterans Programs Enhancement Act of 1998. Public Law 105-368. 105th Cong., 2d Sess.), is not required to consider any evidence on exposure magnitude that would be necessary for a direct service connection. It can offer little or no guidance for making decisions based on exposure magnitude or duration. VA is left to treat all exposures as equally likely to lead to an associated long-term health effect (Brown, 2006; Deyton, 2006).

The Impact of Presumptions

VA does not track the number of presumptive service-connected disability claims granted and/or denied for each condition, nor are health outcomes within the VBA data systems coded in a manner that would permit VA to easily determine how many veterans are presumptively service connected (as stated in Pamperin, 2006b). For various categories of health conditions, some information regarding the number of presumptions may be determined. That is, if it is clear that the only or most readily anticipated method for connection is via presumption (and not direct service connection), then one may conclude that the number of cases for various categories of health conditions are presumptively service connected (Pamperin, 2006b). The Committee was unable to obtain additional data on the number of presumptive cases or their impact to the overall VA system. Table 3-1 provides data that were provided to the Committee during its first open session meeting (Pamperin, 2006b).

Because disability cases adjudicated on the bases of presumptive decisions are not routinely counted, the costs are not known with certainty.

TABLE 3-1 Presumptions in VA's Disability Program

Condition	Number of Veterans	Disability Severity Rating
Chronic Diseases		
Arteriosclerosis	Unknown	Not differentiated
Arthritis	Unknown	Same
Leukemia	Unknown	Same
Raynaud's disease	Unknown	Same
Tropical Diseases		
Malaria	30,000	0%
Leishmaniasis	283	0%
Dysentery	872	0%
Plague	10	0%
Prisoners of War		
Any anxiety	Unknown	Most rated 100%
Stroke and its complications	Unknown	100%
Cirrhosis of the liver	Unknown	100%
Peripheral neuropathy	Unknown	100%
Radiation		
Lung cancer	Unknown	Not differentiated
Colon cancer	Unknown	Same
Lymphomas	Unknown	Same
Stomach cancer	Unknown	Same
Herbicide Agents		
Type II diabetes	197,000	Most are 10% and 20%
Prostate cancer	30,000	1/3 at 100%, average 40%
Respiratory cancer	5,000	Half at 100%
Non-Hodgkin's and Hodgkin's	5,000	Half at 100%, balance 50%
Gulf War		
Undiagnosed illness	3,259	Typically a 10% evaluation

SOURCE: Pamperin, 2006b.

However, estimates are made. VA estimated administrative costs for presumptive radiation decisions (bone, brain, colon, lung, and ovarian cancers) as $33,934,297 over 10 years with benefit costs of $768,601,698 over that same time period (McLenachen, 2005, slide 8). Estimated administrative costs for type 2 diabetes from 2001 through 2005 were $62 million with estimated benefit costs of $3.3 billion during that same time period. VA estimated that there would be 20,399 new type 2 diabetes awards in the first year and 179,000 over the next 5 years. The estimates did not include retroactive payments (McLenachen, 2005, slide 12). Today, the most frequent disability for which Vietnam veterans are receiving service-connected compensation is type 2 diabetes (VBA, 2006, p. 34). "At end of fiscal year

2006, nearly 248,000 veterans were service-connected for diabetes. More than 215,000 of these awards were based upon herbicide exposure in Vietnam" (VA, 2007, pp. 6B-13).

Role of Institute of Medicine (IOM)

The National Academies is a private, nonprofit, and independent entity that advises the nation on science, engineering, and health matters (NAS, 2007a). The IOM is one of four entities within the National Academies. The other entities are the National Academy of Sciences, which was created by Congress during Abraham Lincoln's presidency, the National Academy of Engineering, and the National Research Council.

The National Academies convenes committees of its own members and "other experts to address the scientific and technical aspects of society's most pressing problems" (NAS, 2007b, p. 2). All committee members serve without pay. Committee members are screened to ensure that they do not have conflicts of interest. The committees include "experts with the specific expertise and experience needed to address the study's statement of task" (NAS, 2007b, p. 3).

The National Academies use a systematic study process. Study committees typically gather information through "(1) meetings that are open to the public and that are announced in advance through the National Academies' Web site; (2) the submission of information by outside parties; (3) reviews of scientific literature; and (4) the investigations of the committee members and staff" (NAS, 2007b, pp. 5-6).

Committee deliberations are closed to the public and sponsors in order to "develop draft findings and recommendations free from outside influence. . . . All analyses and drafts of the report remain confidential" (NAS, 2007b, p. 6). A rigorous external peer review by a separate group of volunteer experts is undertaken prior to completion of the study. The National Academies are responsible for the final products and their public release. For additional information on the National Academies and the committee process, see http://nationalacademies.org/.

IOM Perspective

The Committee heard from IOM staff about how studies requested by VA were conducted over several decades (Martinez, 2006). On each occasion that VA has asked IOM to conduct a new study for Agent Orange or the Gulf War in support of a possible presumption, a new committee was selected and convened. Each committee had access to the publically available information regarding the work of previous IOM committees but interpreted their statement of task independent of prior committees.

As a result, each committee's operating assumptions and study plans were similar but not fully identical to those of prior committees. They were free to construct their own evidence criteria and ways to weigh the individual research studies that they considered (see Appendixes H-1 and H-2 for IOM Agent Orange and Gulf War committee study charges).

IOM has completed six full, biennial Veterans and Agent Orange (VAO) reviews (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) and three focused (IOM, 2000b, 2004b, 2006a) Agent Orange reviews (see Appendix H-1). A new VAO update report was recently published (IOM, 2007b); this VAO report was being drafted simultaneously and independently of this report. Each of the VAO committees was composed of experts with diverse backgrounds to address their charge. Because of the unique nature of the Agent Orange biennial reviews, some consistency of membership for subsequent reviews across committees has been sustained. As a result, approximately one-third of each VAO committee's members had served on a previous committee and were familiar with the past literature on Agent Orange. This overlap of membership helped to provide historical perspective and some consistency throughout the review process.

The IOM committees have been faced with significant challenges, including

- few directly applicable epidemiologic studies;
- no contemporaneous exposure measurements;
- uncertainty about which veterans were exposed to which agents;
- multiple, possibly synergistic exposures;
- possible long latency for health effects from some agents; and
- significant confounders. (Martinez, 2006, slides 7-8)

Source reference material includes epidemiologic studies (e.g., occupational, environmental, veterans) and toxicologic studies (e.g., animal health effects, cellular-level mechanistic).

The first IOM VAO committee categorized the strength of the evidence available into the following four categories: "(1) sufficient evidence of an association, (2) limited/suggestive evidence of an association, (3) inadequate/insufficient evidence to determine whether an association exists, and (4) limited/suggestive evidence of *no* association" (IOM, 1994, pp. 6-7). Although there have been minor changes to the characterization of these categories over the past 15 years, each of the committees has continued to categorize evidence in this manner (IOM, 1996, 1999, 2001, 2003b, 2005b; see also Appendix H-3).

The committees carrying out the Gulf War (GW) studies requested by VA have approached their task somewhat differently. Similar to the process outlined for Agent Orange, VA requested IOM to "conduct a study

to evaluate the published scientific literature concerning the association between the agents to which the Gulf War veterans may have been exposed and adverse health effects" (IOM, 2000a, p. 2). The first IOM Gulf War committee began its work in January 1999 and identified an initial list of compounds of greatest concern to veterans. Two public laws (Veterans Programs Enhancement Act of 1998. Public Law 105-368. 105th Cong., 2d Sess.; Making Omnibus Consolidated and Emergency Appropriations for the Fiscal Year Ending September 30, 1999, and for other Purposes. 1998. Public Law 105-277. 105th Cong., 2d Sess.) mandated further studies.

The first IOM Gulf War and Health Study committee decided to categorize strength of evidence into the following five categories: (1) sufficient evidence of a causal relationship, (2) sufficient evidence of an association, (3) limited/suggestive evidence of an association, (4) inadequate/insufficient evidence to determine whether an association does or does not exist, and (5) limited/suggestive evidence of no association (IOM, 2000a, pp. 4-5). Although there have been minor language changes to these categories or description of these categories, the individual, stand-alone committees have continued to categorize evidence in this manner (IOM, 2003a, 2004a, 2005a, 2006b, 2007a; see also Appendix H-4). As in the case of the Agent Orange committees, there has been some overlap of committee membership in the Gulf War series. However, the nature of the individual Gulf War reports and specific statements of task have required less overlap of membership and increased the need for more specific scientific expertise and background in the various areas of biological, chemical, and infectious agents depending upon the specific charge to the committee.

These Agent Orange and Gulf War examples show important similarities and differences relevant to the overall presumptive process. Of note, Agent Orange reports by IOM did not explicitly include a causal category in the evaluation, whereas Gulf War reports did include a category of evidence sufficient to infer causation when characterizing the strength of evidence available for all agents evaluated. Consideration of the actual exposure potential for veterans was beyond the charges to the committees.

The statements of task and conclusions from each of the Agent Orange and Gulf War reports may be found in Appendix H.

Role of Veterans Service Organizations (VSOs)

There are numerous VSOs that voice their members' concerns. VSOs and their advisory committees have played an important role in the evaluations and actions of Congress, VA, and the National Academies (e.g., IOM and NRC). There are also special veteran advisory groups, such as the Advisory Committee on Former POWs, with direct access to the VA Secretary. The impact and voices of the veteran community can be very

powerful. A review of the "Agent Orange Update," which describes some of the actions and influence VSOs and other organizations had in moving the Agent Orange Act forward (Cranston, 1990), provides insight into the role VSOs played in that specific congressional action.

The Committee received extremely helpful and diverse input from representatives of VSOs and individual veterans who attended open session committee meetings or who prepared written material to provide to the Committee for its consideration.

Veterans Perspective

The Committee heard that VSOs struggle with how scientific evidence that is uncertain and sometimes limited is used in evaluating cause and effect relationships. The VSO representatives wanted to make certain not only that the Committee considered past conflicts and practices but also that the Committee took into account what is occurring in today's environment and what future veterans may be facing, including emerging problems such as traumatic brain injuries, a signature wound of the current Gulf conflict (Sullivan, 2006).

Other issues raised included better data collection on exposures and health status during military service, the use of International Classification of Diseases codes for illness and injuries, and seamless transition to VA after discharge. The importance of collecting data for reservists and National Guard members identical to those serving active duty was emphasized (Sullivan, 2006).

The Committee repeatedly heard from representatives of VSOs and individual veterans that they expect a fair, equitable, and scientifically based system for establishing presumptions (Kinderman, 2006; Overstreet, 2006; Selfon, 2006). However, the Committee was also cautioned that more rigorous application of tests for cause and effect may not serve the process well (Violante, 2006).

Each of the VSOs reaffirmed the responsibility and commitment to care for all men and women who have served in our stead—past, present, and future. Each stakeholder brings an important perspective to the presumptive disability decision-making process for veterans. There are clearly factors other than science that are considered in these decisions especially when the science base is weak or absent. The future framework will seek to identify ways to improve information and the methods needed to make the best possible presumptive decisions.

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4

Legislative Background on Presumptions

In previous chapters, the Committee has described the historical background for presumptions and the current approach as it has evolved to include Congress, the Department of Veterans Affairs (VA), the National Academies (Institute of Medicine [IOM] and National Research Council [NRC]) and stakeholders. This chapter addresses the legislative background, in greater depth, for three more recent issues that have been a focus for the National Academies (NRC and IOM) and VA: radiation exposure, Agent Orange, and the Gulf War. The same issues are also a focus for case studies that are summarized in the next chapter and provided in their entirety in Appendix I. The legislative materials covered in this chapter provide a picture of the concerns of veteran stakeholders and congressional responses and intent, as set out in specific legislation.

The complexities and perplexities that encumber the presumptive disability decision-making process are evident if we look at the evolution of presumptions governing radiation exposures, the Gulf War, and Agent Orange. We see a variety of approaches, not always consistent, a diverse group of participants—Congress, VA, the National Academies (NRC and IOM), stakeholders, and the courts—and somewhat opaque standards for making decisions. It should be noted that VA proposes to reorganize and rewrite all of its compensation and pension regulations (see 71 Fed. Reg. 16464 [March 31, 2006]) (VA, 2006b). Notices of Proposed Rulemaking have been published and will continue to be published. The discussion that follows does not take these new rules into account.

PRESUMPTIONS FOR VETERANS, IN GENERAL

VA clearly assumes that all congressional presumptions governing veterans' benefits are type 1 presumptions (see Chapter 2 for an explanation of the difference between type 1 and type 2 presumptions) (Zeglin, 2006). Consequently, the veteran is relieved both of producing sufficient evidence of an exposure that is service connected and of persuading VA that his or her adverse health effect was incurred through a service-connected exposure (Basic Entitlement. 2006. 38 U.S.C. § 1110 provides for disability payments for illnesses that were "aggravated" or "incurred" during service). Once a medical condition is service connected through presumptions, and the veteran can document military service consistent with the given exposure or risk, the veteran only has to show the basic fact that he or she suffers from the condition in order to receive the specified disability payment.

The discussion below will focus on the link between disease and service—the question to which scientific reviews are directed. Equally important to the compensation decision, however, is the creation of a presumption that relieves the veteran of having to provide evidence of a military exposure of sufficient magnitude to account for his or her illness or injury (Brown, 2005). See, for instance, 38 U.S.C.A. § 1116(f) (a veteran who served in Vietnam during a specified period is presumed to have been exposed to herbicide containing dioxin); 38 U.S.C. § 1116(f) (Presumptions of Service Connection for Diseases Associated with Exposure to Certain Herbicide Agents; Presumptions of Exposure for Veterans Who Served in the Republic of Vietnam. 2006. 38 U.S.C. § 1116(f); and *Haas v. Nicholson* (2006). United States Court of Appeals for Veterans Claims, Case Number 04-0491 § 1116[f]) is ambiguous as to whether it required veterans to have set foot in Vietnam, and the court extended the presumption to veterans serving in the waters near the shore of Vietnam. Often, as is evident in the case studies, exposure data are lacking, making it impossible to conduct epidemiologic studies of the veterans. In such cases, the medical evidence for the presumption that links the disease to the exposure will relate to a surrogate group, such as workers exposed to the substances at issue. For a discussion of this problem in connection with the Vietnam War presumptions, see Stellman and Stellman (2005).

In theory, all presumptions, including those that govern a veteran's ability to show exposure, prove health outcomes, establish that a disability did not predate service (*Wagner v. Principi.* 2004. United States Court of Appeals for the Federal Circuit, Case Number 02-7347), or establish some other element of a claim, are rebuttable as provided in 38 U.S.C.S. § 1113 (Presumptions Rebuttable. 2005. 38 U.S.C. § 1113). VA assumes that an individual was medically sound when entering military service. However, that presumption of soundness is sometimes challenged if evidence shows

a preexisting condition. See examples in the *Veterans Benefits Manual* (VA, 2005). Federal circuit court has held that evidence rebutting a presumption must only meet a "preponderance of the evidence" standard unless Congress specifies a higher standard (*Thomas v. Nicholson*, 2005. United States Court of Appeals for the Federal Circuit, Case Number 05-7019).

In practice, presumptions establishing that a veteran's adverse health effects are service connected are rarely rebutted. David Barrans of the VA Office of the General Counsel acknowledged in response to a question after his oral presentation at the July 2005 Veterans' Disability Benefits Commission meeting that VA claims adjusters (veterans service representatives) generally do not seek to develop information to rebut presumptions. Accordingly, one does not see many claims rejected because of evidence that the disease predated the veteran's military service or because the presumptive condition is found to stem from an intercurrent cause. VA does have provisions for developing evidence of "willful misconduct" if it may affect these claims (Basic Entitlement. 2006. 38 U.S.C. § 1110; Basic Entitlement. 2007. 38 U.S.C. § 1131), but the limited provisions are rarely relevant to presumptive claims (see Presumptions Rebuttable. 2005. 38 U.S.C. § 1113; Line of Duty and Misconduct. 2005. 38 C.F.R. § 3.301). Accordingly, in practice the presumptions governing service connection are not rebutted and operate more as rules of law than procedural devices; they mandate finding a nexus between the veteran's service and a specified disability or disease.

If Congress wished, it could specify evidence that may or may not be used to rebut a presumption. It has done so in other statutes, unrelated to veterans' benefits that rely on presumptions to establish benefits under a compensation scheme. For instance, the Back Lung Benefits Act (Congressional Findings and Declaration of purpose. 2007. 30 U.S.C. § 901, et seq.) contains a number of rebuttable type 2 presumptions that operate to prove that a miner was disabled due to pneumoconiosis and that this disability arose out of his employment in coal mines. The regulation accompanying this legislation specifically provides that certain items of evidence shall not suffice to rebut the presumption of disability (Presumption of Entitlement Applicable to Certain Death Claims. 2003. 20 C.F.R. § 718.306[d]). The courts have taken this to mean that a combination of items can be used to rebut the presumption. Similarly, the National Childhood Vaccine Act (Establishment. 2007. 42 U.S.C. § 300aa-1) contains a vaccine injury table (Vaccine Injury Table. 2007. 42 U.S.C. § 300aa-14) setting out presumptions that particular adverse health effects occurring within a specified period after a child was vaccinated were caused by the vaccination. The act also requires showing that "there is not a preponderance of the evidence" that the claimed injury "is due to factors unrelated to the administration of the vaccine" (Determination of Eligibility and Compensation. 1999. 42 U.S.C.S. § 300aa-13[a][1][B]). These factors may, as shown by the claim-

ant's evidence or other material in the record, "include infection, toxins, trauma (including birth trauma and related anoxia), or metabolic disturbances which have no known relation to the vaccine involved, but which in the particular case are shown to have been the agent or agents principally responsible for causing" the claimed injury (Determination of Eligibility and Compensation. 1999. 42 U.S.C. § 300aa-13[a][2][B]).

The claims process becomes more complicated, less certain, and more expensive if evidence has to be scrutinized by a claims adjuster. The current system of creating presumptions that permit "automatic" awarding of benefits when a veteran suffers from a named presumptive disease promotes administrative efficiency. It means, however, that scientific input into decisions about a veteran's entitlement to disability payments occurs only at the front end of the process when a decision is made whether or not to service connect.

PRESUMPTIONS GOVERNING RADIATION, AGENT ORANGE, AND GULF WAR EXPOSURES, IN GENERAL

Many veterans exposed to radiation or Agent Orange in Vietnam or who served in the Persian Gulf War[1] alleged they suffered from adverse health effects incurred through military service. Eventually, as discussed below, Congress legislated with regard to all three situations. Some of this legislation lists specific illnesses and adverse health effects and authorizes VA to adopt presumptions through rule making that would relieve a veteran from having to prove a service connection. Although the statutes resemble each other in some respects, and may have influenced each other, the case studies indicate that the data, decisions, and decision makers underlying the presumptions are quite dissimilar. For example, both Congress and VA have established presumptions for radiation. Only VA has established presumptions for Agent Orange. And although VA was given the authority by Congress to do so, VA has not made presumptions of service connection to date for diseases incurred by Persian Gulf War veterans; however, VA administers compensation for Persian Gulf War veterans who are service connected by the congressionally established presumption of "undiagnosed illnesses" that may become manifest within a presumptive period after service in the Gulf.

Although most radiation exposures occurred considerably earlier than the Agent Orange exposures during the Vietnam War, Congress started to pay attention to both problems at approximately the same time.

[1]As defined in 38 U.S.C. § 101 (33), the term "*Persian Gulf War*" means "the period beginning on August 2, 1990, and ending on the date thereafter prescribed by presidential proclamation or by law."

The Radiation Presumptions

In 1984, Congress passed the Agent Orange and Atomic Veterans Relief Act (Public Law No. 98-592, 98 Stat. 2725 [1984] eventually became Veterans' Dioxin and Radiation Exposure Compensation Standards Act. 1984. Public Law 98-542. 98th Cong., 2d Sess.), which provided benefits for veterans who had participated either in atomic bomb testing or in the postwar occupation of Hiroshima or Nagasaki if they developed leukemia, polycythemia vera, or carcinoma of the thyroid. This was intended to be a temporary measure until further studies were completed (see HR, Report 98-592, 98th Cong. 2d session, U.S. Congress, House of Representatives, 1984). This act does not contain presumptions but directed VA to adopt regulations that would assist veterans who had been exposed to radiation.

In 1988, Congress passed the Radiation Exposed Veterans Compensation Act (1988. Public Law 100-321. 100th Cong., 2d Sess.). The act created a presumption that a veteran who suffered from one of 13 specified cancers, and who had participated in atomic bomb testing or the postwar Japanese occupation or was a Japanese prisoner of war during the specified time period, was entitled to disability benefits and free medical treatment. In 2002, an additional 5 cancers were added to the presumptive list (VA, 2002).

Regulations adopted pursuant to the Veterans' Dioxin and Radiation Exposure Compensation Standards Act (Claims Based on Exposure to Ionizing Radiation. 2006. 38 C.F.R. § 3.311) were designed to assist veterans who are not suffering from one of the presumptive cancers. If the veteran is suffering from a "radiogenic" disease listed in the regulation, VA is required to assess the "size and nature of the radiation dose" that the veteran may have received. When VA receives dose information and the report reflects a range of possible exposure levels, then VA must presume exposure at the highest end of the reported exposure range in making its determination (Claims Based on Exposure to Ionizing Radiation. 2006. 38 C.F.R. § 3.311[a]). Even if the disease is not listed as a "radiogenic" disease, VA is nevertheless required to "consider the claim under the provisions of this section provided that the claimant has cited or submitted competent scientific or medical evidence" of the disease's being "radiogenic" (Claims Based on Exposure to Ionizing Radiation. 2006. 38 C.F.R. § 3.111[b][4]). Claims are referred to the Under Secretary for Benefits who must determine whether "sound scientific and medical evidence supports the conclusion" that "it is at least as likely as not the veteran's disease resulted from exposure to radiation in service. 'Sound scientific evidence' means observations, findings, or conclusions that are statistically and epidemiologically valid, are statistically significant, are capable of replication, and able to withstand peer review, and 'sound medical evidence' means observations, findings, or

conclusions that are consistent with current medical knowledge and are so reasonable and logical as to serve as the basis of management of a medical condition" (Claims Based on Exposure to Ionizing Radiation. 2006. 38 C.F.R. § 3.111c).

Of all the presumptions, those governing exposure to radiation probably rest on the firmest scientific evidentiary basis. As the case study indicates (see Appendix I), a great deal is known about the effects of radiation. Groups other than veterans who were exposed to radiation, such as downwinders, had exposures similar to the veterans, unlike the very different exposures experienced by workers who were treated as surrogates for veterans in studying the effects of dioxin exposures in factory accidents.

Nevertheless, despite the presumptive diseases that have been established, many veterans have difficulty in establishing a service connection; they may be unable to furnish the required evidence of their exposure at a specified location and time, in part because such information may be classified as secret (Podgor, 2005). They may then seek compensation under the nonpresumptive regulations because those provide that if the veteran claims to have been in a specified location on a particular date and the government cannot prove otherwise, it must be assumed that the veteran participated in activities that would have given rise to a presumptive decision. However, because this is a nonpresumptive claim, the veteran will have to show adequate exposure (Podgor, 2005). In 2003, an NRC committee concluded that only about 50 nonpresumptive claims had been successful although thousands had been filed (NRC, 2003, p. 252).

The Agent Orange Presumptions

The historical background that led to the Agent Orange presumptions is set out in Chapter 2. By 1984, the courts had rejected the veterans' claims that their illnesses were caused by exposure to Agent Orange, and VA was not providing disability benefits except for cases of chloracne. The veterans had fared better with Congress, which in 1981 authorized VA to provide hospital and outpatient care for veterans whose health problems allegedly stemmed from Agent Orange exposures (Veterans' Health Care, Training, and Small Business Loan Act. 1981. Public Law 97-72. 97th Cong., 1st Sess.). When in 1984 Congress acted again and passed the Veterans' Dioxin and Radiation Exposure Compensation Standards Act (1984. Public Law 98-542. 98th Cong., 2d Sess.), President Reagan observed in his signing statement that VA had already furnished medical care to over one million Vietnam veterans (Reagan, 1984).

The 1984 act took three steps toward creating service-connection presumptions for diseases suffered by Vietnam veterans (Murphy, 1986). First, the act created some interim presumptions by directing VA to grant

temporary disability benefits, lasting until September 30, 1986, to any veteran who contracted chloracne (a skin condition) or porphyria cutanea tarda (a liver disease) within one year of leaving Vietnam (Murphy, 1986). Second, the act required the Administrator of Veteran Affairs to promulgate guidelines and standards for determining whether claims based on exposure to Agent Orange were service connected (Murphy, 1986). Congress thereby authorized VA to handle dioxin claims via new procedures that it was to devise and promulgate through formal rule making rather than by adjudications in individual proceedings. Third, the act directed the formation of an advisory committee to collect and evaluate scientific studies relating to the possible health effects of exposure to Agent Orange (Veterans' Dioxin and Radiation Exposure Compensation Standards Act. 1984. Public Law 98-542. 98th Cong., 2d Sess.).

In August 1985, after receiving input from the Veterans' Advisory Committee on Environmental Hazards, VA issued final regulations relating to the 1984 act that set out a process for adjudicating claims based on Agent Orange exposure (VA, 1985). The regulations concluded that "sound medical and scientific evidence does not establish a cause-and-effect relationship between dioxin exposure" and any disease other than chloracne (Claims based on exposure to ionizing radiation. 1985. 38 C.F.R. § 3.311a[d]).

In 1987, a number of veterans instituted a lawsuit challenging VA's regulations as violating the 1984 act by adopting too high a standard for finding a connection between exposure to Agent Orange and manifestation of a particular disease (*Nehmer v. United States*, 1989, United States District Court for the Northern District of California, Case Number 86-6160). The plaintiffs contended that "Congress intended only that there be a significant 'statistical association' between dioxin and a particular disease in order to grant service connection for that disease." VA conceded that its regulation required "proof of a causal relationship to grant service connection." The court, after explaining that the issue to be decided was legal—what was Congress' intent—and not the scientific question of which test was scientifically valid, turned to the language of the 1984 act in order to determine congressional intentions (*Nehmer v. United States*, 1989, United States District Court for the Northern District of California, Case Number 86-6160, pp. 4-6).

The court first pieced together a number of different statements in the act because the applicable standard of proof was not directly addressed. The court found that "the language of the act is at best ambiguous, at worst silent" because Congress spoke in terms of both association and cause. Because the text was inconclusive, the court next looked at the legislative history to ascertain Congress' purpose. After reviewing comments by members of House and Senate committees that had jurisdiction over the act, the court concluded "that Congress did not intend VA to use a causal relation-

ship," but suggested that "service connection to be granted on the basis of 'an increased risk of incidence,' or a 'significant correlation' between dioxin and various diseases." According to the court, this standard was consistent with previous practices that had established presumptions of service connectedness for amputees and prisoners of war (*Nehmer v. United States*, 1989, United States District Court for the Northern District of California, Case Number 86-6160, pp. 7-9).

VA announced that it would not appeal the *Nehmer* decision and that it would abide by the court's ruling and issue new Agent Orange regulations. The litigation has continued as to whether veterans denied benefits pre-*Nehmer* are entitled to receive benefits retroactively even for conditions that were service-connected after the date of *Nehmer*. The 9th Circuit Court of Appeals so held on July 19, 2007. Congress also took further steps. In 1991, after numerous hearings and committee reports, it enacted the Agent Orange Act (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.; codified, as amended, Presumptions of Service Connection for Diseases Associated with Exposure to Certain Herbicide Agents. 2006. 38 U.S.C. § 1116).

The Agent Orange Act continued to use both association and causation language, albeit in a somewhat different form. It gave the VA Secretary authority to prescribe regulations providing for a presumption "[w]henever the Secretary determines, on the basis of sound medical and scientific evidence, that a positive association exists between" the Agent Orange exposure and a disease. The act states that

> An association between the occurrence of a disease in humans and exposure to an herbicide agent shall be considered to be positive for the purposes of this section if the credible evidence for the association is equal to or outweighs the credible evidence against the association. (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.)

Rather than relying on an advisory committee to furnish scientific input, the act directed VA to contract with the National Academy of Sciences (NAS) "to review and evaluate the available scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.). In making an association determination, the VA Secretary was instructed to consider the NAS reports and "all other sound medical and scientific information and analyses available to the Secretary," and in evaluating any study, the VA Secretary is to "take into consideration whether the results are statistically significant, are capable of replication, and withstand peer review" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.).

Congress directed the committee to answer "to the extent that available scientific data permit meaningful determinations" (Scientific Determinations Concerning Disease. 2006. 38 U.S.C. § 1116.3[d][1]) about

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
3. whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and disease.

The first IOM Veterans and Agent Orange (VAO) committee that was convened to respond to these questions (IOM, 1994, p. 15) concluded that a lack of exposure data made it impossible to answer the second question. The other two questions required the committee to examine the cause of the particular health effect at issue. This is explicit in question 3, which mandates inquiry into a "causal relationship." Question 1 also requires a causal inquiry, though it makes this request implicitly. As Dr. Hertz-Picciotto, the chair of the 2000 and 2002 IOM committees explained: "[A]ny determination about the existence of 'statistical association' that takes into account 'strength' of the evidence and 'appropriateness' of the methods examines the same concerns that enter into a consideration of evidence for causation" (Hertz-Picciotto, 2005, p. 556).

The first IOM VAO committee began meeting in 1992 and issued its first review in 1994 (IOM, 1994). It decided to place the data it found and reviewed into one of four categories: sufficient evidence of an association; limited/suggestive evidence of an association; inadequate/insufficient evidence to determine whether an association exists; limited/suggestive evidence of no association. It was required to update its reports every 2 years or sooner.

The IOM VAO committees at times changed the category for several particular health outcomes, as successive reviews considered additional evidence. VA's response and establishment of a presumption to the IOM categorization of the particular health outcome was not necessarily consistent. For example, the VAO committees in 1994 and 1996 characterized the evidence linking Agent Orange to prostate cancer as limited/suggestive of an association (IOM, 1994, 1996). VA did not establish a presumption for prostate cancer in 1994. It was not until 1996 that VA decided that prostate cancer should be presumptively service-connected (VA, 1996). In another example, the 1994 IOM VAO committee characterized the evidence linking herbicides to type 2 diabetes to be inadequate/insufficient to determine

if an association existed (IOM, 1994). In 2000, a special Agent Orange committee was constituted at the request of VA to evaluate type 2 diabetes independent of the IOM VAO biennial reviews (IOM, 2000b). The committee characterized the evidence as limited/suggestive of an association (IOM, 2000b). VA then decided that type 2 diabetes should be presumptively service-connected (VA, 2001). It was not clear from the *Federal Register* notice why VA concluded that the existence of limited/suggestive evidence was equivalent to the requirement of "credible evidence for the association is equal to or outweighs the credible evidence against the association" or a "positive association" as required by the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.). The statement in the *Federal Register* reporting the VA Secretary's decision to presumptively service-connect (VA, 2001) did not explicitly explain how these conclusions were reached.

The Persian Gulf War Presumptions

The Persian Gulf War was fought during a very short period in 1991. Almost immediately, veterans began to complain of numerous adverse health effects that they attributed to service in the Gulf. It immediately became evident to Congress and VA that the Persian Gulf veterans' health complaints differed significantly from those voiced by the Vietnam veterans. The Vietnam veterans ascribed their medical woes to herbicides and Agent Orange, and they claimed that the numerous well-defined diseases from which they suffered, ranging from skin and liver diseases to a variety of cancers, could be attributed to exposure to herbicides and Agent Orange. The Persian Gulf War veterans, on the other hand, claimed to be suffering from syndromes and symptoms rather than established diseases, and they blamed these on exposures to a host of toxic environmental substances that were present in the Persian Gulf. Many of the exposures are no different than those experienced by civilians in the United States, and for the great majority of veterans, the magnitude of the exposures was small, and limited to a short period of time (Brown, 2005).

Congress began by authorizing VA to provide health-care services on a priority basis to Persian Gulf veterans (Priority VA Health Care for Persian Gulf Veterans. 1993. Public Law 103-210. 103d Cong., 1st Sess.). An effort was also undertaken to gather data about the nature of the illnesses and symptoms that veterans claimed to have, as well as to conduct research on environmental exposures that occurred during the war. In 1994, Congress passed the Veterans' Benefits Improvements Act (Public Law 103-446. 103rd Cong., 2d Sess., codified as Compensation for Disabilities Occurring in Persian Gulf War Veterans. 2006. 38 U.S.C. § 1117), which authorized VA to compensate veterans for certain chronic disabilities and illnesses that could not be attributed to any known clinical diagnosis. Originally,

these adverse health effects had to manifest within 2 years of service in the Persian Gulf in order for a veteran to receive compensation. This presumptive time period has, however, been extended a number of times. Most recently in December 2006, compensation is now available provided the disability of "undiagnosed illness" becomes manifest by December 31, 2011 (VA, 2006a, p. 75672).

In 1998, Congress passed the Persian Gulf War Veterans Act of 1998 (Public Law 105-277. 105th Cong., 2d Sess., codified, in part, as Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 U.S.C. § 1118) and the Veterans Programs Enhancement Act of 1998 (Public Law 105-368. 105th Cong., 2d Sess.). These acts, which are similar to the Vietnam War Agent Orange legislation, set up procedures for establishing presumptions of service connection for diseases incurred by Gulf War veterans. As in the Agent Orange legislation, "a positive association" is required between an environmental exposure associated with service in the Persian Gulf War and "the occurrence of a diagnosed or undiagnosed illness in humans or animals" (Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 U.S.C. § 1118[b][1][B][ii]). In addition, the Gulf War Act stated that an association "shall be considered to be positive . . . if the credible evidence for the association is equal to or outweighs the credible evidence against the association" (Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 U.S.C. § 1118[b][3]). The same review process as was set up for Agent Orange was established for Gulf War. An agreement was entered into with NAS to establish committees that were charged with answering similar questions as asked of the IOM VAO committees (Persian Gulf War Veterans Act of 1998. Public Law 105-277. 105th Cong., 2d Sess.). As with Agent Orange, the IOM committee provides its Gulf War reports to VA, and the VA Secretary must then determine whether a presumption should be established and announce the decision in the *Federal Register*. IOM has issued several volumes of Gulf War reports (IOM, 2000a, 2003, 2005, 2006, 2007).

Although VA was given the authority by Congress to do so, VA has not made presumptions of service connection to date for diseases incurred by Persian Gulf War veterans pursuant to 38 U.S.C. § 1118 (Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 U.S.C. § 1118). However, VA administers compensation for Persian Gulf War veterans who are service connected by the congressionally established presumption of "undiagnosed illnesses" that may become manifest within a presumptive period after service in the Gulf. In February 2006, the VA Secretary wrote to leaders of the House and Senate Veterans Affairs Committees advising them that the

evidence currently available did not warrant the establishment of Persian Gulf presumptions and that VA would publish notices of its decision in the *Federal Register* "explaining the basis for that determination" (Nicholson letters on file with committee, 2006a,b,c,d). As of the time of report publication, no statement appears in the *Federal Register*, although such statements are required to be filed within 60 days of the receipt of an IOM report (Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 U.S.C. § 1118). Although the presumptive service-connection mechanism has not been a major factor for Persian Gulf veterans, a comparatively large percentage of Persian Gulf veterans have, nonetheless, been able to collect compensation through the direct service-connection route (Brown, 2006).

As of now, the Persian Gulf statutes would govern any presumptions dealing with current service in Iraq or any other area in the Gulf.

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5

Case Studies Summary Chapter

INTRODUCTION

In addressing its charge with regard to characterizing Congress' and the Department of Veterans Affairs' (VA's) presumptive disability decision-making process for veterans, the Committee completed the set of case studies around specific exposures and illnesses listed in Table 5-1. The Committee determined that a thorough evaluation of selected case studies would capture past practices of all participants involved in the presumptive disability decision-making process for veterans—Congress, VA, the National Academies' (Institute of Medicine [IOM] and National Research Council [NRC]), stakeholders, and the courts—and provide a basis for making sound and practical recommendations for the future of this process. The complete, specific case studies are found in Appendix I.

The case studies were selected to reflect the range of presumptive decisions established by Congress and VA, as they made decisions using evidence ranging from abundant and quite conclusive in the case of radiation to much more limited in cases such as Agent Orange and prostate cancer. The examples were also chosen to illustrate approaches taken by IOM and NRC committees in evaluating evidence related to presumptions. In the case studies, the Committee focused on examining the evidence foundation available for evaluation by Congress, the IOM or NRC, and VA; the approaches taken for reviewing the evidence; the schema used to classify the level of evidence for causation; and the translation of the scientific evidence through the conclusions of the IOM and NRC committees into a decision by VA. The case studies also provided insights into principles embedded in the presumptive disability decision-making process.

TABLE 5-1 List of Case Studies (in chronological order of when presumptions were established by Congress or VA)

Mental Disorders' Presumptions
Multiple Sclerosis Presumption
Prisoners of War (POWs) Presumptions
Amputees and Cardiovascular Disease Presumption
Radiation Presumptions
Mustard Gas and Lewisite Presumptions
Gulf War Presumptions
Agent Orange and Prostate Cancer Presumption
Agent Orange and Type 2 Diabetes Presumption
Spina Bifida Program*

*Because spina bifida is a condition that affects the children of veterans, it is not a presumptive decision for veterans; however, the children of Vietnam and Korean War veterans are covered by a VA program.

The case studies were based on detailed review of public laws, legislative background, research reports, National Academies' IOM and NRC committees' reports, and VA materials. However, as described in Chapter 1, the case studies were limited by VA's response to the Committee's request for information, documents, and responses to the Committee's written questions. The case studies synthesize a large body of information. This body of information is summarized in Annex 5-1 at the end of this chapter, and the full case study series is in Appendix I. Additional materials on individual case studies and cost estimates are also referenced at the end of this chapter in Annexes 5-2 and 5-3. This chapter synthesizes the "lessons learned" from each of the case studies. We begin by summarizing each of the case studies and the particular lessons learned and then look across the case studies as a group for more general conclusions. The case studies are presented in chronological order as to when presumptions were established by Congress or VA. In drawing out these lessons as a basis for moving forward, the Committee's commentary should not be construed as a critique of past activities and processes of Congress, VA, and National Academies' IOM and NRC committees. This Committee recognizes that these activities took place over decades during which scientific research and evidence review processes were evolving and that tremendous efforts from all participants in the process went into producing all of the work that we summarize as follows.

MENTAL DISORDERS' PRESUMPTIONS

Description

There have been two major types of presumptive disabilities for mental disorders among U.S. veterans: those presumed to be chronic and those among POWs. The diversity of these disorders has posed a challenge. The presumptive disabilities assigned to posttraumatic stress disorder (PTSD), depression, and any anxiety state for POWs are well grounded in the scientific literature (Beebe, 1975; CDC, 1988; Cohen and Cooper, 1954; Engdahl and Page, 1991; Keehn, 1980; Nefgzer, 1970; Page et al., 1997). The presumptive disability category for psychosis among veterans has a more limited base of evidence (Beebe, 1975; Keehn, 1980) and appears a consequence of its initial inclusion as a presumptive disability when presumptions first began in 1921. At that time, the disorder (then called neuropsychiatric disease) had no treatment and was considered to be chronic.

Lessons Learned

Presumptive decisions for mental disorders have been made for veterans who are former POWs and veterans who developed chronic mental problems during or shortly after military service. Although legislation has been informed by the scientific evidence available at the time, the scientific evidence in some instances has been limited and with inconsistency around the disorders included. For example, if the strength of evidence classification of limited/suggestive evidence led to presumptive decisions for PTSD, dysthymia, and any anxiety state among former POWs, then there does not appear to be a clear basis for excluding other mental disorders with equal or stronger evidence of connection to being a POW, such as major depression. The presumptive decisions established with regard to the previously mentioned mental disorders make clear that these decisions have been influenced by not only scientific evidence but by political and social considerations that apply to these veterans (e.g., POWs) and the specific mental disorders they may manifest. The need to develop a stronger evidence base and consistent evaluation of the evidence base with regard to these mental disorders is great, particularly in light of the anticipated high rates of mental disorders among military personnel assigned to and returning from Iraq and Afghanistan. This case study also illustrates the need for a process to continually carry out research and update the scientific evidence base for presumptions.

MULTIPLE SCLEROSIS PRESUMPTION

Description

This case study examines the 1962 decision to grant compensation for service-connected disability to veterans diagnosed with multiple sclerosis (MS) within 7 years of their separation from the military. This presumption stems from the VA's interest in compensating disease and disability that has its onset *during* military service. Veterans with one of a defined list of chronic diseases may also be compensated if these are diagnosed within 1 year of separation from the military. The rationale here is that these diseases are sufficiently insidious and the diagnosis sufficiently challenging so as to make it impossible to conclude with certainty that the true disease onset *did not* occur during the period of military service.

Multiple sclerosis was eventually singled out from the other chronic illnesses and the period of diagnosis extended from 1 year (Veterans' Chronic and Tropical Diseases Act of 1948. Public Law 80-748. 80th Cong., 2d Sess.; VA, 1949), to 2 (Act of October 12, 1951. ch. 499, 65 Stat. 421 as cited in VA, 1993), to 3 years (Act of August 25, 1959. Public Law 86-187. 86th Cong., 1st. Sess. as cited in VA, 1993), and eventually to 7 years (Veterans' Disability Compensation Increase Act of 1962. Public Law 87-645. 87th Cong., 2d Sess. as cited in VA, 1993) following separation from military service. The rationale for this extension was the growing scientific evidence (much of it generated by VA researchers studying veterans) of the long delay between the onset of MS symptoms and eventual diagnosis, as well as the possibility that environmental factors may play a role in the etiology of MS. However, these studies also failed to find evidence that military service contributes to MS risk, and veterans do not appear to have higher rates of MS than the general population (Berkowitz and Santangelo, 1999; Kurtzke and Page, 1997; Kurtzke et al., 1979, 1985, 1992; Norman et al., 1983; Page et al., 1993, 1995; VA Multiple Sclerosis Study Group, 1956, 1957; Wallin et al., 2000).

Lessons Learned

The rationale for the MS presumption reflects two lines of reasoning used in making presumptions. The first reflects the possibility that MS diagnosed after separation from the military may, in fact, have been present during military service, and therefore subject to the same compensation rules as other direct service-connection disabilities. The second acknowledges that the etiology of MS is unclear and may be related to an environmental exposure received during military service. Understanding that both of these arguments have been used in the MS case is important, because the

evidence required to support each is very different. In the first case, timing is the standard (specifically the possibility of disease onset during military service), and evidence for association between an exposure and outcome is not required. By contrast, in the second case, evidence from some association between exposure during service and future disease is necessary.

Congress did not call for a systematic review of the scientific literature on this topic; such a review might have allowed for more evidentiary discussion of the premise behind this presumption and the type of evidence that might be necessary to support it.

PRISONERS OF WAR PRESUMPTIONS

Description

Disability presumptions concerning American veterans who were captured and interned as POWs almost uniformly developed as a result of congressional initiatives prompted by concerns over the harsh treatment that POWs had endured and practical difficulties that they might encounter in establishing entitlement to benefits. Concerned that World War II POWs might lack official medical records and have difficulties establishing the conditions of their internment, Congress first instructed VA to give special consideration and apply liberal evidentiary standards to POWs' claims. As details of the harsh nature of the POW experience became more widely known, and as members received complaints from some former POWs having difficulties establishing disability benefit claims, Congress began to enact statutory presumptions for certain nutritionally related conditions and mental illness. Studies of mortality and morbidity among POWs suggesting connections of the POW experience with certain diseases and conditions also served as impetus for additional legislation, notwithstanding scientific limitations noted in those studies (Keehn, 1980; Nefzger, 1970; Page and Miller, 2000; Page and Ostfeld, 1994; Page and Tanner, 2000; VA, 1993). Over the course of more than 50 years, certain preconditions that had to be met before a presumption could attach, such as length or internment or the time period in which a condition must first be manifested, were progressively liberalized or eliminated by statute. In 2004 VA established administrative standards for any new POW presumptions based on "limited/suggestive evidence" of an association of the disease with internment provided that it was "biologically plausible" (VA, 2004).

Lessons Learned

Americans and their elected representatives have long been concerned with the welfare of those who protected, defended, and sacrificed for their

country. The extensive system of veteran benefits and their liberalized rules for qualification are a manifestation of this concern. This concern is intensified when those veterans seeking assistance are viewed as having been subjected to extraordinary stresses and sacrifices, as have POWs. As VA declared in its 1980 study, the POW experience was an "extremely harsh and brutal experience," ". . . characterized by starvation, diet, poor quality or nonexistent medical care, 'death marches,' executions, and torture" (VA, 1980, p. 4).

Given this context, the creation of certain presumptions with respect to disabilities claimed to be connected with a veteran's experience as a POW reflects long established concern for their welfare. These presumptions simplify adjudication for otherwise difficult cases because of the lack of specific evidence on exposures and the complexity of the health consequences of having been a POW. A difficult burden of proof for the veteran and VA is removed by a presumption. Presumptions have been particularly helpful in assessing POW claims for which information about individual conditions of internment and complete medical records were frequently unavailable. Presumptions have enabled greater consistency in decision making for POWs; a previous lack of consistency generated much discontent by veterans who strongly communicated their concerns to elected representatives.

Research has been carried out on the health of former POWs (Beebe, 1975; Brass and Page, 1996; Cohen and Cooper, 1954; IOM, 1992; Keehn, 1980; Nefzger, 1970; Page and Brass, 2001; Page et al., 1991, 1997; VA, 1980). The studies, which date back to the early 1950s, have slowly provided evidence on the POW experience, particularly about malnutrition, stress, and the psychological consequences.

At the same time, evidence relevant to particular presumptions was sometimes limited by coming from a single study with a small sample size. Consequently, interpretations of most studies acknowledged the uncertainties of findings and urged caution at drawing unwarranted inferences. As described by one author, the mixture and interdependence of various factors of the POW experience and the variation of their relative intensities "from time to time, from place to place, and from man to man," have "limit[ed] the scope and specificity of the inferences that may be drawn statistically" (Nefzger, 1970, p. 124).

Given the suggestive but scientifically uncertain results of many studies, not surprisingly policy makers frequently decided to create service-connected presumptions when faced with the pressing claims of genuinely sick and disabled former POWs. As one author observed of his 1992 study of POWs, the "descriptive" data obtained had "uses beyond the scientific," specifically in the "discussion of military service-connected disabilities." He added, "[d]espite the fact that sound inferences about the group of all former POWs cannot be drawn from the exam data in this report, policymakers

who must deal with such issues should be able to review this descriptive information" (IOM, 1992, p. 5; emphasis added). VA in its 2004 *Guidelines for POW Presumptions* responds to uncertainty; while expressing an intent to base its determinations on "sound scientific and medical evidence," it adopts a standard of "limited/suggestive evidence" of an association for former POWs and adds the additional caveat that "fairness to former POWs requires that VA fully evaluate the available data and not accord undue significance to the fact that such data are comparatively limited by the small size of the affected population" (VA, 2004, p. 60085).

The POW case study illustrates how uncertainties of the available scientific information have been relatively weighted against other driving factors for compensating POWs. Over time, the requirement that a presumptive decision be "based on sound scientific and medical evidence" has increasing been overshadowed by these other considerations, reflecting the determination to assure that compensation for former POWs has maximum sensitivity.

AMPUTEES AND CARDIOVASCULAR DISEASE PRESUMPTION

Description

This case study examines the 1979 presumption of service connection for cardiovascular disease that develops in veterans with certain types of service-related amputations. This case study was chosen to illustrate several important features. First, in contrast to many presumptions that exist because of the difficulty establishing exposure status among veterans, this presumption applies to a defined group of veterans for whom exposure (i.e., amputation) is not in question. Controversy regarding whether amputation was linked to cardiovascular disease prevented this complication from being compensated through standard individual claims and therefore necessitated the presumption. Second, this presumption was put in place through legislative action on the part of Congress, not administratively by VA, as is the case with many of the other presumptions. Third, the scientific basis for this presumption is a single Medical Follow-Up Agency (MFUA) study of World War II amputees and their mortality from cardiovascular disease (Hrubec and Ryder, 1980). During the more than 30 years of follow-up of the study population, 922 proximal amputees died; 714.1 deaths were expected based on the general U.S. male death rate. Compared with distal amputees and those with disfigurement, proximal amputees had a higher risk of all-cause mortality, diabetes, and cardiovascular disease, particularly atherosclerotic (ischemic) heart disease.

Lessons Learned

The lessons from this case study center around the type of evidence necessary to put a presumption in place, specifically what level of evidence should be required for a presumption; how the scientific base of evidence is updated based on new studies; how to evaluate evidence regarding exposures, outcomes, and potential mediators; and what types of evidence might make the scientific basis for a presumption more robust. This presumption was put into place largely on the basis of one study and further studies on cardiovascular disease in amputees have not been carried out, even though the occurrence, management, and natural history of cardiovascular diseases have changed substantially in the subsequent three decades. In the decades since the presumption was implemented, many aspects of cardiovascular disease have changed; incidence rates have dropped, as has mortality; new preventive approaches are available, and treatments are increasingly effective. However, further studies have not been carried out on cardiovascular disease in subsequent cohorts of amputees, nor were data systems put in place to carry out surveillance for changing disease risks in the amputees. Special populations, such as the amputees, could be closely tracked through registries (i.e., specific cohort studies) to make certain that previous scientific observations hold and to assess if the establishment of additional presumptions is needed.

RADIATION PRESUMPTIONS

Description

The radiation case study is concerned with the experience of the "atomic veterans" who were exposed to ionizing radiation, mainly through participation in nuclear weapons tests. In this case study, unlike most of the others, there is an abundant literature—some relating to dose-response relationships in general populations, some specific to veterans—upon which to base compensation policy (CIRRPC, 1988; IARC, 2000; IOM, 1996a, 2002; Lagakos and Mosteller, 1986; Lubin and Steindorf, 1995; NRC, 1980, 1984, 2003, 2005, 2006; Podgor, 2007; Prentice et al., 1983; RECAC, 1996; UNSCEAR, 2000). In general, most veterans for whom exposure estimates are available appear to have had relatively low doses, and a summary of the epidemiologic evidence suggests that the majority of cancers in this group were not caused by radiation. Despite this, there remain numerous uncertainties, particularly with respect to estimation of an individual's exposures and with respect to the risk for specific rare cancers. These uncertainties in large part are responsible for the shift in emphasis from individual dose-based criteria for compensation in the

Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984 (Public Law 98-542. 98th Cong., 2d Sess.) to the establishment of presumptions in the Radiation-Exposed Veterans Compensation Act of 1988 (Public Law 100-321. 100th Cong., 2d Sess.), illustrating the need for presumptions even in this relatively data-rich situation. It also illustrates that epidemiologic studies of veterans themselves can be less informative than other nonmilitary populations because of such issues as limited sample size, inadequate length of follow-up, low doses, poor dosimetry, other potential biases, and difficulties in teasing out the effects of modifiers such as smoking. Finally, the radiation story illustrates the practical difficulties posed by the secrecy under which these nuclear weapons test operations were conducted, posing difficulties both for researchers and for individual veterans seeking to document their claims.

Lessons Learned

For radiation exposure, in contrast to the factors considered in the other case studies, epidemiological evidence on risks is abundant and the dose-response relationships for cancer have been described with reasonable precision from such major studies as that of the atomic bomb survivors. Epidemiological studies have been carried out on radiation-exposed veterans specifically. General models have been developed for quantifying the probability of causation, given the level of exposure. Additionally, there is a substantial body of research on mechanisms by which radiation causes cancer.

Nonetheless, uncertainties remain in extending this evidence to compensating particular veterans as their exposures are poorly estimated, disease outcomes lack specificity of cause, and for some rare cancers causation remains to be established. These uncertainties in large part appear responsible for the shift in emphasis from individual probability of causation (PC)-based criteria for compensation in the Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984 (Public Law 98-542. 98th Cong., 2d Sess.) to the establishment of presumptions in the Radiation-Exposed Veterans Compensation Act of 1988 (Public Law 100-321. 100th Cong., 2d Sess.). Still unresolved is whether, in light of the uncertainties about site-specific risk, perhaps *all* cancers in radiation-exposed veterans should be treated as presumptively caused by radiation, at least absent very convincing evidence that the specific cancer is not caused by radiation. Arguably, the only site that might be excluded on this basis would be chronic lymphatic leukemia.

While the Committee has called for research and surveillance on the health of veterans, the studies of radiation effects in veteran populations have proven of limited utility, in part because of the relatively small num-

ber of excess cancers expected in the available cohorts and, importantly, because individual exposures were not tracked in a systematic manner. As a result an opportunity to carefully characterize radiation-related cancer risks among veterans may have been missed. Fortunately, there has long been a strong body of evidence from other populations, so that the weak evidence provided by the studies of veterans has not been construed as a basis for holding back on presumptions for radiation. The availability of strong epidemiologic data has made possible the construction of quantitative models to guide compensation policy for radiation-exposed veterans, which has often not been possible for other exposures. These models have not been used to quantify the burden of radiation-caused cancer among veterans.

Specificity is an issue in compensation of cancers in radiation-exposed individuals. Many cancers caused by radiation also have many other responsible risk factors, and cases caused by radiation cannot be distinguished from those caused by other factors. Additionally, for most radiation exposures received during military service, the probability of causation is low. In the example of smoking, which interacts with radiation for lung cancer, evidence-based policies can be developed based on an understanding of the joint effects of radiation and smoking. Potentially, if data are available, similar models could be developed for the interaction of radiation with other agents.

Ultimately, much of the force behind the movement for compensation for the atomic veterans came from the fact that the government deliberately exposed them to harm, while having at least some knowledge of the risks involved at the time. Furthermore, the risks were often denied by government officials, both at the time of exposure when military personnel were not properly informed and later when diseases were manifest and attempts at redress were dismissed. On this basis, veterans consider that the case for their claims for compensation is enhanced by the culpability of the government.

MUSTARD GAS AND LEWISITE PRESUMPTIONS

Description

This case study examines the 1992 and 1994 decisions by VA to establish presumptive service connection for health outcomes related to mustard gas and lewisite exposures among World War II veterans. This case study, the first involving a congressional request for the IOM to develop a report, raises a series of still persistent issues. With the recognition that some World War II veterans had been exposed to mustard gas during laboratory studies, VA in 1992 proposed a presumptive service-connection decision covering this exposure (VA, 1992a). The presumption was based on four primary

factors: (1) the studies were classified, (2) participants were directed not to discuss their participation in the studies, (3) their medical records were sparse, and (4) no long term follow-up was conducted or provided for the participants (VA, 1992a). VA issued a final rule in July 1992 (VA, 1992b).

As a result of public comment to the proposed rule as found in the final rule (VA, 1992a,b), VA contracted with IOM to write a report on the health effects of exposure to mustard gas and lewisite. In early 1994, VA revised the presumption based on the IOM study, *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite* (IOM, 1993), and issued a proposed rule (VA, 1994a). The second presumptive service-connection rule was issued in August 1994. This rule amended the original proposal by (1) adding more diseases to the original list of diseases, (2) adding the compound lewisite to the rule, (3) adding veterans who might have been exposed during World War I and in studies after the end of World War II, and (4) clarifying the extent of exposure (VA, 1994b).

Lessons Learned

A number of concerns are raised by this presumptive decision. Foremost is the unresolved problem raised by secrecy surrounding military/governmental studies involving exposure of military personnel to warfare agents that may have immediate or delayed effects on their health (IOM, 1993). Classifying warfare studies based on national security is necessary in many cases. However, this classification can lead to concerns about health that might not be resolved for decades.

In the case of mustard and lewisite agents, national security took precedence over the long-term health risks to the study participants. Participants in these studies maintained their secrecy oaths for decades even though they developed health problems consequent to their exposures. As health consequences emerged there were problems in finding information about exposure to mustard gas or lewisite in their medical records. Consequently, health-care providers could not provide appropriately targeted screening and care and long-term medical follow-up was not provided to the study participants. A third area of concern is that this classification precluded health-care providers from being aware that symptoms of mustard gas or lewisite exposure might be exhibited by patients. As a result, the health-care providers did not look for these occupationally related symptoms (IOM, 1993).

The consequences of secreting information were partially recognized in several Information Letters from the VA Under Secretary for Health (VA, 2002, 2005, 2006). As indicated in the Presidential Task Force 2003 report (President's Task Force to Improve Health Care Delivery for Our Nation's Veterans, 2003) and a recent Government Accountability Office (GAO)

report (GAO, 2006a), the health of our veterans must be considered in relation to all aspects of military service. The presidential task force specifically cited the lack of exposure data to a known environmental hazard as a root cause for not being able to determine compensatory issues for our veterans (GAO, 2006a,b). While it appears that DoD is addressing the tracking and recording of the Service members' movements to link with exposure data that have been collected, both of these issues remain concerns for the veteran. Inadequate exposure data are collected, and the ability to vector these data to location and troop movement has limited attribution of disease to exposure agents for individual veterans. Exposure assessment is the key to disability benefits for veterans. A recent report (GAO, 2004) indicates that force health protection and surveillance policy are not as good as they could be, but are improving, especially with more current deployments.

The final rule for mustard gas and lewisite (VA, 1994b), based upon the 1993 IOM report, outlined three categories of casual relationships for health consequences of exposure: indicated, suggested, and insufficient evidence of a relationship. VA acknowledged in the final rule that certain health consequences could be linked directly to mustard gas or lewisite exposure and that a second grouping of health consequences had a suggestive linkage based upon the 1993 IOM report. Although the IOM report recommended many diseases that could be associated with exposure to these agents, VA specifically eliminated several of the diseases as not being related to mustard gas or lewisite exposure. Consequently, a precedent was established by VA for causal health consequences associated with specific chemical agents as recommended by IOM. Lastly, this case study indicates an apparent lack of communication and coordination between DoD and VA regarding individual Service members and government workers involved in studies, chemical agents used in these studies, and any actual or potential exposure data for the individuals involved. This lack of coordination was emphatically pointed out in the 1993 report *Veterans at Risk* (IOM, 1993).

GULF WAR PRESUMPTIONS

Description

While the Gulf War presumption process was heavily influenced by the Agent Orange presumptive history, the course of the Gulf War process was different from that of its predecessor. The lengthy Agent Orange process was a culmination of interactions between veterans and their advocates, Congress, the scientific community, the work of the IOM committees, and VA. However, when Congress established the initial Gulf War presumption termed "undiagnosed illnesses," two of the aforementioned four groups—

the scientific community and VA—were not involved in the decision-making process. This initial presumptive provision for "undiagnosed illnesses" by Congress was based on symptom complaints of returning Gulf War veterans and was not related to single organ systems or easily explained by a unifying exposure or mechanism. Rather, nonspecific signs and symptoms were grouped under the "undiagnosed illnesses" category for disability compensation. VA was directed by Congress to administer the program.

After the first two provisions of the Gulf War presumptions had been enacted (unexplained illnesses and chronic multisymptom illness) by Congress, Congress instructed VA to commission a scientific review examining the candidate exposures in the Gulf theater that may have contributed to the health effects experienced by veterans. These reviews were performed by IOM committees and reported in a five-volume series titled *Gulf War and Health* (IOM, 2000a, 2003a, 2005a, 2006, 2007). The reviews found limited evidence of linkages between veterans' health and specific environmental exposures during deployment. The majority of the scientific findings from the IOM Gulf War committees and subsequent decisions by the VA Secretary to presumptively service connect or not service connect have not yet appeared in the *Federal Register* as required by statute, and VA has not yet presumptively connected any health conditions with Gulf War service.

Lessons Learned

Compensation presumptions mandated by Congress in the absence of certain scientific evidence that link Gulf War service to adverse health outcomes, while well intentioned, may have contributed to confusion and suspicion around the presumptive process. In addressing health problems in Gulf War veterans, Congress and VA faced the difficulty of providing compensation for a syndromic illness that had not been linked to specific exposures. Two approaches were followed. The earlier decision (1995), to make "presumptive" a list of conditions, signs, or symptoms clustered under the rubric of "undiagnosed illnesses" allowed medical care and other benefits to be provided to affected veterans by VA. The second approach departed from the initial symptom-based presumption model, and a 1998 act mandated as "presumptive" any additional conditions or symptoms that could be linked to "a biological, chemical, or other toxic agent, environmental or wartime hazard or preventive medicine or vaccine," extending the possible list of potential illnesses considered presumptively linked to service in the Gulf (Persian Gulf War Veterans Act of 1998. Public Law 105-277. 105th Cong., 2d Sess. § 1602). Thus, the presumptive process for Gulf War Illnesses may have been driven by public expectations and pressure on Congress and VA to act more quickly than either Congress or VA had acted with regard to Agent Orange decisions. It was clear that Congress

did not want to wait very long to provide assistance to Gulf War veterans following the experience they had in establishing the Agent Orange Act.

In a politically charged and time-pressured context, decisions about qualification for the initial Gulf War presumption needed to be made, even though the base of scientific evidence was incomplete. Additionally, since Gulf War Illness comprised a symptom complex without any specific diagnostic features, a presumption was established largely in response to reports of numerous individual veterans with inexplicable symptomatology, whose health had deteriorated. Congress made a decision to accept the veteran's self-reported symptom complaints as sufficient evidence and validation of a Gulf War service-connected illness. Congress then directed VA, through legislation, to provide service-connected benefits to veterans with qualifying health complaints.

Little consideration has been given to estimating exposures received by individual veterans and the levels of exposures, or to the potential for using such estimates, based on specific locations in theater, job title, or specific duties, in determining eligibility for a service-connected Gulf War condition. There has been a broad assumption of exposure to harmful agents that are associated with Gulf War Illness, even though the responsible exposures were uncertain. In this example, Congress directed VA to choose to include all possible claims, permitting high sensitivity (including all possible cases), but poor specificity (high false positive claims). These initial policies came from Congress and were implemented by VA with little scientific review.

In subsequent decisions related to the Gulf War, VA has engaged IOM in producing reports that VA considers in the presumptive disability decision-making process. VA has asked IOM to examine adverse health effects rather than the existing "undiagnosed illness" or "chronic diseases" provisions established by Congress with relation to Gulf War service. These reviews have been the basis for subsequent decision making by VA, which has not yet established any presumptions for the Gulf War.

A lack of exposure information has hindered evidence-based decision making. Information for retrospectively estimating troop exposures during military service has been limited by gaps in exposure information, a limitation receiving comment by IOM committees and other groups addressing service-connected disability determinations (IOM, 2000a, 2003a, 2005a). There are obvious barriers to collecting such information, including the complexity of doing so during wartime deployments. On the other hand, there has been increasing understanding of the need for exposure assessment as an element of force health protection and readiness (DoD, 1997, 2006).

This case study also points to the potential for decision making without having a sufficient evidence base to lead to unintended, adverse consequences, including erosion of public trust and confidence in the decision-

making process. The Committee viewed the legislated presumption for Gulf War Unexplained Illness as having some negative consequences. The decision was not evidence-based and it gave credence to the existence of a still poorly characterized and poorly investigated illness complex. Absent research, the presumption may have strengthened the belief that some candidate toxicants, or a mixture of environmental hazards known or unknown, existed in the Gulf War theater and were pervasively present at sufficient concentration to affect the thousands of veterans with symptoms of unexplained illness. Despite acknowledging preventable exposures to environmental chemicals in the Gulf War theater, after several IOM inquires into these hazards, none of the IOM committee reports (IOM, 2000a, 2003a, 2005a, 2006, 2007) has endorsed either a unifying candidate toxicant as a cause for unexplained Gulf War illness or a combination of causes as evidence for the presumptions established by Congress.

AGENT ORANGE AND PROSTATE CANCER PRESUMPTION

Description

Prostate cancer is the second most common cause of cancer deaths in U.S. men (SOURCE: http://seer.cancer.gov/csr/1975_2003/results_merged/topic_mor_trends.pdf). Although the focus of extensive research, few specific etiologic factors that explain the occurrence of the disease have been identified, other than a very strong association with age. The observational evidence available on Agent Orange and prostate cancer risk comes from epidemiological studies of herbicide and dioxin exposed groups in the general population and military personnel exposed to Agent Orange in Vietnam (see Table 6-34 in IOM, 2005b, pp. 277-280).

Beginning with the 1994 Agent Orange report, IOM committees consistently found "limited/suggestive" evidence associating prostate cancer with Agent Orange—with the results of one high-quality study indicating a positive and statistically significant association with phenoxy herbicide exposure, along with weaker evidence and less consistent findings from other studies (IOM, 1994, 1996b, 1999, 2001, 2003b, 2005b). In the populations that have been investigated with higher levels of exposure evidence, excess risk of prostate cancer has been found in some studies and not uniformly across these studies (IOM, 1994, 2005b). However, in addition to the dioxin contaminant, the chlorophenoxy herbicide is a potential causative agent. Based in part upon the IOM finding that there was "limited/suggestive" evidence for association, VA established a presumption in 1996 that provides benefits to Vietnam veterans with prostate cancer (VA, 1996).

Lessons Learned

In this case study, the Committee focused on the use of the scientific evidence on Agent Orange and prostate cancer in the decision to establish a presumption. The Committee assessed the relationship of the congressional language to the IOM's criteria for classifying evidence and the use of the IOM's evidence evaluation for prostate cancer by VA. The Agent Orange Act of 1991 (Public Law 102-4. 102nd Cong., 1st Sess. Section 2[b][3]) states that a positive association is one for which "the credible evidence of the association is equal to or outweighs the credible evidence against the association." This statement is not necessarily equivalent to the category of "limited/suggestive" evidence for association used by IOM committees. The IOM limited/suggestive category covers a broad range of epidemiological evidence from relatively weak to strongly suggestive. In the instance of Agent Orange and prostate cancer, VA made a presumption based on the IOM's conclusion of "limited/suggestive" evidence for association; the evidence at the time was relatively limited, but did include one study showing a statistically significant excess and a number of other studies showing positive, but weak and non-significant associations. Because the Committee did not have documentation of the rationale for VA's decision beyond the *Federal Register* notice (VA, 1996), the basis for making a presumption given the particular IOM conclusion and scope of evidence was unclear to the Committee.

In reviewing evidence on Agent Orange, the 2005 IOM review considered biological and toxicological evidence when evaluating the biological plausibility of the association between prostate cancer and exposure to Agent Orange but did not integrate these other lines of evidence with epidemiological findings to come up with an overall evaluation (IOM, 2005b). In seeking to classify the strength of evidence, prior IOM committees have relied mostly on epidemiological findings, potentially leaving the resulting presumptions open to criticism for having insufficient scientific justification when viewed in a broader context. Additionally, there has been a relatively limited body of relevant toxicological literature on prostate cancer.

The criterion for reaching "limited/suggestive" evidence for association of Agent Orange used by the IOM is that the "[e]vidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent" (IOM, 2005b, p. 8) The Agent Orange Committee evaluations for prostate cancer considered the totality of epidemiological evidence, but there were limitations of the exposure data available to aid in the evaluation of the studies considered. Previous Agent Orange committees also reviewed and reported on toxicological and mecha-

nistic information, but according to their interpretation of their charge, did not integrate this information with the epidemiological evidence to make conclusions about the overall weight of the evidence for causal association. Several studies were of worker groups and measures of exposure to either the chlorophenoxy compounds or dioxin were not available to enable comparisons across studies. Dose-response relationships could be considered for a few studies; for example, the relative risk "of prostate cancer in Ranch Hands correlated with putative exposure to Agent Orange (high 6.04 vs low 2.17 vs background 1.5; $p = 0.01$)" (IOM, 2005b, p. 282). The lack of accurate estimates of exposure from the military experience has limited the study of the association between prostate cancer and exposure to Agent Orange in veterans.

AGENT ORANGE AND TYPE 2 DIABETES PRESUMPTION

Description

This case study examines the 2001 decision to establish presumptive service connection for type 2 diabetes among Vietnam veterans under the Agent Orange Act (Agent Orange Act of 1991. Public Law 102-4. 102nd Cong., 1st Sess.). This case study was chosen because of several features in the events leading to the presumption and because of the implications of this presumption for VA. First, although most of the Agent Orange presumptions have been the result of the biennial IOM review of the scientific literature, the scientific evaluation that resulted in this presumption was conducted by a special IOM panel commissioned by VA specifically for this topic, out of sequence with the biennial IOM reports (IOM, 2000b). Second, after its review, this special IOM committee determined that the evidence linking Agent Orange and diabetes would justify a change from the previous category of "inadequate/insufficient" to "limited/suggestive." Third, VA issued a presumption for type 2 diabetes on the basis of this "limited/suggestive" category of evidence, rather than the using the "sufficient evidence" standard. Finally, as a consequence of this presumption, all veterans who served in Vietnam receive compensation for their type 2 diabetes, as well as the associated complications of this morbid, chronic condition. This presumption will continue to have important financial consequences for VA as type 2 diabetes incidence generally increases with advancing age and as national rates of type 2 diabetes continue to rise in all segments of the population, fueled primarily by the high rates of obesity and inactivity.

Lessons Learned

This case study has several features in common with some of the other case studies. As for radiation and cancer, type 2 diabetes has multiple risk factors, including age, family history, inactivity, and obesity. The extent to which Agent Orange contributes to causation of type 2 diabetes in veterans is uncertain, but likely to be relatively small compared with these other factors.

Some IOM Agent Orange reports have commented on the extent that Agent Orange exposure may contribute to diabetes rates observed among Vietnam veterans:

> It must be noted, however, that these studies indicate that the increased risk, if any, from herbicide or dioxin exposure appears to be small. The known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides. (IOM, 2000b, pp. 3, 37)

Recognition of the relative contributions of multiple factors could be important for the identifying and compensating service-attributable type 2 diabetes that develops among aging Vietnam veterans. The IOM Agent Orange committee reports have not attempted to quantify the attributable burden of disease, although such calculations would be useful for decision making, both to understand the potential burden of disease overall and to anticipate decisions about compensation for individual veterans. An additional explicit analysis of service-attributable risk that attempts to quantify the fraction of disease risk attributable to military service might be more useful to VA and Congress when making legislative and administrative decisions based on complex scientific evidence, although it is recognized that conducting such an analysis for this case would be a challenge given the lack of adequate research in this area and the limited data on exposures to herbicides.

Analyses of high-quality data for a representative cohort of veterans could have been informative for determining the existence of an association between exposures during military service and the risk of disease or disability. A well-designed cohort study might have contributed data for evaluating the link between Agent Orange and type 2 diabetes, particularly if the design had included accurate assessments of exposure during service, evaluation of other risk factors that may have been present during service or developed subsequently (e.g., obesity), and longitudinally assessed occurrence of this disease. In fact, the Vietnam Experience Study (VES) provided an opportunity to initiate a cohort study. Continuation of the study as a cohort might have proven informative for diabetes and other potential health consequences of service in Vietnam.

In evaluating the observational studies, specific and formal methodological protocols did not appear to be used for synthesizing findings of available studies and updating the classification of evidence as the findings of additional studies became available to successive committees. The type 2 diabetes presumption came after the 2000 IOM committee "upgraded" the assessment of the existing evidence from "inadequate/insufficient" to "limited/suggestive" category. Although new studies were considered in this reassessment, no particular study was considered as providing conclusive evidence of association between Agent Orange and type 2 diabetes. Rather, the reclassification reflected the committee's view of the cumulative weight of the evidence. Having a more detailed evidence review algorithm and classification approach, such as IARC (IARC, 2006), could enhance the consistency of assessment of evidence across different committees.

The case study also points to a lack of transparency in the VA's process where scientific evidence is applied to legislative and administrative decisions. The type 2 diabetes presumption signaled an important trend on the part of VA to assign presumption on the bases of "limited/suggestive" classification of the levels of evidence, rather than the highest standard of "sufficient" evidence. This decision may have been influenced by a variety of considerations beyond the scientific evidence, i.e., political, economic, and administrative factors. The interplay of these multiple factors and their relative weighting by VA were not described in any of the materials available to the Committee.

SPINA BIFIDA PROGRAM

Description

This case study examines the 1996 and 2003 decisions to grant monetary compensation and health benefits to children of Vietnam and Korean War veterans with spina bifida based on the scientific evidence suggesting an association between herbicide exposure in Vietnam and Korea and spina bifida in the children of exposed veterans. Reproductive health effects were considered by the first IOM veterans and Agent Orange report issued in 1994 (IOM, 1994). The committee concluded that male exposure to toxins could plausibly be linked to adverse developmental consequences in their offspring:

> Animal and human data indicate that the exposure of the male to various toxic agents may increase the risk of the full spectrum of adverse developmental endpoints from fetal loss to cancer. (IOM, 1994, p. 595)

But the committee found the evidence to support the link between Agent Orange and a range of birth defects to be "inadequate/insufficient"

(IOM, 1994, p. 6). In its response to the IOM report, VA noted that although reproductive effects were considered by the IOM committee, there was no mechanism within the existing VA compensation structure to award benefits to any party other than the veteran; providing compensation to children of veterans with developmental effects attributable to Agent Orange exposure would require additional legislative action (VA, 1994c, p. 346).

Based on new research findings, in the 1996 Agent Orange report, the IOM committee assessed the evidence for the association between Agent Orange and spina bifida as "limited/suggestive" (IOM, 1996b). This reclassification was based on a re-analysis of the Ranch Hand study, in response to a critique in the IOM's 1994 report. In addition the committee considered three other studies, each of which had potential biases that were different and therefore unlikely to be responsible for demonstrating a consistent pattern of results (IOM, 1996b).

Public Law 104-204 (Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriation Act, 1997. 104th Cong., 2d Sess.) was passed in 1996, authorizing benefits for children born to Vietnam veterans with spina bifida. Additional legislation in 2000 (Veterans Benefits and Health Care Improvement Act of 2000. Public Law 106-419 § 401. 106th Cong., 2d Sess.) established benefits to children of "women Vietnam veterans" with birth defects; this law provided benefits to children of female veterans with a broad range of defects that might be attributable to maternal exposure during Vietnam service (excluding defects that were the result of familial predisposition or the injury suffered at birth). In 2003, these benefits were extended to children of veterans of the Korean War (Veterans Benefits Act of 2003. Public Law 108-103. 108th Cong., 2d Sess.).

Lessons Learned

Apart from the programs established by legislative action described above, there continues to be no overall mechanism for compensating offspring for health consequences attributable to maternal or paternal military service. Toxic exposures that occur during military service have the potential to cause adverse developmental effects, and all of the Agent Orange reports have described the biologically plausible mechanisms for these effects in both exposed female and male veterans. Given VA's interest in compensating veterans for adverse health effects incurred as a result of military service and the possibility that such effects may extend to the health of veterans' offspring, the absence of a clear and consistent policy on compensating affected offspring is notable. The need for a clear policy statement will continue to grow as VA considers the health effects of mili-

tary service in the large population of reproductive-aged veterans and the growing number of women in the armed services.

Although the public laws providing compensation for particular categories of offspring with birth defects may have been expedient for these affected individuals, the approach of addressing the more general policy gap described above with these programs runs counter to principles of consistency and equity that should inform the approach to presumptions. Any new adverse reproductive consequences of Agent Orange exposure identified in IOM reports would again require legislative action for these specific effects in order for compensation to be granted; the administrative route that has applied to all other Agent Orange presumptions is not available for reproductive consequences of exposure at present.

It should be noted that the evidence standard for the spina bifida presumption was "limited/suggestive," not the more rigorous "sufficient" standard (IOM, 1996b). The difficulty with using this lesser standard as the basis for presumptions has been described in other case studies related to Agent Orange and type 2 diabetes and prostate cancer.

SYNTHESIS

These case studies offer a diverse set of lessons learned and indicate elements of the current presumptive disability decision-making process for veterans that need to be addressed moving forward. The case studies show that the process has acted to serve the interests of veterans in many instances. Overall, Congress and VA have repeatedly acted to maximize the sensitivity of presumptive decisions so as to ensure that specific groups of veterans are compensated. The particular interest in caring for veterans who have experienced the hardship of being a POW, for example, has led to a range of presumptions that apply to POWs. However, in maximizing the sensitivity of presumptive decision making for particular groups of veterans, substantial numbers of false positives may have resulted, as in the examples of Agent Orange and the Gulf War. Additionally, because no systematic process for approaching presumptive decision making exists, important omissions in this coverage remain without a clear mechanism for expanding coverage, as with potential reproductive health consequences of military service for the offspring of those who serve.

The case studies illustrate the use of presumptions to cover gaps in evidence, gaps that exist in part because of lack of information on exposures received by military personnel and inadequate surveillance of veterans for the occurrence of service-related illnesses. Secrecy is a particularly troubling source of incomplete information, as illustrated by the veterans who participated in studies of mustard gas and lewisite. Research has been carried out on the health of veterans, leading to the decision, for example, on cardio-

vascular disease in amputees. But the research has not been systematic, and in the example of cardiovascular disease in amputees, further evidence relative to a presumption made in 1979 has not been collected. Research on radiation risks in veterans has been severely constrained by a lack of dose information, and the resulting studies have not been informative. A lack of exposure information has hindered research on other agents as well and led to a sweeping exposure presumption with regard to exposure to Agent Orange in Vietnam.

Across the case studies, the Committee believes that prior efforts did not optimally synthesize all of the evidence on the health consequences of military service. In some cases there has not been an independent body that reviews the scientific evidence and updates the medical knowledge and scientific evidence relevant for a specific presumptive decision over time. As a consequence, some presumptions appear inconsistent (as with the psychiatric illnesses) or even aberrant (as with multiple sclerosis) in the face of contemporary medical and scientific knowledge. In other cases where an independent body has reviewed the scientific evidence, the synthesis of the evidence has not always been optimally comprehensive and standardized. The inferential target in IOM reports has shifted between causation (e.g., mustard gas and lewisite, Gulf War) and association (e.g., Agent Orange), and the more recent IOM Agent Orange reports have emphasized findings of observational studies without full attention to other lines of evidence. In the Agent Orange case studies the category "limited/suggestive" for association has been used when the epidemiological evidence base was fairly weak, including only one study with statistically significant findings. In the case of type 2 diabetes, at the time of the Agent Orange and diabetes report, there were multiple studies that were all substantially limited by bias or confounding. The categorization of the evidence as "limited/suggestive" by IOM has led to presumptions on the part of VA that appear to be irreversible once made, even though scientific evidence is dynamic. Stated in another way, even if further scientific evidence were unsupportive of previous research findings and a future IOM committee were to change its classification for strength of evidence, VA may not change its presumption. The Committee notes that presumptive decisions have been made to compensate health outcomes (e.g., type 2 diabetes, prostate cancer), based on evidence characterized by IOM committees as limited/suggestive for association, well below the evidence level needed to establish causation, absent strong mechanistic understanding.

The case studies document the particular problem that arises with regard to presumptions related to common, chronic diseases with multiple causes, such as type 2 diabetes, prostate cancer, and cardiovascular disease. In seeking high sensitivity for presumptions in general, specificity is sacrificed, and the resulting number of false positives may be particularly

large for common conditions with multiple etiologies. These false positives are associated with large attendant costs, both financial and non-financial. Determining the degree to which the onset of a common disease with multiple etiologies may be attributable to prior military service may be particularly useful for presumptions related to such conditions, but neither the IOM committees nor VA have given full consideration to whether the attributable fraction should be estimated for veterans. Later chapters of this report discuss how the attributable fraction might be estimated for veterans, and how such estimates would benefit VA in its presumptive disability decision-making process.

In the case studies, the Committee's analyses were based on the very general information provided by VA about its internal decision-making processes. The case studies did make clear, however, that these processes are neither fully transparent nor consistent. This was further implied by VA's decision to withhold task force documents from the Committee's review, considering them pre-decisional in nature. VA believes that access to pre-decisional documents by outside sources would stifle candid staff opinions on issues. Once IOM carries out its reviews and provides VA with reports documenting the extent of evidence available on associations, the internal processes that follow are not fully open to scrutiny. This practice could degrade the trust of veterans in the presumptive disability decision-making process and may hinder efforts to optimize the use of scientific evidence.

In its proposed approach for future decision making, the Committee offers recommendations that address the strengths and challenges highlighted by the case studies.

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ANNEX 5-1 Legislative Documents Referenced for Case Studies

	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Mental Health	Veterans' Bureau Act of 1921	PL 67-47 42 STAT. 147, 153				Pensions, Bonuses, and Veteran's Relief (1949)	14 FR 571	38 CFR Part 3 Former 39 CFR 3.80, 3.86
	World War Veterans' Act, 1924	PL 68-242 43 STAT. 607, 615				Pensions, Bonuses, and Veterans' Relief (1970)	35 FR 18280	38 CFR Part 3
	Veterans, disability compensation, increase (1970)	PL 91-376 84 STAT. 787, 788	PL 91-376	HR 91-1166	SR 91-784 SR 91-785	Veterans Benefits; Former Prisoners of War (1981)	46 FR 57571	
	Former Prisoner of War Benefits Act of 1981	PL 97-37 95 STAT. 935, 936	PL 97-37	HR 97-28	SR 97-88	Veterans Benefits; Former Prisoners of War (1982) (final regulations)	47 FR 11655	38 CFR Part 3
	Veterans' Compensation and Program Improvements Amendments of 1984	PL 98-223 98 STAT. 37, 40	PL 98-223	HR 98-228 HR 98-425	SR 98-249	Direct Service Connection (Post-traumatic stress disorder) (1992) (proposed rule)	57 FR 34536	
	Veterans Benefits Act of 2003	PL 108-183 117 STAT. 2651	PL 108-183	HR 108-211	SR 107-86 SR 108-169	Direct Service Connection (Post-traumatic stress disorder) (1993) (final rule)	58 FR 29109	38 CFR Part 3

		Compensation for Certain Undiagnosed Illnesses (1994) (proposed rule)	59 FR 63283	38 CFR Part 3	
		Compensation for Certain Undiagnosed Illnesses (1995) (final rule)	60 FR 6660	38 CFR Part 3	
	Multiple Sclerosis	Pensions, Bonuses, and Veterans' Relief (1949)	14 FR 571	38 CFR 3.86	
		Pensions, Bonuses, and Veterans' Relief (1970)	35 FR 18280	38 CFR 3.307, 3.309	
		Compensation and Pension Provisions of the Veterans Education and Benefits Expansion Act of 2001 (2003) (final rule)	68 FR 34539	38 CFR Parts 3 and 13	
		Presumptions relating to certain diseases and disabilities (2006) (38 USC § 1112)			

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ANNEX 5-1 Continued

	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Prisoners of War	Veterans, disability compensation, increase (1970)	PL 91-376 84 STAT. 787	PL 91-376	HR 91-1166	SR 91-784 SR 91-785			
	Former Prisoner of War Benefits Act of 1981	PL 97-37 95 STAT. 935	PL 97-37	HR 97-28	SR 97-88			
	Veterans' Compensation and Program Improvements Amendments of 1984	PL 98-223 98 STAT. 37	PL 98-223	HR 98-228 HR 98-425	SR 98-249			
	Veterans' Benefits Improvement and Health-Care Authorization Act of 1986	PL 99-576 100 STAT. 3248	PL 99-576	HR 99-728 HR 99-729	SR 99-494 SR 99-200 SR 99-444			
	Veterans' Benefits and Services Act of 1988	PL 100-322 102 STAT. 487	PL 100-322	HR 100-191 HR 100-236 HR 100-578	SR 100-15 SR 100-215			
	Veterans Benefits Act of 2003	PL 108-183 117 STAT. 2651	PL 108-183	HR 108-211	SR 107-86 SR 108-169			

Amputees and Cardio-vascular Disease	Veterans Disability Compensation and Survivor Benefit Act of 1976	PL 94-433 90 STAT. 1374	PL 94-433	HR 94-1270	SR 94-1226	Pension, Compensation, and Dependency and Indemnity Compensation, Proximate Results, Secondary Conditions (1979) (final regulations)	44 FR 50339	38 CFR Part 3
Radiation	Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984	PL 98-542 98 STAT. 2725	PL 98-542	HR 98-592 HR 98-828	SR 97-89	Guidance for the Determination and Reporting of Nuclear Radiation Dose for DoD Participants in the Atmospheric Nuclear Test Program (1945-1962) (1982)	47 FR 21853	32 CFR Ch. 1
	Radiation-Exposed Veterans Compensation Act of 1988	PL 100-321 102 STAT. 485	PL 100-321	HR 98-592 HR 100-235	SR 100-215			
	Radiation Exposure Compensation Act of 1990	PL 101-426 104 STAT. 920	PL 101-426	HR 101-463	SR 101-264	Guidance for the Determination and Reporting of Nuclear Radiation Dose for DoD Participants in the Atmospheric Nuclear Test Program (1945-1962) (1983) (final rule)	48 FR 10645	32 CFR Part 218
	Veterans' Benefits Programs Improvement Act of 1991	PL 102-86 105 STAT. 414	PL 102-86	HR 101-857 HR 102-130	SR 101-379 SR 102-139			

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Radiation (continued)	Veterans' Radiation Exposure Amendments of 1992	PL 102-578 106 STAT. 4774	PL 102-578	HR 102-757	SR 101-379 SR 102-139	Guidance for the Determination and Reporting of Nuclear Radiation Dose for DoD Participants in the Atmospheric Nuclear Test Program (1945-1962) (1985) (proposed amendment of final rule)	50 FR 19538	32 CFR Part 218
	Veterans' Benefits Improvements Act of 1994	PL 103-446 108 STAT. 4645	PL 103-446	HR 103-538 HR 103-668 HR 103-669	SR 103-280 SR 103-385 SR 103-386			
	Radiation Exposure Compensation Act Amendments of 2000	PL 106-245 114 STAT. 501	PL 106-245	HR 106-697		Adjudication of Claims Based on Exposure to Dioxin or Ionizing Radiation (1985) (final rules)	50 FR 34452	38 CFR Parts 1 and 2
	Veterans Benefit Improvements Act of 2004	PL 108-454 118 STAT. 3598	PL 108-454	HR 108-211 HR 108-572	SR 106-397 SR 108-169	Claims Based on Exposure to Ionizing Radiation (1989) (final regulations)	54 FR 42802	38 CFR Part 3

Claims Based on Exposure to Ionizing Radiation (1992) (proposed rule)	57 FR 10449	38 CFR Part 3	
Claims Based on Exposure to Ionizing Radiation (Parathyroid Adenoma) (1992) (proposed rule)	57 FR 10853	38 CFR Part 3	
Radiation Exposure Compensation Act of 1990 (1992) (proposed rule)	57 FR 40424	38 CFR Part 3	
Claims Based on Exposure to Ionizing Radiation (1993) (final rule)	58 FR 16358	38 CFR Part 3	
Radiation Exposure Compensation Act of 1990 (1993) (final rule)	58 FR 25564	38 CFR Part 3	
Claims Based on Exposure to Ionizing Radiation (1994) (proposed rule)	59 FR 6607	38 CFR Part 3	

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Radiation (continued)						Claims Based on Exposure to Ionizing Radiation (1994) (final rule)	59 FR 45975	38 CFR Part 3
						Claims Based on Exposure to Ionizing Radiation (Radiogenic Diseases) (1995) (final rule)	60 FR 9627	38 CFR Part 3
						Claims Based on Exposure to Ionizing Radiation (Lymphomas other than Hodgkin's Disease and Cancer of the Rectum) (1995) (final rule)	60 FR 53276	38 CFR Part 3

Claims Based on Exposure to Ionizing Radiation (Prostate Cancer and Any Other Cancer) (1996) (proposed rule)	61 FR 50264	38 CFR Part 3	
Claims Based on Exposure to Ionizing Radiation (Prostate Cancer and Any Other Cancer) (1998) (final rule)	63 FR 50993	38 CFR Part 3	
The Veterans Millennium Health Care and Benefits Act (2000) (final rule)	65 FR 43699	38 CFR Part 3	
Diseases Specific to Radiation-Exposed Veterans (2001) (proposed rule)	66 FR 41483	38 CFR Part 3	
Diseases Specific to Radiation-Exposed Veterans (2002) (final rule)	67 FR 3612	38 CFR Part 3	
Claims Based on Exposure to Ionizing Radiation (2002) (final rule)	67 FR 6870	38 CFR Part 3	

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Mustard Gas/ Lewisite						Claims Based on Chronic Effects of Exposure to Mustard Gas (1992) (proposed rule)	57 FR 1699	38 CFR Part 3
						Claims Based on Chronic Effects of Exposure to Mustard Gas (1992) (final rule)	57 FR 33875	38 CFR Part 3
						Claims Based on Chronic Effects of Exposure to Vesicant Agents (1994) (proposed rule)	59 FR 3532	38 CFR 3.307(b)
						Claims Based on Chronic Effects of Exposure to Mustard Gas or Lewisite (1994) (final rule)	59 FR 42497	38 CFR Part 3

Gulf War	Omnibus Consolidated and Emergency Supplemental Appropriations Act, 1999	PL 105-277 112 STAT. 2681	PL 105-277	HR 105-626	SR 105-362	Compensation for Certain Undiagnosed Illnesses (1994) (proposed rule)	59 FR 63283	38 CFR Part 3
	Veterans Education and Benefits Expansion Act of 2001	PL 107-103 115 STAT. 976	PL 107-103	HR 107-156	SR 107-86 SR 106-122	Compensation for Certain Undiagnosed Illnesses (1995) (final rule)	60 FR 6660	38 CFR Part 3
						Compensation for Certain Undiagnosed Illnesses (1997) (interim rule)	62 FR 23138	38 CFR Part 3
						Compensation for Certain Undiagnosed Illnesses (1998) (final rule)	63 FR 11122	38 CFR Part 3
						Illnesses Not Associated with Service in the Gulf during the Gulf War (2001) (notice)	66 FR 35702	

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Gulf War (continued)						Extension of the Presumptive Period for Compensation for Gulf War Veterans' Undiagnosed Illnesses (2001) (interim final rule)	66 FR 56614	38 CFR Part 3
						Extension of the Presumptive Period for Compensation for Gulf War Veterans' Undiagnosed Illnesses (2002) (final rule)	67 FR 78979	38 CFR Part 3
						Compensation and Pension Provisions of the Veterans Education and Benefits Expansion Act of 2001 (2003) (final rule)	68 FR 34539	38 CFR Parts 3 and 13

Agent Orange and Prostate Cancer	Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984	PL 98-542 98 STAT. 2725	PL 98-542	HR 98-592 HR 98-828	SR 97-89	Adjudication of Claims based on Exposure to Dioxin or Ionizing Radiation (1985) (final rules)	50 FR 34452	38 CFR Parts 1 and 3
	Agent Orange Act of 1991	PL 102-4 105 STAT. 11	PL 102-4	HR 101-672 HR 101-857	SR 100-215 SR 100-439 SR 101-82 SR 101-379	Claims Based on Service in Vietnam (1990) (proposed regulations)	55 FR 25339	38 CFR Parts 3 and 4
	Veterans' Benefits Improvements Act of 1994	PL 103-446 108 STAT. 4645	PL 103-446	HR 103-538 HR 103-668 HR 103-669	SR 103-280 SR 103-385 SR 103-386	Claims Based on Service in Vietnam (1990) (final regulations)	55 FR 43123	38 CFR Parts 3 and 4
	Veterans' Benefits Improvements Act of 1996	PL 104-275 110 STAT. 3322	PL 104-275	HR 104-649	SR 99-101 SR 100-439 SR 104-371	Claims Based on Exposure to Herbicides Containing Dioxin (Soft-Tissue Sarcomas) (1991) (proposed regulations)	56 FR 7632	38 CFR Parts 3 and 4
						Claims Based on Exposure to Herbicides Containing Dioxin (Soft-Tissue Sarcomas) (1991) (final regulation)	56 FR 51651	38 CFR Parts 3 and 4

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Agent Orange and Prostate Cancer (continued)						Claims Based on Exposure to Herbicides Containing Dioxin (Peripheral Neuropathy/Lung Cancer) (1992) (proposed rule)	57 FR 2236	38 CFR Part 3
						Diseases Associated with Service in the Republic of Vietnam (1992) (proposed rule)	57 FR 30707	38 CFR Part 3
						Diseases Associated with Service in the Republic of Vietnam (1993) (final rule)	58 FR 29107	38 CFR 3.309(e)
						Disease Associated with Exposure to Certain Herbicide Agents (1993) (proposed rule)	58 FR 50528	38 CFR Part 3

	Diseases Not Associated with Exposure to Certain Herbicide Agents (1994) (notice)	59 FR 341		
	Disease Associated with Exposure to Certain Herbicide Agents (1994) (final rule)	59 FR 5106	38 CFR Part 3	
	Disease Associated with Exposure to Certain Herbicide Agents (Multiple Myeloma and Respiratory Cancers) (1994) (proposed rule)	59 FR 5161	38 CFR Part 3	
	Disease Associated with Exposure to Certain Herbicide Agents (Multiple Myeloma and Respiratory cancers) (1994) (final rule)	59 FR 29723	38 CFR Part 3	

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ANNEX 5-1 Continued

	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Agent Orange and Prostate Cancer (continued)						Diseases Associated with Exposure to Certain Herbicide Agents (Prostate Cancer and Acute and Subacute Peripheral Neuropathy) (1996) (proposed rule)	61 FR 41368	38 CFR Part 3
						Disease Not Associated with Exposure to Certain Herbicide Agents (1996) (notice)	61 FR 41442	

Diseases Associated with Exposure to Certain Herbicide Agents (Prostate Cancer and Acute and Subacute Peripheral Neuropathy) (1996) (final rule)	61 FR 57586	CFR Part 3
Veterans' Benefits Improvements Act of 1996 (1997) (final rule)	62 FR 35421	38 CFR Part 3
Diseases Not Associated with Exposure to Certain Herbicide Agents (1999) (notice)	64 FR 59232	
Diseases Not Associated with Exposure to Certain Herbicide Agents (2002) (notice)	67 FR 4 2600	

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Agent Orange and Prostate Cancer (continued)						Disease Associated with Exposure to Certain Herbicide Agents: Chronic Lymphocytic Leukemia (2003) (proposed rule)	68 FR 14567	38 CFR Part 3
						Compensation and Pension Provisions of the Veterans Education and Benefits Expansion Act of 2001 (2003) (final rule)	68 FR 34539	38 CFR Parts 3 and 13
						Disease Associated with Exposure to Certain Herbicide Agents: Chronic Lymphocytic Leukemia (2003) (final rule)	68 FR 59540	38 CFR Part 3

Agent Orange and Type 2 Diabetes	Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984	PL 98-542 98 STAT. 2725	PL 98-542	HR 98-592 HR 98-828	SR 97-89	Adjudication of Claims based on Exposure to Dioxin or Ionizing Radiation (1985) (final rules)	50 FR 34452	38 CFR Parts 1 and 3
	Agent Orange Act of 1991	PL 102-4 105 STAT. 11	PL 102-4	HR 101-672 HR 101-857	SR 100-215 SR 100-439 SR 101-82 SR 101-379	Claims based on Service in Vietnam (1990) (proposed regulation)	55 FR 25339	38 Parts 3 and 4
	Veterans' Benefits Improvements Act of 1994	PL 103-446 108 STAT. 4645	PL 103-446	HR 103-538 HR 103-668 HR 103-669	SR 103-280 SR 103-385 SR 103-386	Claims based on Service in Vietnam (1990) (final regulation)	55 FR 43123	38 Parts 3 and 4
	Veterans' Benefits Improvements Act of 1996	PL 104-275 110 STAT. 3322	PL 104-275	HR 104-649	SR 99-101 SR 100-439 SR 104-371	Claims Based on Exposure to Herbicides Containing Dioxin (Soft Tissue Sarcomas) (1991) (proposed regulation)	56 FR 7632	38 Parts 3 and 4
	Veterans Education and Benefits Expansion Act of 2001	PL 107-103 115 STAT. 976	PL 107-103	HR 107-156	SR 107-86 SR 106-122	Claims Based on Exposure to Herbicides Containing Dioxin (Soft Tissue Sarcomas) (1991) (final regulation)	56 FR 51651	38 Parts 3 and 4

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Case Study	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Agent Orange and Type 2 Diabetes (continued)						Claims Based on Exposure to Herbicides containing Dioxin (Peripheral Neuropathy/Lung Cancer) (1992) (proposed rule)	57 FR 2236	38 CFR Part 3
						Diseases Associated with Service in the Republic of Vietnam (1992) (proposed rule)	57 FR 30707	38 CFR Part 3
						Diseases Associated with Service in the Republic of Vietnam (1993) (final rule)	58 FR 29107	38 CFR 3.309(e)
						Disease Associated with Exposure to Certain Herbicide Agents (1993) (proposed rule)	58 FR 50528	38 CFR Part 3

Disease Associated with Exposure to Certain Herbicide Agents (1994) (final rule)	59 FR 5106	38 CFR Part 3
Disease Associated with Exposure to Certain Herbicide Agents (Multiple Myeloma and Respiratory Cancers) (1994) (final rule)	59 FR 29723	38 CFR Part 3
Veterans' Benefits Improvements Act of 1996 (1997) (final rule)	62 FR 35421	38 CFR Part 3
Diseases Not Associated with Exposure to Certain Herbicide Agents (1999) (notice)	64 FR 59232	

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	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Agent Orange and Type 2 Diabetes (continued)						Disease Associated with Exposure to Certain Herbicide Agents: Type 2 Diabetes (2001) (proposed rule)	66 FR 2376	38 CFR Part 3
						Disease Associated with Exposure to Certain Herbicide Agents: Type 2 Diabetes (2001) (final rule)	66 FR 23166	38 CFR Part 3
						Disease Associated with Exposure to Certain Herbicide Agents: Chronic Lymphocytic Leukemia (2003) (proposed rule)	68 FR 14567	38 CFR Part 3

Compensation and Pension Provisions of the Veterans Education and Benefits Expansion Act of 2001 (2003) (final rule)	68 FR 34539	38 CFR Parts 3 and 13	
Disease Associated with Exposure to Certain Herbicide Agents: Chronic Lymphocytic Leukemia (2003) (final rule)	68 FR 59540	38 CFR Part 3	
Change of Effective Date of Rule Adding a Disease Associated with Exposure to Certain Herbicide Agents: Type 2 Diabetes (2004) (final rule)	69 FR 31882	38 CFR Part 3	

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ANNEX 5-1 Continued

	CONGRESS					EXECUTIVE BRANCH (DEPARTMENT OF VETERANS AFFAIRS)		
Case Study	Public Law Name	Public Law Statute	CIS Index	House Report	Senate Report	Rule Name	Federal Register	Code of Federal Regulations
Spina Bifida						Disease Not Associated with Exposure to Certain Herbicide Agents (1994) (notice)	59 FR 341	
						Disease Not Associated with Exposure to Certain Herbicide Agents (1996) (notice)	61 FR 41442	

ANNEX 5-2

The following National Academies' reports were evaluated by committee members for inclusion in the individual case studies (see Appendix I). The reports appear below in chronological order:

NRC (National Research Council). 1982. *Possible long-term health effects of short-term exposure to chemical agents*. Vol. 1. Washington, DC: National Academy Press.

NRC. 1984. *Assigned share for radiation as a cause of cancer: Review of radioepidemiological tables, assigning probabilities of causation*. Washington, DC: National Academy Press.

NRC. 1984. *Possible long-term health effects of short-term exposure to chemical agents: Cholinesterase reactivators, psychochemicals and irritants and vesicants*. Vol. 2. Washington, DC: National Academy Press.

NRC. 1985. *Mortality of nuclear weapons test participants*. Washington, DC: National Academy Press.

NRC. 1985. *Possible long-term health effects of short-term exposure to chemical agents: Final report. Current health status of test subjects*. Vol. 3. Washington, DC: National Academy Press.

NRC. 1988. Overview. In *Health risks of radon and other alpha-emitters: BEIR IV*. Washington, DC: National Academy Press.

NRC. 1990. *Health effects of exposure to low levels of ionizing radiation: BEIR V*. Washington, DC: National Academy Press.

IOM (Institute of Medicine). 1991. *Epidemiology in military and veteran populations: Proceedings of the Second Biennial Conference, March 7, 1990*. Washington, DC: National Academy Press.

IOM. 1992. *The health of former prisoners of war*. Washington, DC: National Academy Press.

IOM. 1993. *Veterans at risk: The health effects of mustard gas and lewisite*. Washington, DC: National Academy Press.

IOM. 1994. *Health effects of herbicides used in Vietnam*. Washington, DC: National Academy Press.

IOM. 1994. *Veterans and Agent Orange: Health effects of herbicides used in Vietnam*. Washington, DC: National Academy Press.

IOM. 1995. *Health consequences of service during the Persian Gulf War: Initial findings and recommendations for immediate action*. Washington, DC: National Academy Press.

IOM. 1995. *Recommendations for research on the health of military women: Bibliographies*. Washington, DC: National Academy Press.

IOM. 1995. *A review of the dosimetry data available in the Nuclear Test Personnel Review (NTPR) Program*. Washington, DC: National Academy Press.

IOM. 1996. *Health consequences of service during the Persian Gulf War: Recommendations for research and information systems*. Washington, DC: National Academy Press.

IOM. 1996. *Interactions of drugs, biologics, and chemicals in U.S. military forces*. Washington, DC: National Academy Press.

IOM. 1996. *Mortality of veteran participants in the Crossroads nuclear test*. Washington, DC: National Academy Press.

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

IOM. 1997. *Characterizing exposure of veterans to Agent Orange and other herbicides used in Vietnam: Scientific considerations regarding a request for proposals for research*. Washington, DC: National Academy Press.

IOM. 1997. *An evaluation of radiation exposure guidance for military operations: Interim Report*. 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. 1998. *Assessing readiness in military women: The relationship of body, composition, nutrition, and health*. Washington, DC: National Academy Press.
IOM. 1998. *Measuring the health of Persian Gulf veterans: Workshop summary*. Washington, DC: National Academy Press.
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ANNEX 5-3

The VA provided the Committee with the following cost estimates (in chronological order):

VA (Department of Veterans Affairs). 1988. *Cost estimate of Agent Orange legislation: Non-Hodgkin's lymphoma*. Washington, DC: VA.
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6

Establishing an Evidence-Based Framework

OVERVIEW

The Committee's review of Congress' and the Department of Veterans Affairs' (VA's) approach to establishing presumptions has identified multiple elements of the process for reconsideration. In the next four chapters, the Committee develops a conceptual foundation for implementing an evidence-based system for compensation and offers recommendations for future approaches in Chapter 12. This chapter serves as an introduction to this section of the report, offering general considerations on the basis for making presumptions and their role in compensation by VA.

There are two ideas that underpin these four chapters:

- Decisions about presumptions should be grounded in a scientific evaluation of the full range of evidence that the exposure of interest *causes* the disease or disability.
- If there is sufficient evidence to infer a causal relationship, the amount of disease attributable to the exposure should be estimated.

Chapters 7 and 8 address the first question of whether a causal relationship exists. Chapter 7 makes explicit what is meant by *cause* in contrast to statistical *association* and details the sources of evidence necessary to reach a conclusion as to whether there is a causal relationship. Chapter 8 then discusses quantitative and qualitative approaches for integrating epidemiological, laboratory, and other kinds of evidence to reach conclusions about the strength of evidence for association and causation. This background

provides a foundation for the Committee's specific recommendations in Chapter 12, which outlines a classification system for characterizing the strength of evidence in support of a general causal relationship. Assuming that such a causal relationship has been established, Chapter 9 discusses how to quantify the strength of the causal effect, using measures most relevant to compensation decisions under the presumptive process: the *attributable fraction* for the population of exposed veterans, and the *probability of causation* for an individual. Chapter 10 covers the various types of data necessary to assess the existence of a causal relationship and to quantify the size of the causal effect. It proposes future comprehensive exposure and health data collection strategies for military personnel and veterans.

Provision of compensation to a veteran, or to any other individual who has been injured, on a presumptive basis requires a *general* decision as to whether the agent or exposure of concern has the potential to *cause* the condition or disease for which compensation is to be provided, in at least some individuals, and a *specific* decision as to whether the agent or exposure has caused the condition or disease in the particular individual or group of individuals. The determination of causation for veterans is based on review and evaluation of all relevant evidence including (1) measurements and estimates of exposures of military personnel during their service, if available; (2) direct evidence on risks for disease in relation to exposure from epidemiologic studies of military personnel; (3) other relevant evidence, including findings from epidemiologic studies of nonmilitary populations who have had exposure to the agent of interest or to similar agents; and (4) findings relevant to plausibility from experimental and laboratory research. Scientists and scientific organizations, such as the Institute of Medicine (IOM), have developed approaches for reviewing evidence and determining if causation can be inferred. Typically, these approaches involve a comprehensive review and the judgment of a panel of experts as to whether the evidence supports causation and with what degree of strength. The determination of causation for a particular veteran is based first on the general determination as to whether the exposure causes disease, and then on information on the exposures and possibly on clinical features of the individual being evaluated for compensation.

Compensation decisions critically depend on determinations of cause, but the information available for determining general or specific causation may be incomplete or inconclusive. For a group, the evidence may be insufficient or still evolving, and for an individual, information on exposure may be lacking, or there may be uncertainty as to the role of service-related factors versus the roles of other factors in causation. In the Agent Orange example, information on cancer risk in exposed veterans was not available until they had been followed for a sufficient time, reflective of the latency

between exposure and disease risk for carcinogens. For individual Vietnam veterans, exposure to Agent Orange cannot be estimated with any certainty, and VA has made a presumption with regard to exposure of Vietnam veterans to Agent Orange (VA, 2002). VA has also presumptively linked certain outcomes, such as prostate cancer and type 2 diabetes, based on evidence for association to Agent Orange exposure. By contrast, presumptions are not needed for combat-related casualties for which there is no uncertainty as to causation.

The role of presumptions becomes evident when the complete suite of information needed by VA for making compensation decisions for groups and for particular individuals is considered. Figure 6-1 describes information gathering and how information may be used for making general and specific judgments about causation and for making evidence-based decisions with regard to compensation. The schema in the figure assumes that the availability of information for making these determinations, as well as the roles of factors beyond the scientific evidence, such as costs and political considerations, are all figured into the process. Presumptions are made when there are gaps in the information related to exposure and causal classification. Factors other than the evidence relevant to the causal classification may affect the compensation decision.

If complete information were available, the process in the table could flow without presumptions, but the review of presumptions in Chapter 2 shows that this ideal has been infrequent and many presumptions have been made. The military workplace and particularly combat can lead to many exposures that may affect future health status and disease occurrence. Military personnel sustain a variety of exposures, some specific to the military and others not, that may increase risk for disease. If exposures of potential concern were tracked during military service and disease surveillance were in place and maintained, even for those who have left active duty, evidence could be generated directly relevant to the causation of disease in veterans. Disease rates could be compared in exposed and nonexposed veterans, for example. Lacking such evidence, reviewing groups turn to epidemiologic studies of other populations and gauge the relevance of the findings for the exposures of veterans. Such groups also give consideration to toxicological and other research information. For a specific individual, the determination of eligibility for compensation would be based ideally in full knowledge of that individual's risk and an estimation of his or her probability of causation, given exposure history and observational information on the associated risk from similarly exposed people. However, this level of information and scientific understanding has not yet been fully achieved for individual causation for any agent.

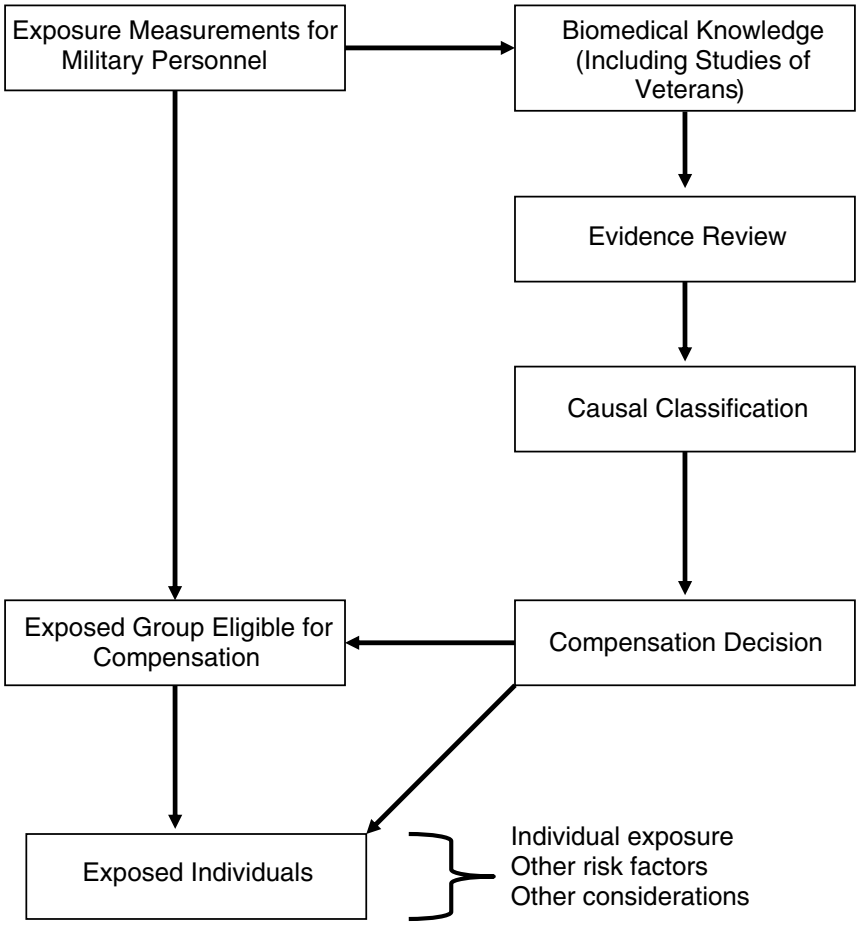

FIGURE 6-1 Information gathering and its use in making general and specific compensation decisions.

A FRAMEWORK FOR PRESUMPTIONS

For all veterans or a particular group of veterans, the evidence may be sufficient to identify a causal relationship between an exposure and a health outcome. However, certainty as to whether an individual veteran's service caused his or her disability or illness will vary depending on clinical characteristics and the availability of information on the veteran's exposures during service.

In decisions to award compensation, two types of errors may occur: giving compensation to a veteran whose illness was not caused by the service-related factor (false positive) and denying compensation to a veteran whose illness was caused by the factor (false negative). These two types of errors need consideration in the design of compensation schemes.

This section establishes a framework for reasoning about compensation for service-attributable disability and illness and for making presumptions, and discusses the concept of a disability or illness being *service attributable*—that is, *caused by* a veteran's service. (A more detailed discussion of models of causation is presented in Chapter 8 and Appendix J.) This section also describes the types of errors that can be made and the potential costs of each. It then addresses presumptions, viewed as one approach to completing gaps in the evidence needed for making decisions about compensation. The Committee emphasizes the need to address the false positive and false negative rates of particular decisions.

To simplify this chapter, the Committee considers the onset of a particular definable disease, a dichotomous outcome. Of course, some diseases are non-specific in their characteristics and the extent of disability associated with a particular disease may be a continuum from mild to very severe.

Service-Attributable Disease

In the circumstance that a veteran has a specific medical disease, the primary question for presumptive compensation is whether the disease is *attributable*, that is, caused by exposures during military service. We ask whether, absent service, the disease would have occurred at all or would have been less severe. The answer for any particular veteran can never be known exactly because it is not possible to observe the same person as exposed and non-exposed. The needed comparison for what would have happened to the exposed person, had they not been exposed, is referred to as the "counterfactual"—in other words, counter to the actual facts. We use information from unexposed but similar persons to describe the counterfactual. For example, the rate of posttraumatic stress disorder (PTSD) in former prisoners of war (POWs) could be compared to the rate in veterans with combat service who had not been POWs. There is an implicit assumption that the rate in non-POWs represents the rate in POWs, had they not been POWs. The excess in the POWs reflects the contribution of having been a POW.

The degree of certainty as to whether a disease is caused by service will vary substantially across different exposures and diseases. At one extreme, if the health problem is the direct result of an event during service, such as a battle wound, then full service attribution can be made with certainty. For chronic diseases with multiple causes there may be much less certainty. For example,

consider a Vietnam veteran who develops diabetes. His service has been established as a potential risk factor based on findings of epidemiologic studies and knowledge that some Vietnam veterans were exposed to Agent Orange, leading to a presumption of exposure of all Vietnam veterans. However, other factors, such as obesity and age, also contribute to the development of diabetes. Service attribution for diabetes in this particular veteran is much more uncertain than for disability from the battle wound. The uncertainty comes both from gaps in the general evidence linking Agent Orange to diabetes and from limitations of the information available on exposure and other relevant characteristics for the particular veteran.

In deciding whether to compensate a group of veterans on a presumptive basis, review is needed of all relevant data to assess if the disease is service attributable, including information about wartime exposures and other risk factors (such as obesity, age, and gender, in the example of diabetes). This information would then be used to estimate the likelihood, that is, the chance that exposure during military service contributed to the disease in the group. Currently, with the exception of radiation for which quantitative risk approaches are available, VA takes a more qualitative approach to determining service attribution, while using information about the exposure and other factors, as available. For some diseases of current concern with several causes, the causal agents contributing in a particular individual cannot be known with certainty so that presumptions will lead to false positive and negative errors.

Errors

The two possible errors that can be made in deciding service attribution (assuming knowledge of whether or not a veteran's disease was caused by exposures during service) are summarized in Table 6-1. A false positive decision is made when the veteran's disease is not caused by his or her service, but VA decides that it was. A false negative decision is made when the disease is caused by service, but VA does not determine it to be service attributable.

The rates of correct decisions are called the *sensitivity* or true positive rate (TPR) and the *specificity* or the true negative rate (TNR). In other words, the proportion of all truly service caused cases that are correctly classified as service attributable is called *sensitivity*, whereas the proportion of all truly non-service caused cases that are correctly judged not to be service attributable is called *specificity*. Sensitivity is the probability of correctly deciding that a person's disease was caused by service. Specificity is the probability of correctly deciding that it was not.

The example above addresses the correct classification of veterans with regard to the causation of disease by exposures during military service. The

TABLE 6-1 Possible Decisions About Service-Attributable Diseases (SADs) with Associated Errors and Losses

Decision	Truth	Error	Rate of Error	Loss
Disease NOT caused by service	Disease NOT caused by service	No error	Specificity [True Negative Rate (TNR)]	0
Disease NOT caused by service	Disease IS caused by service	Failure to attribute disease to service	1-Specificity [False Negative Rate (FNR)]	Failure to cover veteran with SAD • Monetary loss to veteran • Injustice to veteran
Disease IS caused by service	Disease NOT caused by service	False attribution of disease to service	1-Sensitivity [False positive rate (FPR)]	• Monetary loss to society • Incorrect disease label and consequences
Disease IS caused by service	Disease IS caused by service	No error	Sensitivity [True positive rate (TPR)]	0

same concept and terminology is used with regard to classification of exposures and diseases. Exposure status is often classified on the basis of incomplete or imperfect information so that some persons designated as exposed were not (false positives) and some designated as non-exposed were (false negatives). The same considerations extend to disease classification. For some diseases, there are relatively specific and firm diagnostic criteria (e.g., type 2 diabetes), while for others, the diagnostic picture is more ambiguous, (e.g., some neuropsychiatric disorders), and both false positive and false negative errors of diagnostic classification may be made.

Losses

As is nearly always the case, errors of classification have associated costs or losses. False negative errors are readily understood: a veteran who should receive compensation does not. The consequences of false negative errors elicit strongly motivated responses from all parties: veterans, VA, Congress, and society in general. Because there is strong motivation to avoid false negative decisions, a compensation scheme may be constructed to minimize the risk of making them by maximizing sensitivity (the probability of deciding in favor of compensation when a service-attributable disease has

occurred). In avoiding false negatives, however, there is usually a trade-off with the numbers of false positives, as increasing sensitivity will generally reduce specificity. In other words, planning for as few false negatives as possible increases the number of false positives. In balancing the risks of false negative decisions against numbers of false positives, VA presenters and past congressional staffers at public Committee meetings indicated a strong motivation to compensate veterans who may have been harmed by their military service, even if false positives are incurred (as stated during Pamperin, 2006; as stated during Petrou, 2006; as stated during Ryan, 2006; as stated during Scott, 2006; as stated during Yoder, 2006).

However, false positive errors may also come with losses. These include the injustice of inappropriately awarding compensation to veterans not actually harmed by their service and the unnecessary expenditure of public funds. A compensation system that tends to have a high false positive rate may become generally suspect, particularly if compensation costs escalate rapidly. Uncompensated veterans may be troubled by the seemingly high rate of compensation among fellow veterans. Balancing the losses of false negatives and false positives is difficult, as the loss from a false negative is the injustice done to deserving but uncompensated veterans and that from false positives includes economic costs along with non-economic consequences of having a non-specific system.

Service-Attributable Fraction of Disease

In public health, calculations have long been made on the amount of disease caused by a factor. One well-known example is the number of deaths each year in the United States attributable to cigarette smoking. Similarly, it is possible to estimate the amount of disease among veterans with a given exposure and given risk profile that exceeds what is observed in otherwise similar, but unexposed persons. That is, one can compare the rate of disease in exposed veterans to the rate in otherwise similar persons who were known not to be exposed. If there is a difference between these two rates, and the assumption is that the difference is due to a causal effect of the exposure on disease occurrence, then the fraction of disease *attributable* to the exposure can be quantified. If for a subgroup of veterans with a homogeneous risk profile, the rates of disease among exposed and unexposed are r_1 and r_0, respectively, then the fraction of disease *attributable to service* is the relative increase associated with exposure expressed as a fraction of the rate among the exposed. That is, assuming causation, the service-attributable fraction (SAF) can be calculated by the following equation:

$$\text{SAF} = (r_1 - r_0)/r_1 \text{ or } = 1 - r_0/r_1$$

As r_1—the additional risk from exposure—increases, the term r_1 becomes smaller and the SAF increases towards 1.0. Consider again the examples of battle wounds and diabetes. Because all battle wounds occur only among those in combat, $r_0 = 0$ so that the attributable fraction is 1.0 for battle wounds. For diabetes, however, the fraction of cases attributable to service in Vietnam is likely to be much smaller than 1.0, given the existence and strength of other factors (e.g., obesity) that contribute to its causation.

Rates of disease for exposed veterans and for otherwise similar veterans who were not exposed are required to estimate the SAF of disease for a population of exposed veterans. The rates are needed for each subgroup as defined by the exposure of interest, other risk factors, and perhaps other covariates. Of course, taking account of all the various subgroups defined by the resulting array of variables is likely to be difficult or even impossible in practice. If relevant data are available, an analytic approach using a statistical model can be used for taking the covariates into account so that the SAF can be calculated for each subgroup.

To illustrate the estimation of service-attributable disease, consider the hypothetical data in Table 6-2 showing diabetes occurrence in 5,000 veterans exposed to Agent Orange and 5,000 otherwise similar, but unexposed, persons in a particular stratum of demographic and other risk factors.

In this hypothetical example, 150 of the 10,000 veterans have diabetes. Again in this example, only 100 of the diabetics were exposed to the putative cause, and thus 100/150 = 67 percent of the total funds spent on diabetes are for exposed individuals. Even among the exposed veterans, not all cases of diabetes were caused by the exposure, as 50 would be expected absent exposure, based on the experience of the unexposed veterans of whom 50 of 5,000 developed diabetes. Therefore, we can assume, absent exposure (i.e., the counterfactual), that 50 of the 100 cases among the exposed veterans would have occurred, even if those veterans had not been exposed. Hence, only the remaining 50 or 50/100 = 50 percent are attributable to the exposure associated with service in Vietnam. In this example, providing compensation for all exposed veterans with diabetes means that the false positive rate is 50 percent.

TABLE 6-2 Hypothetical Example of the Estimation of Service-Attributable Disease

	Diabetes	No Diabetes	Total
Exposed veterans	100	4,900	5,000
Unexposed veterans	50	4,950	5,000
Total	150	9,850	10,000

In this example, the costs of compensation can be apportioned between the true positives and false positives. Assume funds of $10,000 per person compensated and three scenarios: (1) knowledge of who is exposed and has disease caused by exposure, (2) knowledge of who is exposed and no knowledge of which cases were caused by exposure, and (3) no knowledge of who is exposed or which cases were caused by exposure. In the first situation, $500,000 would be awarded, only to true positives. In the second, if the exposure status of specific individuals were known but individual causation not known, $1,000,000 would be awarded. With a SAF of 50 percent, $500,000 would be for true positives and $500,000 for false positives. If exposure status were unknown for all individuals, then the compensation scheme would award $1,500,000 including $1,000,000 for false positives. Applying the SAF of 33 percent (67×50 percent) to the total disability costs ($150 \times \$10{,}000$) again gives $500,000 in costs attributable to the exposure. In the first situation, with known exposures and disease causation, only those exposed receive payment, while, in the third, all with disease receive payment.

This simple example shows that the attributable costs for a population with a given set of characteristics are determined by two fractions:

- Probability that a veteran was actually exposed to the putative cause given that he or she has the disease and given his or her estimated or measured exposure data and information on other relevant factors
- Probability that the disease in an exposed veteran was caused by his or her exposure given that the veteran has the disease, and given his or her estimated or measured exposure information and information on other relevant factors

These probabilities can be estimated, if the requisite data are available; otherwise, values must be assumed. Presumptions for exposure or causation, as currently implemented by VA, correspond to assuming that these probabilities are equal to 1.0. Service in a particular theater may lead to a presumption of exposure, an assumption meaning that the probability of exposure is 1.0; with regard to causation, there may be a further assumption that the disease is caused by the exposure, again acting as though the second probability is 1.0. If either of these two probabilities were assumed to be 0, then compensation would not be awarded.

In the illustration above, we calculated a single SAF from the rates of disease among exposed and otherwise similar unexposed veterans. This calculation is based upon the assumption that we are comparing like to like persons, except for the exposure. It can be difficult to form groups of exposed and unexposed veterans that are the same with respect to

other factors affecting the disease process. Typically, statistical methods for adjustment are used to attempt to achieve this comparability.

Statistical methods, however, are only as good as the data to which they are applied. Accurate and precise estimates of SAFs depend on detailed data on exposure, key covariates, and disease outcomes. Chapter 10 provides a detailed discussion of approaches to compiling such data as an element of surveillance of veterans. To the extent that data are incomplete, a frequent situation, the estimates of the SAF will be subject to uncertainty to a degree that will depend on the extent of missing data.

Making Presumptions

To this point, we have described the concept of service-attributable disease for a population and for an individual. We have indicated that application of a presumption can be thought of as equivalent to acting as though the probability of exposure and/or the probability that an exposed veteran's disease is caused by his or her service are equal to 1.0. We show that any scheme may lead to two types of error and that avoiding false negatives, a desirable property of a compensation system, may increase the false positive rate. One key consideration is the basis for setting the sensitivity of the approach. We have set out the losses associated with each of the two types of error. When a veteran's illness is not attributed to a service-related exposure when it should be, he or she is denied benefits to which entitled, and an injustice is rendered. When a veteran's illness is attributed to a service-related exposure even when he or she was not exposed (or, if exposed, the disability was not caused by that exposure), compensation is provided that is not truly warranted.

Uncertainty

Uncertainty, lack of complete and perfect knowledge, inherently affects the presumptive disability decision-making process. Presumptions are needed because information is incomplete, in relation both to causation generally and to whether specific individuals have an illness caused by service in the military. Because uncertainty is inevitably present, a vocabulary to express its extent, including adjectives such as *unknown*, *improbable*, *possible*, *likely*, or *certain* is needed. In using uncertain scientific evidence for decision making, we depend upon quantification of uncertainty for guidance on how to weigh more and less certain evidence.

In attributing disease to military service, uncertainty may be unavoidable for some exposures, although obviously not for others, such as a wound and its consequences. As described in Chapters 7 and 8, one necessary step in the presumptive disability decision-making process is to determine whether a disease was caused by factors related to military service.

The counterfactual notion of cause compares disease occurrence in two worlds, one with and the other without the exposure. Because only one of these worlds is observable, the likelihood of an event in the other must be predicted, and the outcome of the prediction is inherently uncertain.

The determination of whether a particular military exposure has the potential to cause a disease or condition is often subject to substantial uncertainty. Experimental studies have the advantage of having an explicit comparison group selected at random so that the counterfactual state is experimentally established. However, data from controlled experiments in human populations are generally not available and would generally not be applicable to exposures that cause disease only after a substantial period of time, as is true for many chemicals and risk for cancer. Findings from observational or epidemiologic studies of risk in exposed compared to unexposed persons, while attempting to control for other factors, are often used instead. The effort to control for other factors and to thereby assure comparability of exposed and nonexposed persons may not be fully successful, and other sources of bias may also add to uncertainty in results of observational studies. Typically, results of in vitro and animal studies of biological mechanisms are also considered. However, in using the results of such research, uncertainty arises from the extrapolation of results from cells, animals, or other systems to humans. Approaches for quantifying these diverse sources of uncertainty about causation have been developed but do not fully reflect the scope of the uncertainty and its implications for decision making. Most often, judgment of expert panels to gauge the degree of uncertainty is used as a guide to decision making.

Even if general causation is established, assignment of causation in a particular veteran may still be subject to uncertainty. Limited or no information may be available on exposure. Exposures in a war theater may vary greatly over space and time, and without detailed information on the spatiotemporal profiles of exposure and on locations of individual Service members, exposure estimates will be imprecise and possibly invalid.

Uncertainty as to individual causation would not be eliminated by having "perfect" exposure data. Conditions and diseases often have multiple causes, each possibly causing some proportion of the observed cases. Absent some marker that indicates that a particular case of disease was attributable to a specific factor, uncertainty as to causation by military service, when other factors also contribute to etiology, is inherent. Variation in susceptibility to an exposure is a further source of uncertainty in considering causation in individuals.

Uncertainty also affects the SAF, a statistic recommended by the Committee as an index of the extent of disease that is attributable to an exposure. The *attributable fraction* is defined as the fraction of an exposed and diseased population whose disease was caused by the exposure, meaning it

is the fraction of the population who, but for the exposure, would not have developed the disease. The value of the attributable fraction may depend on multiple factors, including the level and the timing of exposure, the dose-response curve, the time since exposure, and the baseline susceptibility of the population. The true function relating the attributable fraction to exposure is unknown in terms of both its general form and its specific values. We estimate the function describing the attributable fraction from finite data that are subject to variability. Hence, there is typically uncertainty in estimates of the attributable fraction used to describe the burden of disease attributable to an exposure and to assess whether disease in an individual veteran was caused by service.

Scientists have constructed mathematical systems to quantify uncertainty; the theory of probability is the most widely applied. There are two distinct notions of probability: frequentist and subjectivist. In the former, probability represents the long-run frequency of events. For example, the probability of a heads or tails represents the fraction of heads or tails out of a large number of coin tosses. Subjectivist probability is instead an expression of belief about the likelihood of an event. For example, we represent an individual's risk of disease as a probability between 0, indicating no chance, and 1, indicating certainty. For either notion, there is the same precise calculus for representing, combining, and manipulating probabilities as measures of uncertainty.

In subsequent chapters, the Committee sets out concepts related to general and specific causation that are critical for improving the current approach to making presumptions.

SUMMARY

This chapter introduces some of the key concepts involved in using scientific evidence as the basis for compensation of groups of exposed individuals. It sets out the need to determine general causation and to consider how much disease is attributable to exposure. These concepts are elaborated in subsequent chapters. Gaps in the scientific evidence on exposure and causation lead to a need for presumptions. Chapters 10 and 11 address how surveillance of exposures and disease among active duty personnel and veterans could reduce these gaps.

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7

Scientific Evidence for Causation in the Population

INTRODUCTION

This chapter describes the kinds of scientific evidence used for establishing a general causal relationship between exposure and disease, an important input to presumptive service-connection decisions. Unlike individual service-connection claims, in which a particular veteran has to make a case that a particular condition affecting him or her was caused by or aggravated by military service, a presumptive service connection applies to a group, or population of veterans. Presumptive service connections remove the burden of proof from individual veterans, but establishing presumptions necessitates an assessment of the scientific evidence for *population causal claims* (i.e., was some group of veterans *exposed* to conditions or substances that *aggravated* existing or *caused* new health problems after service separation). More specifically, the goal is often to establish whether, in a *population* of individuals, exposures received by members of the population resulted in a change in the *frequency of occurrence or in the average severity* of a disease. For example, we might ask whether the frequency of non-Hodgkin's lymphoma (NHL) among Vietnam veterans who were exposed to benzene during service is higher than the frequency among those who were not. If so, then we might assert that exposure to benzene is capable of *causing* NHL. The causal claim about the population does not mean that every veteran exposed to benzene during service will develop NHL or that every case of NHL would not have happened but for benzene exposure. On the population level, causal claims typically involve how risk (the *probability* of disease) changes in *response* to exposure.

In this chapter we will focus on the scientific issues involved in establishing these sorts of causal claims. We will review the issues facing scientists or others who review evidence to collectively decide on population causal claims. The next chapter provides a framework for doing so. At the start of this chapter, we discuss the types of scientific information considered in evaluating the strength of evidence for inferring causation. Then we discuss how epidemiologists define and assess association and how association differs from causation. This distinction is essential to understanding prior approaches to presumptive disability decision making and also this Committee's proposed approach. In Appendix J, we offer an extended discussion of what we mean by causation and how it is modeled statistically. We have placed this material in an appendix, not as a reflection of its importance, but because the topic is too complicated to cover in a short section.

Next we discuss the scientific strategies used to establish association, and lastly we discuss the scientific strategies used to move beyond just determining the presence of an association to inferring causation. We conclude the chapter by discussing uncertainty—both with respect to association and with respect to causation. We leave to the next chapter a discussion of strategies for synthesizing potentially diverse sources of evidence into a single overall judgment of the strength of evidence for a causal claim.

SOURCES OF EVIDENCE

Evidence about population causal claims (hereafter just "causal claims") comes from a variety of sources. In some cases, we have extensive knowledge about the mechanism by which exposure causes disease. For example, we do not need a randomized clinical trial to establish that bullet or shrapnel wounds have a deleterious effect on health. In other cases, such as low levels of exposure to lead and cognitive deficits in children, we know much less about the mechanisms and turn to other types of scientific evidence including findings of epidemiologic studies. Any scientific assessment of a causal claim combines the mechanistic knowledge and statistical evidence from epidemiologic studies. In this section we briefly survey the types of statistical evidence used to establish causal claims, and then we sketch the types of toxicologic, biologic, and mechanistic knowledge used to support or reject causal claims. By statistical evidence we mean the quantitative relationships between a set of measured variables in a sample. Case reports about individual patients may be useful for suggesting etiologic hypotheses, particularly with exposures that are followed quickly by disease onset.

Randomized Clinical Trials

The most persuasive human evidence for establishing a causal relationship comes through experimental studies in which investigators control exposure. Randomized clinical trials (RCTs) are the counterpart in humans to the controlled laboratory experiment with animals. In clinical trials, the exposure (usually considered as potentially beneficial, such as a new medication) is allocated randomly to the study population in such a way that the treated and untreated groups are otherwise equivalent, at least in expectation. If the randomization process has been successful, then any differences between the treated and comparison groups should reflect a causal relationship between treatment and disease (or outcome) risk. Randomization assures comparability of the two groups on factors that may affect the occurrence of the outcome.

Although the RCT is simple in concept, proper execution in human populations is often quite challenging and complicated. Even if randomization is successful in assuring comparability of exposed and comparison groups, validity of results for causal inference is not assured. For example, there are powerful placebo effects that operate in humans, which can be eliminated, in some instances, by concealing treatment status from the study participants. More subtle problems can arise when the doctors or others administering the treatment and collecting the outcome data are aware of treatment status. This potential for bias has prompted the use of the "double-blind" design, in which neither the study personnel in contact with participants nor the participants themselves know the treatment status. A refinement of this design is the crossover study, in which treatment and nontreatment are given in random order to each participant, allowing each person in the study group to be his or her own control. This design illustrates the kind of evidence we would like to have to draw causal claims, since we directly observe the response of the same person when they are treated and not treated, so that the treatment can be reasonably inferred to be the "cause" of any differences in response under the two conditions. Unfortunately, crossover trials are a practical approach only for studying short-term responses to agents for non-fatal conditions, so that they cannot be used for assessing effects of environmental exposures on chronic diseases.

In most other designs, including RCTs of standard design and most observational studies, we have to base such conclusions on differences in rates between exposed and unexposed groups of *different* individuals, rather than on the responses of the same individual in exposed and unexposed states. Interpretation of differences in outcome frequency as a causal effect when comparisons are made between different groups requires a form of inference known as "counterfactual." Using the counterfactual (i.e.,

counter to the facts) we infer what would have happened in the exposed group had the exposure been some alternative by making a comparison with the outcomes of others who actually experienced the different exposure. The counterfactual approach needs comparability of the exposed and comparison groups.

RCTs and other experiments involving humans are ethically limited in the range of questions to which they can be applied. Many of the major questions of public health—for example, the effects of air pollution or pesticides on human health—cannot be addressed through RCTs because it is not ethical to expose humans experimentally to substances in quantities that are presumed harmful. For such questions, we are limited to passively observing the health of people "naturally" exposed—that is, to observational studies. Nonetheless, the model of the RCT remains useful as a framework for considering limitations of findings of observational studies. Randomized interventions can be ethically carried out to reduce exposure to harmful agents (e.g., tobacco use).

Observational Studies

In an observational study, the investigator does not control exposure of the people in the study and does not intervene in any way in the population under study. Although observational studies may lack the comparability of exposed and non-exposed characteristic of controlled experiments, they are nonetheless capable of providing evidence about the relationship between exposure and health and are generally the only option available to obtaining human evidence of the effect of potentially harmful exposures.

Broadly speaking, observational study designs fall into three categories: cross-sectional studies, cohort studies, and case-control studies. In cross-sectional studies, a variety of factors are recorded at a particular point in time. In cohort studies, persons exposed or unexposed to a given factor are observed over a period of time for health effects related to the exposure. The case-control study compares persons with a given disease (*cases*) to those without the disease (*controls*) with regard to their history of exposure. Each of these general designs has appropriate analytic strategies, and each design has its own strengths and weaknesses. There are variations of each of these approaches, and a few additional approaches as well (for example, case-crossover studies). These designs are well described in standard epidemiologic references.

One general difficulty of observational studies, regardless of design, is that exposure is not randomized. Rather, exposure status may be determined by where people live or work, what they eat, what social group they belong to, or by a host of other factors that can be associated with disease risk. As a consequence of these other factors, associations between expo-

sures and disease risk may occur even if the exposure does not cause the disease. Conversely, no association may be measured when the exposure actually does cause disease because these factors act to reduce the effect.

Toxicologic, Mechanistic, and Biologic Knowledge

In addition to randomized clinical trials and observational studies, which provide statistical evidence of a relationship between exposure and disease, a wide variety of other types of scientific evidence may be crucial for inferring a causal relationship between exposure and disease (IOM, 2006a,b; IOM/NRC, 2005). Controlled laboratory experiments with animals and research in in vitro systems and other relevant biological, physical, or even social data can be used to assess the likelihood that a given substance or circumstance can cause a particular human health effect. Approaches to assessing the combined evidence from human and animal investigations, as well as from in vitro systems, have been formulated by a number of agencies including the International Agency for Research on Cancer (IARC, 2006b), the Institute of Medicine (IOM) (IOM, 2006b; IOM/NRC, 2005), and the Environmental Protection Agency (EPA, 2005). These formalized approaches offer guidance on assessment of evidence and relative weighting of various lines of evidence.

Even without statistical evidence from epidemiologic studies, the findings of animal studies and mechanistic investigations on how an agent causes a health effect can be sufficiently convincing to support a causal conclusion. For example, IARC identified benzo(a)pyrene as a human carcinogen primarily based on non-epidemiologic evidence (Straif et al., 2005). However, we infrequently amass this level of biological understanding for agents affecting human health. More typically, non-epidemiologic lines of research are considered to support the conclusion that a substance, or chemical, "probably" causes, or is "likely" or "reasonably anticipated" to cause an adverse effect such as cancer or other health endpoints (e.g., EPA, 2005; IARC, 2006b; NTP, 2005; NTP CERHR, 2003, 2005). When there are epidemiologic findings supporting an association between an agent and disease, however, experimental or other biological evidence may provide sufficient weight and understanding for scientists to conclude that the association is due to a causal relationship. For example, in several species the agent may produce the same effect as observed in human studies, and by a mechanism that is conserved and relevant across species with key features of the mechanism observed through experiments in human cell lines or other systems.

As a case in point, epidemiologic, animal, and mechanistic data were all considered in establishing that industrial exposure to butadiene can cause lymphohematopoietic cancers (IARC, 1999). Epidemiologists showed that

styrene-butadiene exposed rubber workers had elevated lymphohematopoietic cancer rates. Toxicologists showed that potentially carcinogenic metabolites of butadiene in butadiene-exposed workers activated potential oncogenes, providing mechanistic knowledge on carcinogenesis, and biologists induced tumors in mice and rats, both with exposure to butadiene and to a known metabolite that occurs in humans and mice and rats, providing animal evidence.

Formaldehyde provides a contrasting example. IARC (2006a, sec. 5-2) noted that epidemiologic studies found "strong but not sufficient evidence for a causal association" between formaldehyde exposure and leukemia. Their interpretation of the finding as causal was guarded because of some limitations in the several positive studies (e.g., small numbers of deaths) and lack of finding of effect in a high-quality study. There was uncertainty with regard to possible underlying mechanisms. The IARC monograph noted lack of good rodent models for human acute myeloid leukemia. It also considered various possible mechanisms, "such as clastogenic damage to circulatory stem cells" (IARC, 2006a, sec. 5-4). Unable to identify a mechanism for the induction of leukemia in humans from formaldehyde and data to support it, IARC did not conclude that formaldehyde was a known cause of human leukemia. Golden et al. (2006) have advanced arguments that the relationship could not be causal. For example, they argued that inhaled formaldehyde is so reactive that it is unlikely to travel as formaldehyde from the upper airways to the bone marrow; also they argued that "there is no indication that formaldehyde is toxic to the bone marrow/hematopoietic system" as are other known leukemogens benzene, ionizing radiation, and chemotherapeutic agents (Golden et al., 2006, p. 146).

ASSOCIATION AND CAUSATION

Association

Absent strong mechanistic understanding, the first step towards establishing a causal relationship between exposure experienced by people and a disease is to establish a statistical *association* between exposure and the disease. Exposure and disease are positively associated in a group if the incidence of disease among those exposed is higher than the incidence among those not exposed. For example, in the early 1950s Doll and Hill demonstrated that tobacco smoking and lung cancer mortality were associated. In a cohort of British physicians, lung cancer mortality was much higher among people who smoked 25 g of tobacco daily compared with those who didn't smoke (Doll and Hill, 1954, p. 1530). Even though a detailed mechanism between inhaling smoke and contracting lung cancer was not evident, a vague but plausible mechanism based on the carcinogenic proper-

ties of tobacco tar allowed scientists to hypothesize that the association was produced by a causal relationship. Had there been no observed difference in lung cancer mortality between smokers and nonsmokers, they would have likely assumed that smoking had no causal influence on lung cancer.

The strength of association between exposure and disease is typically measured with a statistic called the *relative risk* (RR). RR is the ratio of the incidence of disease among the exposed over the incidence in the unexposed:

$$RR = \frac{incidence(\text{exposed})}{incidence(\text{unexposed})} = \frac{\#\text{ exposed with disease} / \#\text{ exposed}}{\#\text{ not exposed with disease} / \#\text{ not exposed}}$$

An RR of 1.0 means that the frequency of disease among the exposed is the same as among the unexposed. An RR of 10 means that the rate of disease among the exposed is 10 times as high as among the unexposed.

A high RR does not imply a high absolute risk in the population. If, for example, one in a million unexposed individuals and 10 in a million exposed individuals get the disease, then the RR is 10, even though the chances of getting the disease among those exposed is only 1 in 100,000.

Another measure of association, commonly used in case-control studies, is the *odds ratio* (OR):

$$OR = \frac{\#\text{ with disease \& exposed} / \#\text{ with disease \& not exposed}}{\#\text{ without disease \& exposed} / \#\text{ without disease \& not exposed}}$$
$$= \frac{\#\text{ with disease \& exposed} / \#\text{ without disease \& exposed}}{\#\text{ with disease \& not exposed} / \#\text{ without disease \& not exposed}}$$

From this formula, it can readily be seen that the OR, expressed in the first line as the odds of exposure in cases divided by the odds of exposure in controls, is also (second line) the odds of disease in the exposed divided by the odds of disease in the unexposed. The OR has the desirable property of being approximately equal to the RR if the disease is rare (Greenland and Thomas, 1982). This is true even though the absolute risks in exposed and unexposed cannot be estimated from case-control studies.

Association Is Not Causation

Association is not the same as causation. It is prima facie evidence for causation, but not sufficient by itself for proving a causal relationship between exposure and disease. For example, although they did not record its presence, Doll and Hill would presumably have found a high positive

association between having tar-stained fingers and lung cancer mortality in their study. Clearly having tar stains on one's fingers does not by itself *cause* lung cancer, but it could be associated with lung cancer risk because heavier smokers, at greater risk for lung cancer, would also be more likely to have tar-stained fingers.

Unlike associations, causal claims support making counterfactual claims, that is, claims about what the world would have been like had something been different, or changed. For example, what *would have* been the rate of lung cancer mortality among a group of smokers had they been prevented from smoking? For this, the counterfactual claim would be the rate of lung cancer mortality among never smokers. What would have been the rate of lung cancer mortality among those with tar-stained fingers had we eliminated their stains with special soap? Although tar stains and smoking are both associated with lung cancer, we can answer these questions because we know the causal mechanisms: smoking is a common cause of tar stains and lung cancer, but tar stains by themselves have no effect on lung cancer mortality. Service-connection claims require the same attention to counterfactual questions: what would have been the rate of adult-onset type 2 diabetes had Vietnam veterans not been exposed to Agent Orange, for example.

Claims about association alone do not support the sorts of claim that must underlie presumptive service connections, while causal claims do. We call an association that arises in a population from an exposure that causes disease a *causal association*. Associations are termed *spurious* if they arise for some other reason. For example, the association between tar-stained fingers and lung cancer is spurious.

Spurious associations can arise in many ways. One is from a common factor (confounder) that is associated with the exposure under study and also a cause of the disease of interest, and another is from reverse causality (the disease is a cause of exposure) as depicted in Figure 7-1.

In the context of presumptive service connections, exposure typically occurs prior to the medical condition under consideration. Thus, we can almost always rule out the possibility that a medical condition was a cause of exposure, but the development of disease may influence apparent exposure. For example, it has been speculated that early subclinical manifestations of diabetes could increase storage of polychlorinated biphenyls (PCBs) in the body, leading to apparent associations of PCBs with diabetes even when the exposure is measured years before the emergence of the disease. More intuitively, people developing asthma might choose to not have cats if the presence of a cat exacerbated their asthma. The inverse association that would be observed between asthma and cat ownership would represent reverse causation and not a causal, protective effect of cats on risk for asthma. Thus, reverse causation may produce a spurious association even with carefully collected prospective data.

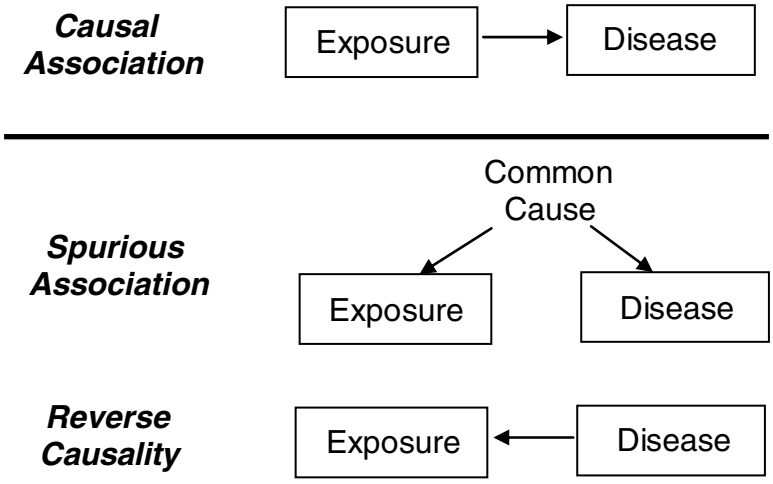

FIGURE 7-1 Causal and spurious associations.

If we can measure potential confounders (i.e., common causes) that might give rise to spurious association, then statistical adjustment can be used to remove the part of the observed association that arises spuriously from confounders. We discuss this strategy in a later section.

There is also the possibility that exposure causes disease, but that the two are *not* associated in the population under study. For example, if a confounder produces negative association between exposure and disease, but the true causal relationship produces positive association, and the two associations (true and confounded) are of roughly same magnitude, then the observed association will be small as represented in Figure 7-2. Note that dropouts are excluded from this example. Fortunately, because hiding a causal association requires a spurious association of similar magnitude but opposite sign as the causal association, this situation occurs infrequently.

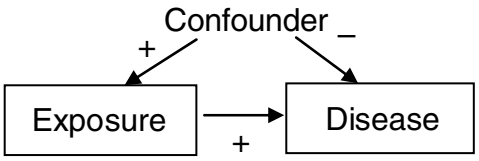

FIGURE 7-2 Scenario for causation without association.

The Problem of Bias

Even if confounding and reverse causation can be ruled out (or statistically controlled for, as we discuss below), observational studies might still be affected by other forms of bias, including information bias and selection bias. *Bias* in this context does not suggest prejudice on the part of the researcher, but rather denotes systematic error arising from the collection of information or the selection of participants that produces an observed association not attributable to an underlying causal relationship between exposure and disease. For example, systematic error might occur in a case-control study of patients with pancreatic cancer in which most of the cases have died before they could be interviewed. If the interviewer relies on family members for information about exposures of the dead person but on living controls themselves, then the quality of the exposure information is likely to differ for the cases and the controls. Differential quality of data for cases and controls can in turn easily distort the true association between an exposure and a disease. This would be an example of *information bias*, a broad class of bias that relates to the quality of data collected. Another kind of bias is *selection bias*, which occurs when the selection process by which the study sample is derived distorts the relationship between exposure and outcome. For example, suppose half of the patients in the treatment arm of an RCT drop out of the study from side effects, while no one from the control arm drops out, and suppose that the dropouts are the ones who began the study in worse health. Even if the treatment has no benefit whatsoever on the outcome, the treated group will appear to fare better than the untreated group. Once possible biases are identified, their possible impact on the results can be assessed through sensitivity analysis (discussed below).

EVIDENCE FOR ASSOCIATION

Although it is not sufficient for establishing causation, association is nevertheless prima facie evidence for causation, and the lack of association is prima facie evidence for lack of causation. Thus, if mechanistic knowledge is insufficient to settle the issue, a first stage in any evidence-based approach to presumptive service connection is to empirically establish and quantify the level of association in the service population under consideration, or in similarly exposed populations.

Epidemiologists (e.g., Rothman, 2002) use risk measures such as the RR and the OR to quantify the association between exposure and disease in a population. Other measures might also be of interest, such as the *attributable fraction (AF)*—the proportion of disease in either the total population or an exposed subgroup that is caused by exposure—which is

particularly relevant for compensation policy (see next chapter). This report uses the terminology *service-attributable fraction (SAF)* when the subgroup of interest is a military population. More complex conceptual and statistical models are needed when there are several risk factors to be considered in combination, as will be discussed later in this chapter.

Risk measures are estimated by applying statistical techniques to data from a particular sample drawn from the population of interest (e.g., a study of 1,000 randomly selected veterans of a particular conflict). The result of this process is an estimate of the population risk measure (e.g., the RR), together with a measure of the uncertainty in those estimates (a standard error or confidence interval) caused by the inherent variability in a random sampling process. Note that these uncertainty estimates usually account only for random variation, not the consequences of any bias.

Statistical techniques are also used to test specific hypotheses, particularly the null hypothesis that there is no association between exposure and disease in the population. The null hypothesis is of particular interest—unless it can be rejected, there is insufficient empiric evidence to conclude the existence of an association in the population.

The statistical tests related to the null hypothesis are referred to as significance tests, and the test results are commonly expressed in the form of a *P* value, the probability of observing a sample result at least as extreme as that observed in the sample if the null hypothesis were true. Note that the *P* value does not provide the probability that the null hypothesis is true given the observed data. That would require specification of one's prior belief in the null hypothesis before seeing the data. Additionally, failing to find the *P* value needed to reject the null hypothesis at some level of probability does not exclude the possibility of an association. There should be enough precision to rule out a counter explanation that the study was inadequate to detect a meaningful effect size.

EVIDENCE FOR GOING BEYOND ASSOCIATION TO CAUSATION

If an association has been established, the next (and more difficult) task is to assess the evidence for causation by trying to eliminate alternative explanations to causality for the association. For example, tobacco companies and some academic researchers initially dismissed the association between smoking and lung cancer by proposing explanations other than causation. Arguments were advanced such as: perhaps a poor economic background would expose someone to conditions besides smoking that would lead to lung cancer and would also make them more likely to smoke or perhaps there are genes that dispose people to smoke and also to be more susceptible to lung cancer. Only after some years of epidemiologic research, animal studies, and scientific debate did the scientific community

reject all alternative explanations and conclude that the association between smoking and cancer is causal. Postulating and eliminating alternatives are core skills in observational research. This process can use data from many sources, including the basic sciences and toxicology. If reasonable alternatives are possible, then we cannot move beyond association to a firm causal conclusion.

Experimental Control: Inferring Causation in RCTs

Randomized clinical trials remove two of the possible alternative explanations of an observed association: confounding and reverse causality. By assigning treatment (exposure) randomly, the design removes the influence of any confounder that might influence exposure (Figure 7-3a), and the influence of the outcome on exposure, if there is any (Figure 7-3b). Done properly, and setting aside the play of chance, only a causal relationship from exposure to health outcome should produce observed association in an RCT (Figure 7-3c). However, RCTs are generally not possible for the kinds of causal questions facing VA in presumptive disability decision making.

Statistical Control: Inferring Causation from Observational Studies

Adjusting for Confounding

When associations are found in observational studies, the first approach for removing spurious associations from confounders is statistical control of characteristics that may differ between exposed and unexposed persons (i.e., adjustment). Multiple regression models are one way to estimate the association between exposure and outcome after adjusting for charac-

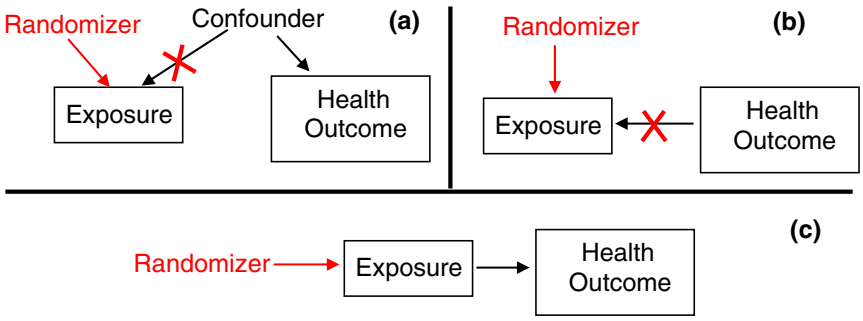

FIGURE 7-3 The power of randomization.

teristics of participants that might confound the results. If investigators have successfully measured characteristics that distort the results, then adjustment of these factors will help separate a spurious from a causal association.

For example, suppose we conduct an observational study of veterans, each exposed during service to some level of a toxin that can permanently degrade respiratory function. Suppose further that older veterans are more likely to have been exposed to more of the toxin, as it was used more frequently in the early segment of a war. Since age (after military service) also naturally degrades respiratory function, it is a confounder of the association between the exposure and respiratory function in this study (Figure 7-4) and must be included as a *covariate* in a multiple regression to adjust for its biasing effect. If age is the only such confounder in the study, and it is measured accurately, then we can indeed separate the spurious from the causal association statistically.[1]

Two problems are common in such an approach, however. First, unlike randomization, which can eliminate the influence of all confounders without having to identify and measure any of them, appropriate statistical adjustment for confounders requires identifying and measuring *all* of them. If, for example, age were not the only confounder of the association of exposure with respiratory function (Figure 7-5), then the association between exposure and respiratory function, statistically adjusted for age, would still combine both spurious and causal association, and thus present a misleading estimate of the effect of exposure on respiratory function.

Deciding which variables to control for in a statistical analysis of the association between exposure and disease depends upon knowledge about the possible mechanisms connecting them. For example, dozens of observational studies, some involving thousands of subjects, have shown an association between watching TV and childhood obesity (IOM, 2006a). Can we move beyond an association and say that watching TV causes childhood obesity?

These studies include a variety of statistical adjustments, depending on the mechanisms the researchers consider important. The primary mechanisms thought to connect TV and obesity are shown in Figure 7-6. Thus, several studies controlled for socioeconomic status (SES), as a child from a low socioeconomic status home might be allowed to watch more TV and also allowed to eat a higher proportion of high-calorie/low-nutrition foods

[1]Assuming all relations are linear, that is, Respiratory Function = β_1Exposure + β_2Age + an "error" term $\varepsilon \sim N(0,\sigma^2)$, and all boxed variates standard normal, then the expected observed covariance (association) between exposure and respiratory function is $\beta_1 + \beta_2\phi$. The expectation of the estimate of the association between exposure and respiratory function adjusting for age in fact equals β_1.

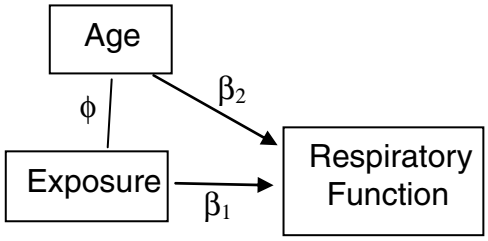

FIGURE 7-4 Age as a confounder.

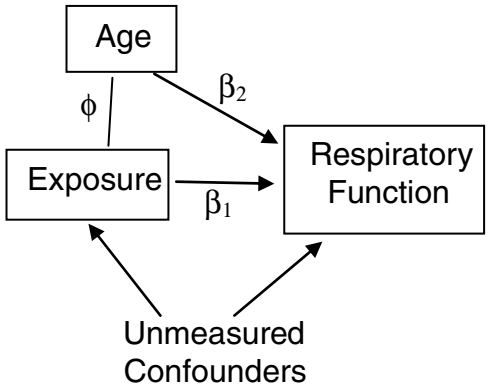

FIGURE 7-5 Unmeasured confounders.

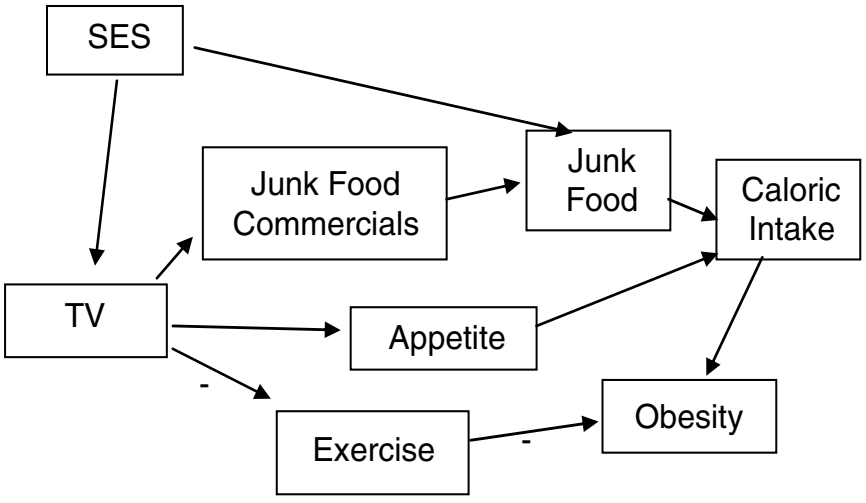

FIGURE 7-6 TV and obesity.

("junk" foods). Several studies attempted to separate out the potential contribution of TV to obesity through replacing or suppressing exercise, which in turn would lead to more obesity, or by increasing caloric intake, either through increasing exposure to food marketing, or by increasing appetite through other means (e.g., people like to snack when they are relaxing passively in front of a TV). Being able to identify these mechanisms allows us to identify and control for potential sources of spurious association and also to tease apart the importance of a variety of possible mechanisms.

Measurement Error

A further problem in adjusting for spurious associations involves measurement error. If a confounder has been included in the statistical analysis as a covariate but has been measured poorly, then the included variable is only a surrogate for the true variable. This is equivalent to partially omitting the variable and thus does not allow all confounding bias to be removed from the estimate of the causal association (Kennedy, 2003). The more measurement error in the confounding variables the greater the potential for incomplete control of bias.

Another problem similar to measurement error occurs when covariates are measured too coarsely. If, for example, TV was not measured in minutes per day, but rather as high, medium, and low, then differences in TV watching levels within these coarse categories could still affect the probabilities of exposure to junk food commercials. Statistically adjusting for this imprecise measure of TV would fail to remove all confounding.

To summarize, statistically adjusting for confounders can separate the causal from the spurious association between exposure and disease, but it can do so completely only if all confounders have been identified, measured accurately, and represented in a valid statistical model. Thus, in assessing a report on a study that claims that adjustment for confounding has been made, the adjusted association estimates the causal association if the study has

- included all reasonable confounders,
- measured them with reasonable precision and accuracy, and
- used them in a valid statistical model.

Instrumental Variables

An alternative to measuring and adjusting for confounders is *instrumental variable* estimation, a technique favored by econometricians (Kennedy, 2003) but not yet widely used in epidemiology (Greenland, 2000). An instrumental variable must be related directly to the putative cause but independent of all

potential confounders. Under this condition, we can separate variation in the cause that might spuriously come from the confounders or from reverse causation from true variation in the cause that will translate to variation in the effect. By using the instrument to show how much of the variation is *not* from the confounders and *not* from reverse causation, we can then statistically adjust the observed association between cause and effect without even measuring the confounders or being concerned about reverse causation.

An example of an instrumental variable might be distance from the hypocenter for veterans of a nuclear weapons test. The true causal variable here would be their ionizing radiation exposure. For some participants this may have been measured by a film badge dosimeter, but these measurements are incomplete and inaccurate. However, one could use the mean of the measured doses for all participants located at the same distance from the hypocenter as an instrumental variable for assigning dose to all participants, and then examine the relationship between these assigned doses and subsequent cancer risk. Assuming a Service member's assignment to a particular location during the test was effectively at random with respect to potential confounders (Service members weren't assigned to locations based on their future cancer risks), this would be expected to yield an unbiased assessment of the exposure-response relationship (Figure 7-7).

Although instrumental variable estimation is a potentially powerful strategy for separating causal from spurious association, it depends heavily on the availability of an informative instrumental variable and on the untestable assumption that the *instrument* is independent of all the other potential confounders and not an independent risk factor for disease given radiation dose. Thus, its practical applications in epidemiologic research are limited.

Other Guides to Causal Knowledge

There have been several attempts to create sets of criteria to guide scientific judgments when moving beyond observed association to causa-

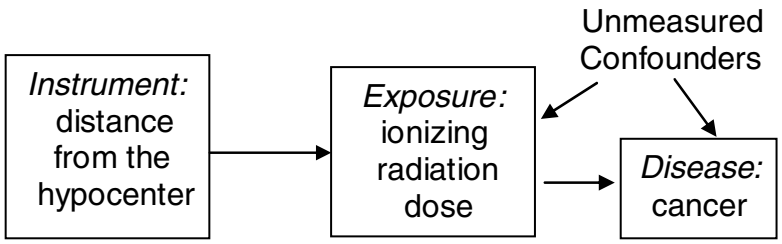

FIGURE 7-7 Instrumental variable.

tion. Some of these criteria can be traced to the "canons of inference" proposed by John Stuart Mill (1862). In the early days of microbiology, Koch developed his famous "postulates" as formal criteria for establishing a causal association of a clinical infectious disease with a microorganism. Koch's postulates include the identification of the suspect causal organism in people with the disease and the causation of the illness in an animal by infection with the organism (Koch, 1884). Unfortunately, such experimentally based criteria are of little help in establishing the causality of an environmental exposure with a chronic disease. The version of the criteria most familiar to epidemiologists and other public health researchers is the Bradford-Hill criteria, which are: the strength of the association, consistency, specificity, temporality (logical time sequence), dose-response (biologic gradient), plausibility, coherence, experimental evidence, and analogy (Hill, 1965). Although each of these criteria has limitations or exceptions, they can be useful guides to assessing the overall evidence. For example, see the introductory chapter in the 2004 Surgeon General's report on smoking (DHHS/CDC, 2004).

As we discussed above, background knowledge about the biologic mechanisms by which an exposure might or might not cause disease can prove crucial in establishing a causal claim or its negation. The tools of experimental biology have been extraordinarily valuable in developing insights into human physiology and pathology. Such laboratory tools have been extended to explore the effects of putative toxins on human health, especially through the study of model systems in other species. The field of toxicology has flourished in recent decades, allowing arguments of plausibility to be developed for a range of environmental toxicants. At the same time, species can differ in fundamental aspects of physiology (e.g., metabolism, hormonal regulation) that limit extrapolation from one species to another.

REALISTIC CAUSAL INFERENCE

Multifactorial Causation

Epidemiologists have long recognized that most chronic diseases, such as cancer or coronary heart disease, result from a complex "web of causation," whereby one or more external agents (exposures) taken into the body initiate a disease process, the outcome of which could depend upon many factors including age, genetic susceptibility, nutritional status, immune competence, social factors, and others. Exposures may occur over an extended period of time with some cumulative effect, and exposure to multiple agents together could result in synergistic or antagonistic effects different from what might result from each separately. These general notions were formal-

ized by Rothman (1976) in a "sufficient component causes model," which postulates that disease can result from a number of different constellations of causal factors, each of which may comprise several components (e.g., exposure plus susceptibility plus timing) that are all necessary to make them a complete cause. This framework is useful in thinking about exposure to multiple causal factors. For example, consider the diagram in Figure 7-8.

Consider the data from a hypothetical epidemiologic study of veterans exposed to some particular exposure illustrated in Table 7-1. In this hypothetical example, smoking is a much larger contributor to risk than is the military exposure of the participants, but the two factors are not confounded, since among the population at risk, the proportion of smokers is the same in the exposed and unexposed. It is also evident that the two effects on risk are multiplicative, since individuals with both factors

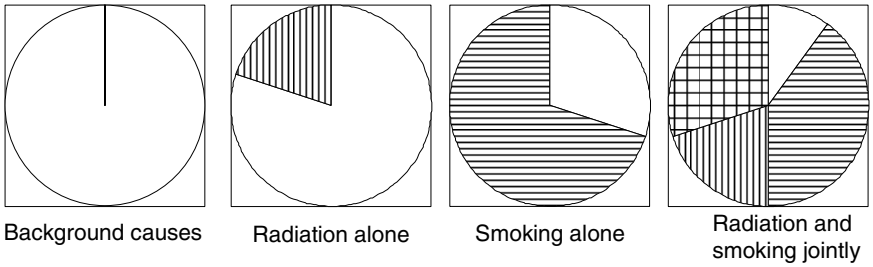

FIGURE 7-8 Rothman's sufficient component causes model.
NOTE: Each circle represents a different constellation of factors that is sufficient to produce disease; within any circle, the sectors represent specific factors that are all necessary to comprise a complete cause. Blank space represents host susceptibility plus background exposures; vertical bars, ionizing radiation; horizontal bars, tobacco smoking; cross-hatched, joint action of smoking and radiation.
SOURCE: Rothman, 1976.

TABLE 7-1 Hypothetical Example of Military Radiation Exposure, Smoking, and Cancer

Military Radiation Exposure	Smoking Habit	Number at Risk	Cancer Cases	Relative Risk
No	Never	1,000	10	1
No	Current	1,000	100	10
Yes	Never	1,000	30	3
Yes	Current	1,000	300	30

have an RR of 30, the product of the RR for smoking (10) and for military exposure (3). In other exposure situations, the pattern of combined effects could be less than multiplicative, or greater. Two specific models have special relevance to compensation policy. The first is the multiplicative model just illustrated, which can be represented mathematically as

$$RR_{mult} = RR_E \times RR_S,$$

where RR_E is the RR for exposed nonsmokers relative to nonexposed nonsmokers, and RR_S is the RR for unexposed smokers relative to unexposed nonsmokers. Under this model, the effect of exposure is the same in both nonsmokers ($RR_{E|NS} = 3$) and smokers ($RR_{E|S} = 30/10 = 3$). The other important situation is an additive model of the form:

$$RR_{add} = 1 + (RR_E - 1) + (RR_S - 1)$$

$$= RR_E + RR_S - 1$$

In other words, the risk from exposure to both factors is the background risk plus the sum of the additional risks from each factor separately. Thus, in our hypothetical example, if the single-factor risks were as before, we would have expected an RR for exposed smokers of 1 + (10 − 1) + (3 − 1) = 12, rather than 30 as above. Under this model, the excess RR ($ERR = RR - 1$) for exposure is the same in nonsmokers ($ERR_{E|NS} = 3 - 1 = 2$) and smokers ($ERR_{E|S} = 12 - 10 = 2$). Of course, the actual joint effect could be different from either of these specific models. The effect when both exposures are present could be less than additive (e.g., a joint *RR* of 11), greater than multiplicative (e.g., 50), or in between (e.g., 20).

Models for Interaction

Epidemiologists use the term *interaction* (or *effect modification*) to denote the departure of the observed joint risk from what might be expected based on the separate effects of the factors. However, any estimate of interaction is model specific, meaning it depends on what model of interaction we expect (multiplicative, additive, or some other). In claiming interaction, one must therefore specify the model for the combined effect from which the observed data deviate. For example, one could define a multiplicative interaction RR as

$$RR_{Int(mult)} = \frac{RR_{joint}}{RR_E \times RR_S},$$

or an additive interaction RR as $RR_{Int(add)} = RR_{joint} - RR_E - RR_S + 1$. For the data illustrated in the table above, $RR_{Int(mult)} = 30/(3 \times 10) = 1$ and $RR_{Int(add)} = 30 - 3 - 10 + 1 = 18$, indicating no departure from a multiplicative model but a large positive deviation from an additive model. Likewise, if the joint *RR* were 12, the multiplicative interaction *RR* would have been 0.4 and the additive interaction would have been 0, indicating a less than multiplicative joint effect and no departure from an additive model. These concepts have natural extensions to more than two risk factors, such as the inclusion of main effects and interactions in the widely used logistic regression model (which assumes a multiplicative model). The following chapter will describe how these parameters can be used to estimate the proportion of disease among exposed individuals that is attributable to the separate or joint action of each factor or other unknown factors, and the relevance and limitations of such estimates for attributing causation in individuals.

The previous example presumes that there is no causal connection between the military exposure and smoking—that prior smoking did not cause the individual's exposure in the military or vice versa. If this assumption did not hold, a very different analysis would be required. For example, suppose a nonsmoking recruit received a serious battle wound leading to amputation, which subsequently caused him or her to take up smoking for self-medication, and he or she ultimately developed lung cancer. In this case, one might wish to estimate the direct effect of battle trauma on lung cancer risk and the indirect effect mediated through smoking. However, as a policy matter, one might conclude that both routes were ultimately the consequence of battle trauma and should not be distinguished for the purpose of deciding on compensation. In other words, an individual's smoking history would be irrelevant.

UNCERTAINTY

The science of estimating the causal influence of an exposure on disease, especially in cases where controlled experiments are not feasible, is fraught with uncertainty. Dealing with uncertainty in a principled way is one of the goals of statistics, however, and it need not stop us from rational analysis. In this section we provide a framework for dealing with the uncertainty inherent in assessing *population causal claims*.

There are three levels of uncertainty in making a case for a service connection:

1. Uncertainty as to the correct causal model
2. Uncertainty as to the statistical (parameter) estimates within each model
3. Uncertainty about the specifics of a given individual within a group

The uncertainty about the correct causal model involves uncertainty about whether exposure in fact causes disease at all, about the set of confounders that are associated with exposure and cause disease, about whether there is reverse causation, about what are the correct parametric forms of the relations of the exposure and confounders with outcome, and about whether there are other forms of bias affecting the evidence. One currently used method for making this uncertainty clear is to draw a set of causal graphs, each of which represents a particular causal hypothesis, and then consider evidence insofar as it favors one or more of these hypotheses and related graphs over the others. We explain this approach in more detail in Appendix J.

Uncertainty about the model is not just limited to the qualitative causal structure; however, it also involves uncertainty about the parametric form of the model specified, the variables included, whether or not measurement error is modeled, and so on. When mechanistic knowledge exists, this sort of uncertainty is mitigated. Nevertheless, model uncertainty is perhaps the most important level of uncertainty.

By comparison, uncertainty about the parameter estimates (regression coefficients) for a *given* model is a well-studied problem. When the newspaper reports that a political poll is accurate to "within 3 percentage points," it is attempting to report the uncertainty about the estimates reported by the poll. When a regression analysis produces an OR with a confidence interval (or a *P* value for the null hypothesis that the adjusted association is 0), it is quantifying the uncertainty caused by the random variation that we can expect from one sample to another. The important point is that these reports of uncertainty are *conditional on the model being a sufficiently adequate approximation to reality so that the inferences drawn are valid*. The overall scientific inference involves uncertainty about the model *and* uncertainty about the parameter estimates given each model. It would be misleading to neglect the uncertainty in the model, and act as if the *P* values and confidence intervals delimit and make precise our overall scientific uncertainty.

Beyond model uncertainty and parameter estimate uncertainty, we still face uncertainty in applying causal models to individuals. Typically, causal models will provide a prediction about the chances or severity of a disease, given a particular level of exposure and particular levels of the covariates, such as age or social class. For a given individual, we might be highly uncertain about the level and duration of exposure, as well as uncertain about the levels of covariates. This level of uncertainty is also important to presumptive service-connection claims, as will be discussed in the following chapter.

There are two systematic, quantitative approaches for including uncertainty about the model into an assessment of overall uncertainty about a

causal inference. The first is sensitivity analysis, and the second is model averaging. In sensitivity analysis we attempt to quantify the sensitivity of the parameter estimate to assumptions about the model. In model averaging, we attempt to provide an overall uncertainty to our estimate by calculating the estimate of a common parameter or target and its uncertainty for each model we consider plausible, and then by weighting the estimates and the uncertainties by the likelihood of each model. It is essential that the target have the same interpretation in each model, or the combination of the estimates has no meaning.

Sensitivity Analysis

In general, sensitivity analysis is the attempt to systematically explore the sensitivity of a particular parameter estimate, such as the size of the causal effect of exposure on disease, to any assumption made in the model that itself can be parameterized. For example, in estimating the effect of cumulative exposure to lead on a child's IQ, cumulative lead exposure for a child can be estimated by measuring the concentration of lead in the child's shed baby teeth. Although this is an improvement over blood lead, it still involves error. The estimate of the effect of lead on IQ is sensitive to the amount of measurement error for lead, and the measurement error can be parameterized by the proportion of the variance of the measure thought to come from actual lead as opposed to error. A sensitivity analysis can then be performed by estimating the effect under a progression of levels of this proportion. This provides an assessment of how sensitive the causal estimate is to various possibilities of measurement error, and provides a more specific statement of what we must assume about measurement error in order to reach the causal conclusion.

Paul Rosenbaum (2002), along with Charles Manski (1995), has developed a formal technique for dealing with unmeasured confounding or bias called *sensitivity analysis*. The essential idea is to make reasonable guesses as to the range of distortion introduced by possible bias, or the extent of the associations underlying the possible confounding, and then to use those ranges to estimate the extent to which the outcome is changed under those assumptions. If the outcome turns out to be highly sensitive to such perturbations, one cannot rule out the possibility that the observed association is an artifact. Greenland (1996) has advocated a more quantitative approach to directly modeling multiple sources of bias.

Model Averaging

Given the inevitable uncertainty about the true model form, one might ask how one should estimate the RR (or any other epidemiologic effect

parameter derived from it) and an "honest" confidence interval for it that allows for this possibility of model specification error. There is an extensive statistical literature on this question (see, for example, Leamer, 1978, for a review), but in practice the problem is frequently ignored. Frequently, an investigator conducts a number of different analyses and ends up reporting only a single best-fitting model, or the one model in which he or she holds the strongest belief, and reports confidence limits on the parameters of that model, as if it were the "true" model. Sometimes, an investigator may acknowledge this uncertainty about model form by reporting a range of alternative models in the spirit of sensitivity analyses. This can leave the reader uncertain as to which specific set of estimates to use, particularly if several models fit the data more or less equally well, yet yield different estimates and confidence intervals. There are, however, a number of formal approaches to this problem from both a frequentist and a Bayesian perspective.

Here we summarize briefly just one of them, known as Bayesian model averaging (Hoeting et al., 1999). Suppose we have a parameter of interest β (measuring the effect of interest) and a range of alternative models $m = 1, \ldots M$, yielding estimates $\hat{\beta}_m$ and variances estimates $V_m = \mathrm{var}\left(\hat{\beta}\middle| M = m\right)$ of this same parameter under different models (for this purpose, we must assume that the parameter β has the same interpretation under each of the different models, i.e., the effect of exposure, conditional on different choices of adjustment variables). Let $\pi_m = \Pr\left(M = m\middle| D\right)$ denote the posterior probability of model m, conditional on the observed data D. Then a natural estimator of β that takes account of model uncertainty might be a simple weighted average of the model-specific estimators, $\bar{\beta} = \sum_m \hat{\beta}_m \pi_m$ with variance $\mathrm{var}\left(\bar{\beta}\right) = \sum_m \left(V_m + \left(\beta_m - \bar{\beta}\right)^2\right) \pi_m$. This formal approach has seldom been applied in practice, although there are some examples in the epidemiologic literature. It also has some potential for misuse, as when many highly correlated variables are considered in the same model. In model averaging, we attempt to deal with model uncertainty by calculating the estimate of a common parameter or target and its uncertainty for each model we consider plausible, and then by weighting the estimates and the uncertainties by the likelihood of each model.

SUMMARY

Presumptive service-connection decisions depend on population-level causal questions, such as "Were some cases of type 2 diabetes among Vietnam veterans caused by exposure to dioxin in Agent Orange during military service?" Assessing such claims scientifically involves review of statistical

evidence from epidemiologic studies, evidence from experiments in other animals, and mechanistic evidence from basic biologic science.

Because a statistical association between exposure and disease does not prove causation, plausible alternative hypotheses must be eliminated by careful statistical adjustment and/or consideration of all relevant scientific knowledge. Epidemiologic studies that show an association after such adjustment, for example through multiple regression or instrumental variable estimation, and that are reasonably free of bias and further confounding, provide evidence but not proof of causation. Mechanistic knowledge about how particular agents might produce adverse health effects provides further evidence. For example, ionizing radiation is known to cause mutations in DNA that can result in cancer. Animal studies may provide further evidence by showing that an agent may induce in several different species the same effect observed in human studies, and by a mechanism that is conserved across species with key features of the mechanism observed.

Uncertainty about a causal claim can arise because of uncertainty about which among a set of plausible models is correct, or because of uncertainty about study design and execution, or it can arise because of uncertainty caused by simple sampling variability, or it can arise because of uncertainty in the basic science required to analyze other evidence. The overall uncertainty about the claim in question is some combination of all of these uncertainties.

Additional information on causation and statistical causal methods can be found in Appendix J.

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8

Synthesizing the Evidence for Causation

In Chapter 7 we discussed the challenges of inferring a causal relationship between an exposure and a health outcome, and the range of evidence typically considered in making such inferences. In this chapter we discuss the problem of combining potentially diverse types of evidence in making a single, overall judgment about whether an exposure causes a health outcome. We begin by discussing the problem of integrating the evidence from multiple epidemiologic studies. We then describe a framework for combining epidemiologic and other evidence into a single *quantitative* judgment about the strength of causation. Next we discuss *qualitative* frameworks that have been used by expert committees for categorizing the overall strength of evidence for or against a causal claim. And lastly we propose a qualitative framework for causal reference to be used in the presumptive disability decision-making process.

We include this material because the scientific group that we propose in our new approach will review evidence on the health of veterans and will have the task of integrating an accumulating stream of results and interpreting new findings in the context set by previous findings and prior reviews. The successive Institute of Medicine (IOM) Agent Orange committees are illustrative. While the methods are presented in a theoretical fashion, they would be key components of the approach recommended by this Committee and, in reality, they are already inherent to the approaches used by the IOM committees.

META-ANALYSIS: COMBINING EVIDENCE FROM MULTIPLE STUDIES

Scientific evidence relevant to causal relationships between exposure and disease comes from different types of investigation, including randomized clinical trials (RCTs) on humans, epidemiologic studies, animal experiments, and cell studies, and also from fundamental biological knowledge. We use the term *human studies* to refer to RCTs or observational studies involving people. Although an evidence-based approach must combine all forms of scientific evidence, in this section we limit our discussion to the problem of synthesizing the information from multiple human studies.

The idea of pooling information from multiple studies has a long tradition in statistics that goes back at least to Karl Pearson in 1904. A meta-analysis involves gathering all studies with evidence related to a particular question, and statistically combining the results of these studies. In many contexts, health researchers have mathematically combined the results from multiple, yet comparable RCTs to derive a summary estimate of the effect of some substance on health; the estimate appropriately combines the results of all the individual studies. Such summaries are often carried out, for example, to determine if there is a benefit of a drug or perhaps an excess occurrence of an unwanted side effect. One approach for combining evidence, random effects meta-analysis, allows for heterogeneity between studies; with this technique, a meta-analysis is not strictly limited to studies involving similar populations.

In observational studies, there may be more variability in findings from study to study because study variables are not under the investigator's control. The populations studied may vary considerably in their characteristics, and the variables measured as covariates for statistical adjustment may also differ. Nevertheless, meta-analysis is applied to observational study results as well as to RCT data. Meta-regression (Greenland and O'Rourke, 2001) allows pooling of data across observational studies with some unexplained heterogeneity, and recent work by E. Kaizar (2005) improves on meta-regression for situations with data available from both RCTs and observational studies.

Although the development of meta-analytic methods has generated extensive methodological discussion (see, for example, Berlin and Antman, 1994; Berlin and Chalmers, 1988; Dickersin and Berlin, 1992; Greenland, 1994a,b; Stram, 1996; Stroup et al., 2000), it is a technique that can be quite useful when there are multiple studies on the same question. For example, for each of a number of different cancers, the 2006 IOM Committee on Asbestos and Selected Cancers (IOM, 2006a) did a quantitative meta-analysis on studies that combined the effect of asbestos exposure on risk based on multiple studies for each of a set of cancers. The report pre-

sented the results of individual studies as well as an overall estimate that came from the combination of the estimates from the individual studies.

THE BAYESIAN APPROACH

No matter how sophisticated the meta-analytic technique, it is still limited to combining statistical evidence from different studies into a single statistical estimate of the effect size. As we discussed in Chapter 7, the scientific evidence germane to causal claims also includes mechanistic knowledge, findings of animal or cell and molecular studies, and other knowledge relevant to biological plausibility. A technique for combining all the available evidence into a single judgment needs to accommodate these other types of information. One approach for combining all the evidence available into a single quantitative judgment uses a *Bayesian* approach.

Bayesian methodology conceives of probability as degrees of belief. Any proposition can be given a degree of belief. For example, one person might have a personal degree of belief of 0.30 (30 percent) in the proposition that garlic prevents colds, while another might give the proposition 0.80. The Bayesian approach provides a rule for updating the existing degree of belief in response to additional evidence (Bayes' rule, see below). Provided that no experts are inflexible in their belief,[1] a group of experts who update their beliefs by Bayes' rule will almost certainly converge to the same degree of belief after considering enough of the same relevant evidence.[2] Thus, a group of scientists considering the overall evidence for a causal claim such as "formaldehyde causes leukemia" might begin with a *prior* degree of belief about the claim and then update their belief in the light of accumulating evidence, regardless of the type of evidence. In more detail, if we consider each separate causal model relating formaldehyde (exposure) and leukemia as a separate hypothesis, H_i, then we can begin by using background knowledge or the results of previous studies, to assign a *prior probability* to each such hypothesis.

The Bayesian approach then seeks to compute the *posterior probability* $\Pr(H_i \mid D)$, namely the probability of (i.e., degree of belief in) hypothesis H_i given the new observed data D. The computation of these posterior probabilities is given by the famous rule first described by the Rev. Thomas Bayes, known as Bayes' theorem or rule, which in simple form is

$$P\left(H_i \middle| D\right) = \frac{P\left(H_i\right) P\left(D \middle| H_i\right)}{P\left(D\right)}.$$

[1]That is, assigns degree of belief 0 to what turns out to be the "true" proposition.
[2]And a raft of other assumptions—see Howson and Urbach, 1989.

Loosely translated, this formula reflects the prior probability for the hypothesis $P(H_i)$, the *likelihood*, meaning the probability of the data D given the hypothesis H_i is true, and $P(D)$, the probability of the data before any hypothesis.

The Bayesian framework provides a useful perspective on how weak additional evidence may have little impact on a strong prior probability or strong additional evidence may have substantial impact on a weak prior probability. For example, assume that we have very strong prior radiobiological and epidemiologic evidence that ionizing radiation can cause cancer, but a study of veterans who participated in nuclear weapons testing maneuvers fails to provide strong evidence of an association. In this example, assume that the data from the study do not lead to rejection of the null hypothesis of no association in a study of veterans exposed to radiation. This null finding might arise because the available sample size or length of follow-up was too small to yield an adequate number of cancers in the study group or because of inherent biases in the study design, such as inaccuracy of the available radiation dose information. If the veterans' data are highly uncertain, then a null result might change the prior estimate of population radiation risk (e.g., the synthesis of the world literature by expert committees such as the National Research Council's [NRC] Biological Effects of Ionizing Radiation [BEIR] committee) downward for this group, but by only a very modest amount. The posterior probability would still strongly favor a presumption (Figure 8-1a).

On the other hand, assume that there was very little prior knowledge about the effect of dioxins on cancer risk and a large, well-designed study of Vietnam veterans yielded a large and highly significant positive relative risk for non-Hodgkin's lymphoma (NHL) (Figure 8-1b). In this case the absence of prior knowledge would have little influence on the degree of judgment given to the estimates from the veterans' study.

A further example is provided by the National Research Council's Biological Effects of Ionizing Radiation (BEIR) IV Committee (NAS, 1988), which addressed the cancer risk of plutonium in humans. The available human data were very limited: no bone cancers were observed among 18 patients injected with plutonium for experimental purposes or among a small number of others occupationally exposed in the Manhattan Project. The BEIR IV committee adopted an empirical Bayes approach that assumed that the ratio of carcinogenic potencies of plutonium to various other radionuclides would be roughly constant across species. As there are substantially more human data about the carcinogenicity of various isotopes of radium and extensive animal data about plutonium, radium, and other radionuclides, it was possible to estimate the risk of plutonium in humans from a combined analysis that incorporated animal and human data. The committee carried out an uncertainty analysis that incorporated the variability in the ratios

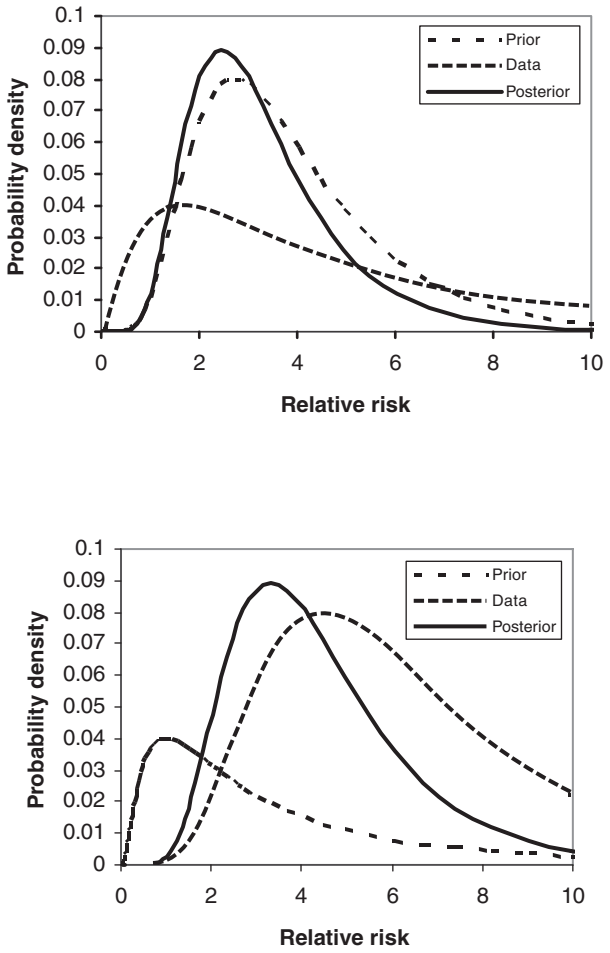

FIGURE 8-1 Hypothetical illustrations.
NOTE: Hypothetical illustrations of the combination of prior knowledge or judgment with study data to yield posterior estimates of a causal parameter, here the relative risk: (a) strong prior probability for a nonnull effect combined with weak data showing little or no effect in the study sample, and (b) weak prior probability combined with strong data showing a major effect.

of the relative carcinogenicities of the radionuclides across species. In this analysis, the limited human data for plutonium shifted the posterior probability distribution of the carcinogenicity estimates only slightly downward relative to the prediction resulting from the animal data.

The Bayesian approach can also focus scientific attention as new evidence becomes available. For example, as discussed in Chapter 7, there are many ways to generate an observed association between an exposure and a health outcome. The association might be the result of the exposure causing the health outcome, confounding, other forms of bias or of chance. In carrying out an observational study, epidemiologists try to measure and adjust for confounders and eliminate bias with good study design and appropriate data analysis. Scientific opinion about how much of the adjusted association might still be from unmeasured confounding or bias is useful in judging the degree of confidence about the estimate of an association.

To illustrate, consider the diagram in Figure 8-2, which graphically depicts the epidemiologists' concerns. Assuming a simple linear model, for illustration, the parameter β represents the *causal association*, that is, the amount of observed association between exposure and health due to the causal influence of exposure on health. The parameter α represents the amount of association from confounding that we *can* statistically adjust for,

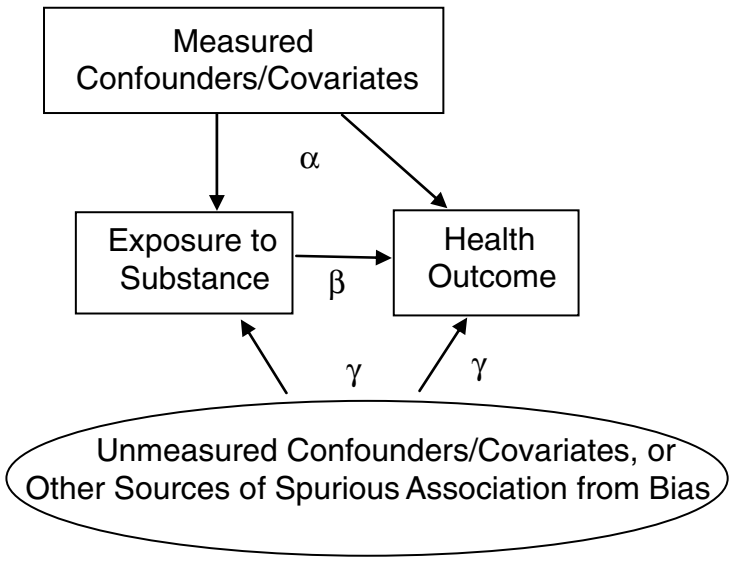

FIGURE 8-2 Focusing on unmeasured confounders/covariates, or other sources of spurious association from bias.

given the right model, and the parameter γ represents the amount of spurious association that we *cannot* statistically adjust for. Because the estimate of the causal association β will be biased in proportion to the size of γ, scientific attention should be focused on γ. In a Bayesian approach, we can encode scientific opinion about the size of γ into a prior probability, and then compute a posterior probability over β that appropriately takes into account uncertainty over γ.

In principle, then, the Bayesian approach provides an entirely quantitative framework for combining theoretical beliefs and evidence from previous studies along with the data at hand to update estimates of model parameters or of the probability that a particular hypothesis is true. In principle, each researcher undertaking a new study would apply the procedure to interpret the new evidence from the study in the context of already existing evidence, arriving at a posterior probability that is a methodologically appropriate combination of prior beliefs and accumulated evidence.

In practice, however, the Bayesian approach is *far* from a panacea for the complex task of combining diverse types of evidence. In typical scientific contexts, it may be difficult to move from fairly inchoate and diverse sorts of background knowledge to a communal "prior." By their nature, these prior odds are a matter of judgment, about which consensus amongst scientists can be difficult to obtain.

Further, although "updating" a posterior probability from certain kinds of evidence is reasonably straightforward, updating from other kinds of evidence is not. For example, consider estimating the relative risk of leukemia as a function of benzene exposure. After specifying a prior probability over this function, updating from a new sample of 400 veterans who were exposed to twice the usual level of benzene and who have a relative risk of 1.8 for leukemia is fairly straightforward mathematically. How are we to update based on experimental evidence showing that rats exposed to 50 times the background level of benzene develop leukemia at 3 times the rate of those exposed to background levels? What is the likelihood of this evidence, assuming any particular hypothesis about humans? Here we move beyond mathematics and statistics and into opinion about the comparability of leukemia and its causation in rats and humans.

QUALITATIVE FRAMEWORKS USED BY EXPERT COMMITTEES

Faced with diverse mechanistic and biological evidence that cannot be incorporated into a single statistical meta-analysis, and with opinions and judgments too varied and vague to employ a formal Bayesian approach, expert committees have resorted to qualitative categorizations of the strength of evidence for causation. There is a lengthy history of doing so, dating back to the 1950s as evidence began to develop on disease causa-

tion by radiation and tobacco smoking (Bayne-Jones et al., 1964). Judgments as to the level of evidence for causation can have substantial impact and often have regulatory implications. For example, the International Agency for Research on Cancer (IARC) (2006b), the U.S. Environmental Protection Agency (EPA) (2005), and the National Toxicology Program (NTP) (NTP, 2005) have developed systems for classifying the level of evidence in support of a causal relationship between chemicals and cancer. Similar classification systems have been developed for causal relationships for other health-specific effects such as reproductive outcomes (see e.g., NTP CERHR, 2003, 2005; Shelby, 2005), or between agents and health outcomes in general (IOM/NRC, 2005), or between smoking and disease (DHHS/CDC, 2004).

Each of these classification systems relies on evidence from a variety of research sources: epidemiologic, toxicological, and biological. The approach of combining diverse sources into an overall judgment on the strength of evidence for general causation, at least in a public health context, can be traced back to the 1964 *Report of the Advisory Committee to the Surgeon General on Smoking and Health* (Bayne-Jones et al., 1964), as well as other early summary reports on smoking and health. In the introductory chapters to the 1964 report, the committee described the different sorts of evidence to be considered. They specifically listed animal experiments, clinical and autopsy studies, and population studies, but were expansive in the evidence considered. They described the importance of expert evaluations of the quality of published reports, wrote two pages on their working definition of causation, and codified a subset of Sir Bradford Hill's criteria for establishing causation in epidemiology and public health contexts: consistency of the association, strength of the association, specificity of the association, temporality of the association, and the coherence of the association. The report that followed was an extended attempt to review all the evidence then available and synthesize it into an overall judgment: smoking causes lung cancer, bronchitis, emphysema, and is a "health hazard of sufficient importance in the United States to warrant appropriate remedial action" (Bayne-Jones et al., 1964, p. 33).

Although the Surgeon General's 1964 report did not explicitly categorize the *level* of evidential support for any of its conclusions, the 2004 Surgeon General's report does, as do recent reports from IARC (2006b) and IOM (2006a). A variety of categorizations exist. For example, the 2004 Surgeon General's report on smoking (DHHS/CDC, 2004), as well as the 2006 IOM Committee on Asbestos (IOM, 2006a, p. 20), employed a four-level categorization of the strength of evidence of causation (the latter was based on the 2004 Surgeon General's Report on Smoking [DHHS/CDC, 2004]):

1. Sufficient to infer a causal relationship
2. Suggestive but not sufficient to infer a causal relationship
3. Inadequate to infer the presence or absence of a causal relationship
4. Suggestive of no causal relationship

IARC forms expert committees and instructs them to first categorize the level of evidence within three subcategories—human, animal, and mechanistic—and then to synthesize the subcategories of evidence into an overall evaluation on a five-category scale ranging from carcinogenic to probably not carcinogenic. Figure 8-3 depicts the IARC evaluation scheme.

Several groups, including some IOM committees on Agent Orange (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) and other veterans' health issues, have based their approaches on the IARC (2006b) system for classifying the evidence in the *subcategory* pertaining only to human evidence. Within this subcategory, IARC systematically reviews available epidemiologic studies, considering study quality, relevance, and strength of findings. It then classifies the overall epidemiologic evidence as *sufficient evidence* if there is a finding that "a positive relationship has been observed between the exposure and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence" (IARC, 2006b, p. 19). For *limited evidence*, a "positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence" (IARC, 2006b, pp. 19-20). With *inadequate evidence*, either there are no epidemiologic data or study quality, or power, or consistency across studies precludes a conclusion regarding causal association.

The IOM committees assessing the impact of Agent Orange have published biennial reports since 1994. Table 8-1 contains the four-level categorization for the strength of epidemiologic evidence used in the 1994 report (IOM, 1994), which is quite similar to IARC's subcategory scheme for human evidence (IARC, 2006b). Subsequent reports have used a similar classification scheme.

IOM committees (IOM, 2000, 2003a, 2004, 2005a, 2006b, 2007) examining Gulf War and health have added a causal category to those used by the IOM Agent Orange committees (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b). Table 8-2 shows the classification scheme from Volume 1 of the Gulf War and Health series (IOM, 2000). The additional category makes causation explicit and includes evidence beyond that found in just epidemiologic studies.

The IOM Agent Orange categorization (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) relies less on mechanistic and animal evidence and more

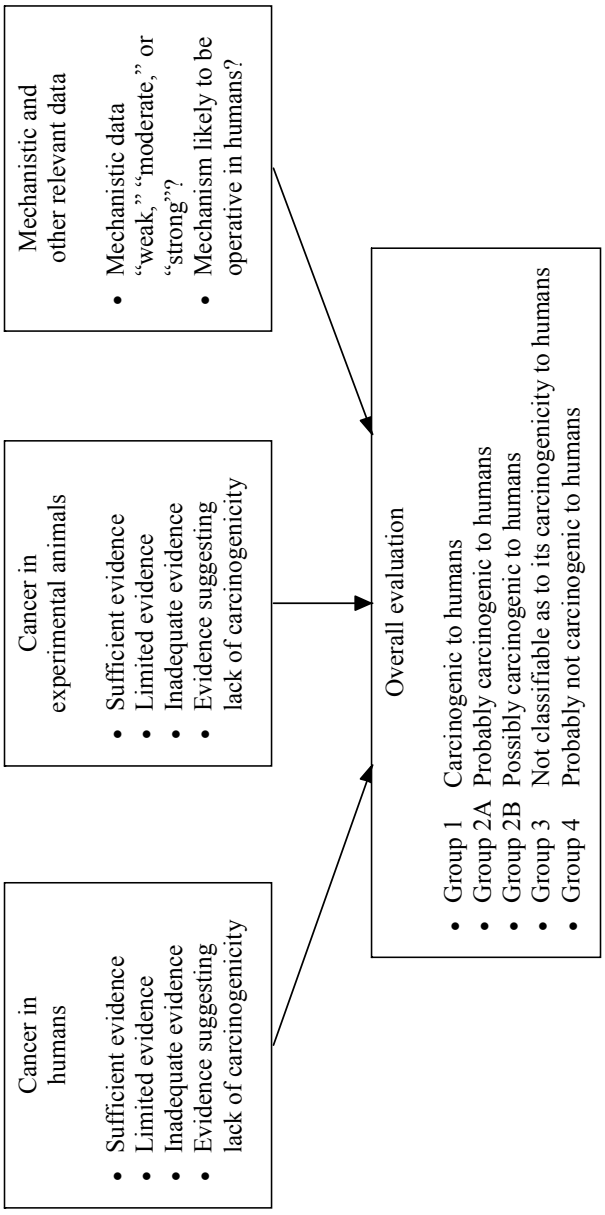

FIGURE 8-3 IARC evaluation scheme.
SOURCE: Adapted from Cogliano, 2006.

TABLE 8-1 IOM Categorization from the Executive Summary of *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*

Sufficient Evidence of an Association	Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence of an association.
Limited/Suggestive Evidence of an Association	Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent.
Inadequate/Insufficient Evidence to Determine Whether an Association Exists	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency.
Limited/Suggestive Evidence of No Association	Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. *In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.*

SOURCE: IOM, 1994.

on epidemiologic data than do the IARC, NTP, or EPA models. As there may be many cases relevant to presumptive service connection in which the epidemiologic evidence on veterans specifically is extremely thin or even non-existent, giving animal and mechanistic evidence a more prominent and systematic role in the overall evaluation scheme is warranted. The causal category added by the Gulf War committees is a step in this direction. Previous IOM Agent Orange committees also reviewed and reported on toxicological and mechanistic information, but according to their interpretation of their charge, did not figure this information into the conclusions about the strength of evidence for association and causation.

TABLE 8-2 IOM Categorization from the Executive Summary of *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines*

Sufficient Evidence of a Causal Relationship	Evidence is sufficient to conclude that a causal relationship exists between the exposure to a specific agent and a health outcome in humans. The evidence fulfills the criteria for sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose-response relationship, consistency of association, temporal relationship, specificity of association, and biological plausibility.
Sufficient Evidence of an Association	Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between an exposure to a specific agent and a health outcome in human studies in which chance, bias, and confounding could be ruled out with reasonable confidence.
Limited/Suggestive Evidence of an Association	Evidence is suggestive of an association between exposure to a specific agent and a health outcome in humans, but is limited because chance, bias, and confounding could not be ruled out with confidence.
Inadequate/Insufficient Evidence to Determine Whether an Association Does or Does Not Exist	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between an exposure to a specific agent and a health outcome in humans.
Limited/Suggestive Evidence of No Association	There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, that are mutually consistent in not showing a positive association between exposure to a specific agent and a health outcome at any level of exposure. A conclusion of no association is inevitably limited to the conditions, levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

SOURCE: IOM, 2000.

A PROPOSED QUALITATIVE FRAMEWORK FOR EVALUATING CAUSAL CLAIMS

Incorporating the Full Range of Evidence

The new process recommended by this Committee involves a categorization of the strength of evidence in support of a causal claim that incorporates the full weight of all evidence, including expert opinion, findings from

epidemiologic and animal studies, and mechanistic knowledge. Reliance on the broad range of pertinent scientific data is also in keeping with the original congressional language that specifies consideration by NAS of the biological plausibility of any association. Before describing our proposed classification scheme, we briefly consider the consequences of extending the range of evidence considered. One issue is whether a seemingly more rigorous bar of evidence would reduce the likelihood of reaching a classification level at which compensation is made.

We approach this issue through case studies. Incorporating information derived from mechanistic studies and animal toxicology can lead to an upgrading or downgrading of a classification based on the weight of evidence classification. Some examples are described below.

Particulate Air Matter

Deployed personnel in the first Gulf conflict were exposed to airborne particles from the oil fires in Kuwait, exhaust from military vehicles and other combustion sources, and dust stirred by troop movements. The health effects of airborne particles are of general concern and the scientific evidence is subject to periodic review in the setting of the National Ambient Air Quality Standard (NAAQS) by the U.S. Environmental Protection Agency (SOURCE: http://epa.gov/pm/naaqsrev2006.html). The standard is evidence-based and the process of setting a new NAAQS involves a comprehensive review of all relevant scientific evidence, including epidemiologic and toxicological data as well as information on exposure patterns. For the last two reviews of the NAAQS, 1996 and 2006, the epidemiological evidence has been extensive, showing significant associations of airborne particles with increased risk for premature mortality and morbidity. The effects are relatively small, however, and biological plausibility has been a major consideration in evaluating the evidence and determining if the associations can be judged as causal. Information relevant to the plausibility of the associations comes from studies of the chemical and physical properties of particles and from toxicological studies that have addressed responses to particles in in vitro and in vivo models. Using a "weight of evidence" approach, the Environmental Protection Agency has judged the associations of airborne particles with adverse effects to be causal (SOURCE: http://epa.gov/pm/naaqsrev2006.html).

2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)

TCDD, a potent dioxin, was listed in 1997 as a Group 1 carcinogen by IARC based on limited evidence in humans, sufficient evidence in experimental animals, and abundant mechanistic information including data

demonstrating that TCDD acts through the aryl hydrocarbon receptor (AhR), which is present in both humans and animals (IARC, 1997).

Formaldehyde

IARC has recently concluded that formaldehyde should be added to that group of agents that are carcinogenic to humans (Group 1 carcinogen) (IARC, 2004, p. 1). This upgrade was based upon new epidemiologic evidence of an association with nasopharyngeal cancer. "[T]here is now sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans, a rare cancer in developed countries" (IARC, 2004, p. 1). Previous laboratory, animal, and mechanistic evidence supported this association. The IARC found "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde," falling "slightly short of being fully persuasive because" of limitations in the cohort and conflict with nonpositive findings in another cohort (IARC, 2006a, p. 5). IARC noted findings of lymphomas and leukemias in one study in male rats, and several possible mechanisms for the induction of human leukemia, such as clastogenic damage to circulatory stem cells. However IARC also noted the lack of good rodent models that simulate the occurrence of acute myeloid leukemia in humans, and did not identify a mechanism for its induction in humans (IARC, 2006a).

Saccharin

Saccharin was originally classified as "reasonably anticipated to be a human carcinogen" by NTP (NIH, 2000, p. 1) and "possibly carcinogenic to humans" by IARC (IARC, 1987, p. 334) based on data clearly showing bladder cancer in rats. Although there was some limited epidemiologic evidence associating bladder cancer with saccharin sweeteners, the epidemiologic evidence was classified by IARC as inadequate. Subsequent mechanistic studies attributed the animal cancer findings as being due to a mechanism that would only occur at high doses in rats. "Saccharin produces urothelial bladder tumours in rats by a non-DNA-reactive mechanism that involves the formation of a urinary calcium phosphate-containing precipitate, cytotoxicity and enhanced cell proliferation. This mechanism is not relevant to humans because of critical interspecies differences in urine composition" (IARC, 1999, p. 50). Saccharin has since been delisted as a reasonably anticipated carcinogen by NTP and deemed "not classifiable as to its carcinogenicity to humans" by IARC (IARC, 1999, p. 50; NIH, 2000).

These case studies illustrate the potential contributions of mechanistic information as evidence relevant to causation is evaluated. A certain under-

standing of mechanism of action may have substantial impact in considering the overall weight of evidence.

Committee Recommended Categories for the Level of Evidence for Causation

In light of the categorizations used by other health organizations and agencies as well as considering the particular challenges of the presumptive disability decision-making process, we propose a four-level categorization of the strength of the *overall evidence* for or against a *causal relationship* from exposure to disease:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

We use the term "equipoise" to refer to the point at which the evidence is in balance between favoring and not favoring causation. The term "equipoise" is widely used in the biomedical literature, is a concept familiar to those concerned with evidence-based decision making, and is used in VA processes for rating purposes as well as being a familiar term in the veterans' community.

Below we elaborate on the four-level categorization that the Committee recommends.

Sufficient

If the overall evidence for a causal relationship is categorized as Sufficient, then it should be scientifically compelling. It might include

- replicated and consistent evidence of a causal association: that is, evidence of an association from several high-quality epidemiologic studies that cannot be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding), or
- evidence of causation from animal studies and mechanistic knowledge, or
- compelling evidence from animal studies and strong mechanistic

evidence from studies in exposed humans, consistent with (i.e., not contradicted by) the epidemiologic evidence.

Using the Bayesian framework to illustrate the evidential support and the resulting state of communal scientific opinion needed for reaching the Sufficient category (and the lower categories that follow), consider again the causal diagram in Figure 8-2. In this model, used to help clarify matters conceptually, the observed association between exposure and health is the result of (1) measured confounding, parameterized by α; (2) the causal relation, parameterized by β; and (3) other, unmeasured sources such as bias or unmeasured confounding, parameterized by γ. The belief of interest, after all the evidence has been weighed, is in the size of the causal parameter β. Thus, for decision making, what matters is how strongly the evidence supports the proposition that β is above 0. As it is extremely unlikely that the types of exposures considered for presumptions reduce the risk of developing disease, we exclude values of β below 0. If we consider the evidence as supporting degrees of belief about the size of β, and we have a posterior distribution over the possible size of β, then a posterior like Figure 8-4 illustrates a belief state that might result when the evidence for causation is considered Sufficient.

As the "mass" over a positive effect (the area under the curve to the right of the zero) vastly "outweighs" the small mass over no effect (zero), the evidence is considered sufficient to conclude that the association is causal. Put another way, even though the scientific community might be uncertain as to the size of β, after weighing all the evidence, it is highly confident that the probability that β is greater than zero is substantial; that is, that exposure causes disease.

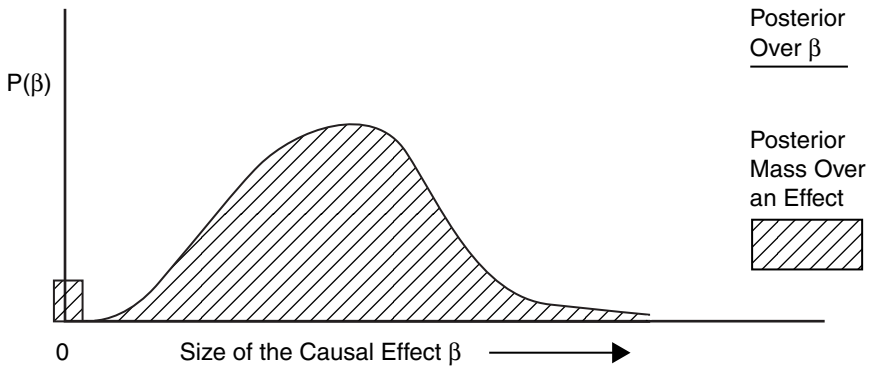

FIGURE 8-4 Example posterior for *Sufficient*.

Equipoise and Above

To be categorized as Equipoise and Above, the scientific community should categorize the overall evidence as making it more confident in the existence of a causal relationship than in the non-existence of a causal relationship, but not sufficient to conclude causation.

For example, if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above. Alternatively, if there is strong evidence from animal studies or mechanistic evidence, not contradicted by human or other evidence, then the overall evidence might be categorized as Equipoise and Above. Equipoise is a common term employed by VA and the courts in deciding disability claims (see Appendix D).

Again, using the Bayesian model to illustrate the idea of Equipoise and Above, Figure 8-5 shows a posterior probability distribution that is an example of belief compatible with the category Equipoise and Above.

In this figure, unlike the one for evidence classified as Sufficient, there is considerable mass over zero, which means that the scientific community has considerable uncertainty as to whether exposure causes disease at all; that is, whether β is greater than zero. At *least* half of the mass is to the right of the zero, however, so the community judges causation to be at least as likely as not, after they have seen and combined all the evidence available.

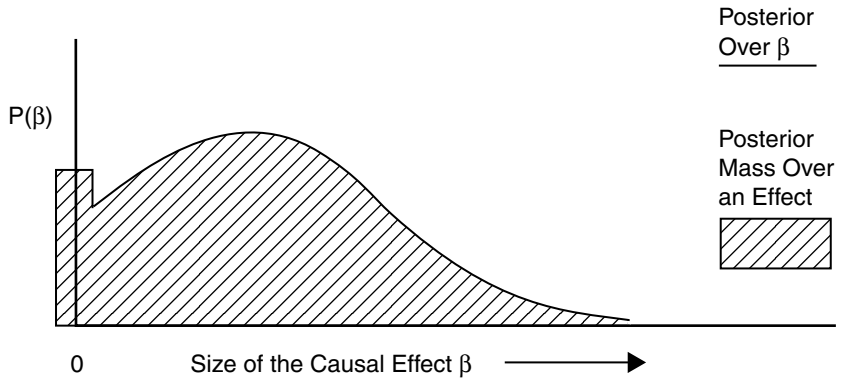

FIGURE 8-5 Example posterior for *Equipoise and Above*.

Below Equipoise

To be categorized as Below Equipoise, the overall evidence for a causal relationship should either be judged not to make causation at least as likely as not, or not sufficient to make a scientifically informed judgment.

This might occur

1. when the human evidence is consistent in showing an association, but the evidence is limited by the inability to rule out chance, bias, or confounding with confidence, and animal or mechanistic evidence is weak, or
2. when animal evidence suggests a causal relationship, but human and mechanistic evidence is weak or inconsistent, or
3. when mechanistic evidence is suggestive but animal and human evidence is weak or inconsistent, or
4. when the evidence base is very thin.

Figure 8-6 shows a posterior probability distribution that is an example of belief compatible with the category Below Equipoise.

Against

To be categorized as Against, the overall evidence should favor belief that there is no causal relationship from exposure to disease. For example, if there is human evidence from multiple studies covering the full range of exposures encountered by humans that are consistent in showing no causal association, or there is animal or mechanistic evidence supporting the lack of a causal relationship, and combining all of the evidence results

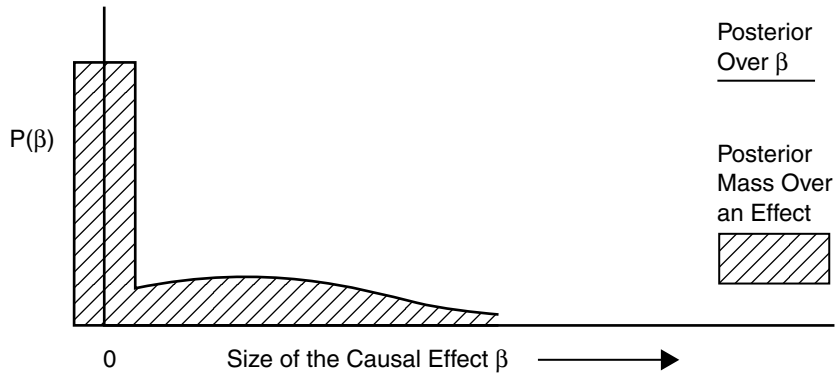

FIGURE 8-6 Example posterior for *Below Equipoise*.

in a posterior resembling Figure 8-7, then the scientific community should categorize the evidence as *Against* causation.

Comparison of the Committee's Proposed and Previous Frameworks

The Committee's proposed framework departs from that used by previous IOM committees in assessing Agent Orange (Table 8-1) in at least three respects. First, as noted, previous IOM committees evaluating Agent Orange (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) relied primarily on epidemiologic studies to classify strength of evidence for association and did not systematically incorporate evidence from animal toxicology and mechanistic studies.

Second, the Agent Orange categorization differentiated between levels of evidence for *association* instead of *causation* (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b). As we have proposed in the previous chapter, the claims at issue related to compensation of veterans are causal claims, not associational claims. Association, especially association adjusted for potential confounders, is *evidence* for the causal claim, but it is *not identical to* the causal claim. In fact, making a presumptive decision to compensate on the basis of "limited/suggestive" evidence of an association presents the possibility that there is no causal link at all, and all of those receiving compensation because of such a presumption could be false positives. A causal category was added by previous IOM committees on Gulf War and Health, but the categories below "Sufficient evidence of a causal relationship" retain the language of association (IOM 2000, 2003, 2004, 2005a, 2006b, 2007). This Committee recommends, therefore, a categorization

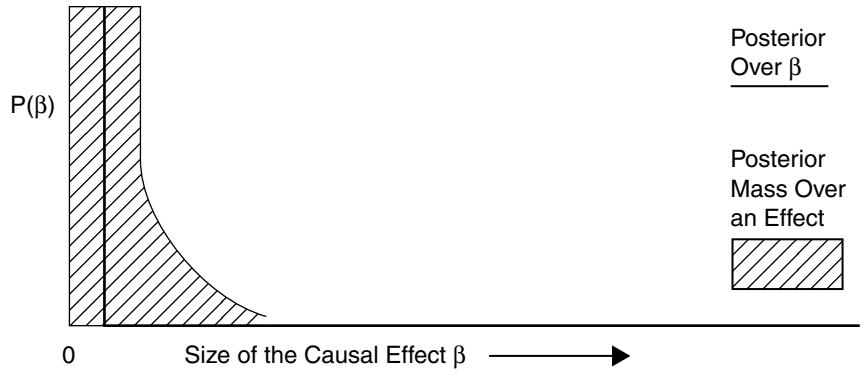

FIGURE 8-7 Example posterior for *Against*.

that makes explicit the evidential role of association, but that keeps the clear and explicit overall goal of assessing causation.

Third, we created the category of Equipoise and Above to capture the spirit of presumption: the tie goes to the veteran, and to stay true and scientifically consistent to the evidential standard suggested by Congress in the Agent Orange Act of 1991 (Public Law Number 102-4, 102d Cong., 1st Sess.), which gave the VA Secretary authority to prescribe regulations providing for a presumption "[w]henever the Secretary determines, on the basis of sound medical and scientific evidence, that a positive association exists between" herbicide exposure and a disease. Section (4)(b)(3) states the following:

> An association between the occurrence of a disease in humans and exposure to an herbicide agent shall be considered to be positive for the purposes of this section if the credible evidence for the association is equal to or outweighs the credible evidence against the association.

In our categorization, Equipoise and Above represents a state in which there *is* credible evidence, and the credible evidence *for* causation is equal to or greater than the credible evidence *against* causation. We also intend this categorization to be flexible over time. We expect that, as the evidence base grows, evaluations about the state of evidence for a causal claim may be upgraded *or* downgraded over time. The descriptive categorization language used by previous IOM Agent Orange committees for "limited/suggestive" evidence of an association implies that a single high-quality epidemiologic study can in some circumstances be sufficient for the "limited/suggestive" category:

> Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. (IOM, 1994, p. 97; IOM, 1996, 1999, 2001, 2003b, 2005b)

If a scientific committee's conclusion were based on a single study and later studies were to show more definitive evidence of an association, a subsequent committee could upgrade the "limited/suggestive" classification of this association to Sufficient. On the other hand, if definitive studies were reported that supported an overall weight of the evidence of below "limited/suggestive," a subsequent committee could downgrade the classification. Under the current approach, however, it is unclear if any reclassifications of evidence may lead to a change in a presumptive decision that VA has established based upon the classification of "limited/suggestive" evidence of an association.

SUMMARY

Combining human evidence with meta-analysis is very useful when several reasonably exchangeable studies are to be combined. However, the technique cannot be used to combine the full range of evidence relevant to classifying the level of evidence for causation. A very general technique for combining diverse evidence into a single, quantitative description of belief about the causal claim at stake is the Bayesian approach, but its usefulness in a presumptive disability decision-making context may be limited. As a result, other organizations such as IARC have resorted to a qualitative categorization of the strength of evidence for causation. These agencies base the overall categorization on separate judgments about the strength of evidence from epidemiologic studies, animal studies, or other mechanistic, toxicological, or biological sources.

For the presumptive disability decision-making process, this Committee recommends categorizing the level of overall evidence for a causal relationship between exposure and health outcome in one of the following categories:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

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9

Applying Population-Based Results to Individuals: From Observational Studies to Personal Compensation

The previous chapters address problems of inferring causation from observational studies in the context set by other types of evidence. We also provide a classification scheme for the level of evidence in support of causation in general. Having determined that the level of evidence is sufficient to infer causation, two additional matters are of interest: (1) What is the burden of disease among those exposed that is caused by the exposure? and (2) What is the likelihood that the disease was caused by exposure in a particular individual? Information pertinent to the first question is relevant to forecasting the administrative and financial implications of the causal determination. Information relevant to the second question may be of value in handling individual cases.

In the present chapter we address these topics, beginning with the simplifying assumption that a causal association has been established in the population, and that we have an accurate estimate of relative risk (RR) among exposed people. We turn to an epidemiologic measure, the attributable fraction (AF), to answer these questions. This chapter also addresses the complexities of using the AF in devising compensation approaches. It provides a conceptual foundation that should prove useful in the further elaboration of the Committee's framework and its implementation.

ATTRIBUTABLE FRACTION

Definitions and Assumptions

The *attributable fraction* (AF) is used several ways in the literature (Rothman and Greenland, 1998). We use the term in a way most relevant to compensation by the Department of Veterans Affairs (VA), namely as the proportion of disease *in an exposed group* that can be attributed to the exposure. This report uses the terminology *service-attributable fraction* (SAF) when the exposed group is a military population. We begin with two simplifying assumptions: (1) exposure produces new cases of the disease that would not have occurred otherwise, and (2) the additional RR from exposure is stable over age and across subgroups within the population of exposed veterans. Later we discuss complications that might occur when these assumptions do not hold. Under these two assumptions, the AF is interpreted as the probability that among the exposed people with the disease, their disease has actually been caused by the exposure.

Crucial Properties of the AF

In applying the AF, there are two key properties. First, it is *not* a statement about whether the exposure is *able* to cause the disease. In calculating the AF, we take as given that the exposure does, in fact, cause the disease. However, even among exposed persons, the exposure does not necessarily cause *all cases of* the disease—most diseases have many possible causes. When an exposed person gets the disease, the chance that the disease is caused by the exposure is almost certainly less than one. The AF represents this probability.

The second important aspect of the AF is that it cannot specifically tell us which exposed people have their disease because of the exposure. All the AF can provide is an estimate of the average probability for all exposed persons. We can refine this estimate in various ways (e.g., by age or levels of exposure), but even with perfect information it is seldom, if ever, possible with current methods to identify which particular cases of a disease with multiple causes were caused by the exposure and which were not.

Estimating the AF

An AF is based on an estimation of RR, which is the ratio of disease risk among exposed persons compared to the risk among otherwise similar, but unexposed persons. RR is the most common expression of disease risk in epidemiologic studies. As discussed in Chapter 7, odds ratios from case-control studies approximate the RR.

The AF is calculated by the following formula:

$$AF = \frac{[Risk\ (exposed) - Risk\ (unexposed)]}{Risk\ (exposed)}$$

This may also be expressed as: $AF = (RR - 1)/RR$.

Consider the example of smoking and lung cancer. The RR for lung cancer among smokers is around 20. Applying the formula above, a RR of 20 yields an attributable risk of 95 percent, $AR = (20 - 1)/20$. In other words, 95 percent of all lung cancers among smokers can be attributed to their smoking, possibly acting in combination with other factors, while the remaining 5 percent of the lung cancers of smokers come from other causes. For another example, smoking and cardiovascular disease, the RR is close to 2. Thus, only half of the cases of cardiovascular disease among smokers, 50 percent = (2 – 1)/2, can be attributed to smoking. The lower the RR, the less likely it is that the disease in an exposed person is caused by the exposure, and the more likely that other factors are the cause.

Factors That Can Distort the AF

Broadly speaking, there are two problems that can bias an estimate of disease burden due to an exposure when using the AF. One is *portability*—that is, the degree to which the RR estimated from one population can be properly applied to another population. The second problem is error in the measurement of exposure. We consider each of these limitations below.

Problems in Portability

Chapter 7 discusses the biases and confounding that can distort estimates of RR. Even if these problems have been carefully handled in the original estimation of RR, the application of a valid RR to a new group introduces a fresh set of opportunities for distortions. This problem goes under the general rubric of portability, that is, the ability of a valid RR in one population to be applied to a new population. The portability of RRs and hence of AFs is often uncertain because of differing characteristics of the population in which the AF was estimated compared to those in which it is to be applied.

A simple example of a problem with portability is effect modification by gender. Suppose that, at a given level of exposure, the RR of disease differs by gender of the exposed person (a common observation). If the distribution of men and women in the study group is different from the exposure group to which the RR is being applied, and gender is ignored,

the resulting AF will be incorrect. This particular problem can be handled by applying gender-specific RRs to gender strata of the exposed population. However, more complicated scenarios of confounding or effect modification can be readily anticipated; methods to handle these have been proposed by Bruzzi et al. (1985) and Benichou (2001). Although such methods work in principle, they may require detailed data for subgroup-specific RRs that are difficult to obtain.

A similar problem can arise when the RR is estimated in a population with high exposure (as in an occupational setting) and then applied to a population with lower levels of exposure. The RR will tend to overestimate the AF for the lower-exposed population. With enough information from epidemiologic studies on exposure-specific risk and information on levels of exposure in the population of interest, the appropriate adjustments of the AF can be made to account for exposure.

In summary, problems of portability do not call into question the validity of the original RR, but rather its generalizability—that is, the validity of its application to a new population and the estimate of the AF. Even when the causal association is certain (as we assume here), the problems of portability raise questions about the strength of the disease risk in the population of interest—and thus the size of the AF.

Problems in Exposure Classification

The second distortion that can occur with the AF is when the RR is applied to a population in which some persons classified as exposed were not in fact exposed. (This problem is especially relevant in the context of the charge of this Committee, in that VA is frequently unable to establish actual exposure during military service, and therefore must infer it—with inevitable error.) Usually the decision is to err in the direction of assuming people are exposed when they may not be exposed.

When an "exposed" group includes some people who are not actually exposed, the AF for the whole "exposed" group would be

$$AF_{\text{“}exp\text{”}} = \frac{\left(P_{exp}\right)\times\left(RR_{exp}-1\right)}{\left[P_{exp}\times\left(RR_{exp}-1\right)\right]+1},$$

where $AF_{\text{“}exp\text{”}}$ = the AF for an "exposed" group containing some unexposed people, P_{exp} = the proportion of the supposedly "exposed" group who are truly exposed, and RR_{exp} = the RR for the truly exposed group.

Typically, we do not know what proportion of those reported as exposed were actually exposed. However, we can make reasonable assumptions and

see how much difference such errors might make. In our previous smoking example, if only half of the "exposed" group had truly been exposed, then the true AF for the "exposed" group would be 90 percent instead of 95 percent. Thus, exposure misclassification introduces a trivial difference between the true AF and the calculated AF when the RR is high.

This is not true when the RR is lower (as is often the case). Taking the example of $RR = 2$ (for smoking and cardiovascular disease), the true AF is 50 percent when every person in the "exposed" group was truly exposed, but only 33 percent, if half of the "exposed" group had actually been unexposed. Thus, when the RR is low, misclassification of exposure results in an estimated AF that is an overestimate of the true AF.

Reconsidering the Assumptions of the AF and Alternatives

A basic assumption in calculating the AF is that the RR is known. In the real world, RRs are only estimates and typically include some measure of the statistical imprecision of that estimate. The implications of such uncertainty can be explored by calculating a range of AFs under different assumptions for the RR.

What if other assumptions about the AF are untrue? For example, what if the exposure accelerates disease among persons who were going to get the disease anyway, instead of causing disease in persons who would not otherwise have gotten the disease? In this more complex scenario, the AF may not adequately capture the total burden of disease caused by the exposure. Alternatives to the AF that attempt to capture the total impact of exposure on disease include "years of life lost" (YLL) (Robins and Greenland, 1989a; Steenland and Armstrong, 2006) and "years of life lived with disability" (YLD).

Methods for the calculation of YLL, YLD, and disability-adjusted life years (DALYs) have been recently reviewed (Steenland and Armstrong, 2006). YLL is the total number of deaths caused by the disease of interest multiplied by the average number of years of survival expected beyond the age of death from that disease. YLD is the product of the number of incident cases, a disability weight, and mean duration of disease; in the absence of incidence data an estimate can be based on mortality data and case-fatality rates. The total burden of disease can be estimated as the sum of YLL and YLD and is known as disability-adjusted life years, or DALYs. YLL, YLD, and DALYs caused specifically by military service exposure can be calculated by multiplying them by the AF (Steenland and Armstrong, 2006). In the case of military service, we refer to this as the service-attributable fraction (SAF). Because the AF is a fundamental element of these alternatives to the AF, they are subject to the same caveats about portability and misclassification of exposure as the AF itself. In the section

"Promoting the Use of AFs in Determining Compensation for Veterans" we return to this discussion with regard to the AF and the SAF.

Further Refinements of the AF

Once we have estimated the *total* disease burden caused by the exposure using the AF, it may be possible to refine this estimate further by considering characteristics of persons, including features of their exposure, that make their individual risk of disease higher or lower than in the exposed population as a whole. In other words, we can move from an estimate of overall AF, applied equally to all, to estimates for subgroups or even individuals, based on additional information regarding their risk factors. This refined expression of the AF as estimated for individuals has usually been designated as the *probability of causation*, or PC, although in actuality it is simply the AF estimated for subgroups of those exposed.

PROBABILITY OF CAUSATION FOR AN INDIVIDUAL

The AF attempts to apportion the disease burden in a population between the exposure and other factors causing the disease. In contrast, the PC attempts to address the question of whether the exposure could have caused a particular disease in an individual, given that individual's particular characteristics of genetic makeup, lifestyle, and personal history—that is, the characteristics that determine individual susceptibility. For the past two decades, estimates of the PC have been available to guide the compensation of atomic veterans and others exposed to ionizing radiation (DHHS, 2002; NIH, 1985; Thomas, 2000). These estimates have been possible because of the extensive information on cancer risk in relation to radiation exposure.

PC Definition

A precise definition of PC will help illustrate the challenges in estimating it. Following the National Institutes of Health (NIH) Working Group (1985), the PC_i is the probability that individual *i*'s disease was caused by the exposure, given *i*'s unique set of characteristics (call them X_i). Symbolically, $PC_{i,}$ is defined using two terms—the probability that the individual would have developed the disease given no exposure, $\left(\bar{E}\right),\left[P\left(D,\bar{E}\middle|X_i\right)\right]$, and the probability that the individual developed the disease given the exposure, $\left[P\left(D,E\middle|X_i\right)\right]$:

$$PC_i = \frac{\left[P\left(D,E\middle|X_i\right) - P\left(D,\bar{E}\middle|X_i\right)\right]}{P\left(D,E\middle|X_i\right)}$$

PC_i = probability of causation for an individual
P = probability
D = disease
E = exposure
$\bar{E}$ = no exposure
X_i = an individual's unique set of characteristics

Notice the equation represents an allocation of the probability of disease between the exposed and unexposed. The probability that the background caused the disease in individual *i* is simply 1 – PC_i. If everyone in the population is identical in susceptibility to the disease and in the extent of exposure, and if the exposure-induced cases are completely independent of other cases (i.e., cases that were caused by something else), then the PC for every individual in the population is given by the population AF. Implications of not meeting these assumptions are discussed below in "Promoting the Use of AFs in Determining Compensation for Veterans." Still, additional information on the levels of exposure, age at exposure, time since exposure, mechanism of disease causation, and other factors can be used to define subgroups within populations, and then to estimate AFs for these subgroups. As described below, these subgroup measures provide the basis for better estimates of PCs for individuals within these classes.

Because individuals may vary in susceptibility to a particular exposure because of genetics, lifestyle, and other factors, estimates of PCs are not necessarily expected to resemble the true probability that an individual's disease was caused by the exposure. The term *assigned share* (AS) has been used in place of *PC*, especially as it pertains to issues of compensation (Lagakos and Mosteller, 1986). The NIH Ad Hoc Working Group to Develop Radioepidemiological Tables (NIH, 1985) (for use in compensating cancer victims exposed to ionizing radiation) found itself constrained by legislative mandate to use the term *probability of causation* rather than *assigned share*. Reflecting on the history of the use of the terms, a more recent National Research Council (NRC) committee decided to use the terms synonymously (NRC, 2000).

Refining Estimates by Differences in Exposure Levels

Exposures to any given chemical or other disease-causing factor would be expected to vary substantially among veterans in any theater of war or duty, with corresponding large differences in individual risk and hence PCs. Also, the pattern of exposure can be important. For the same cumulative dose, the dose rate, timing, and duration may play a significant role in determining those who get the disease and those who do not. Route and exposure pathways are also to be considered. Although obtaining accurate estimates of exposure among veterans will typically be challenging, in some cases exposures may differ by orders of magnitude, and it may be possible to develop at least crude exposure estimates.

If exposure can be quantified and the relationship between risk and exposure is understood, the AF can be expressed as a function of exposure. For example, dose-response relationships can be derived from occupational epidemiologic data for various carcinogens. As the example below shows, it can be important to stratify by the degree of exposure if this information is available, because the AF can vary substantially with exposure level.

Consider the following simple relationship between the lifetime probability of cancer *P,* or risk, and the air concentration, *D,* and the duration of exposure *t*, $P(D) = 1 - \exp(-a - bDt)$, which at *P* less than 10 percent is closely approximated by a simple linear relationship $P(D) = a + bDt$, where *a,* the intercept, is the risk in the absence of exposure, and *b,* the slope, describes the incremental increase in risk with increasing air concentration and time. Here RR is given by

$$RR = \frac{\left(a + bDt\right)}{a} = 1 + \frac{bD}{a},$$

and the AF is given by

$$AF = \frac{\left(RR - 1\right)}{RR},$$

which, substituting in the above, reduces to

$$AF = \frac{\left(\frac{bD}{a}\right)}{\left(1 + \frac{bDt}{a}\right)} = \frac{bDt}{\left(a + bDt\right)}.$$

P = lifetime probability (or risk) of cancer
D = air concentration
t = duration of exposure
a = risk in the absence of exposure
b = incremental increase in risk with increasing air concentration and time
RR = relative risk
AF = attributable fraction

Benzene provides an example of how very different AFs can result from differently exposed subgroups. We show how when exposure is taken into account PC estimates can be made for individuals with different levels of exposure. Benzene is an established cause of acute myelogenous leukemia (AML) in humans (Austin et al., 1988). Benzene exposures are ubiquitous; for example, benzene is a constituent of gasoline and also cigarette smoke. The general population in the United States is exposed to levels averaging from 1 to 5 ppb in indoor and outdoor air, and it would be anticipated that Service members would be similarly exposed. In addition, some in the service may have duties that result in exposures to considerably higher levels of benzene (e.g., those servicing airplanes or working in garage facilities). We might assume that some service jobs result in exposures as high as 10 ppm.

AML is relatively uncommon, with a lifetime risk of diagnosis (an estimate for parameter a in the equation above) of about 0.3 percent. A lifetime exposure to 1 ppm causes AML in roughly 5 percent of those so exposed, corresponding to an estimate of b in the above equation of 0.00062/ppm-years (= 0.05/ppm/78 years). Applying these parameter estimates, AFs can be derived, while acknowledging the caveats and limitations noted above, including the issue of portability since the b was estimated from occupational cohorts in China and the United States (OEHHA, 2001). Service members who contract AML after being exposed during a tour of duty of 3 years to general background levels (e.g., 5 ppb) have a 0.2 percent chance that their leukemia arose because of their military exposure (AF = [0.00062 × 0.005 × 3]/[0.003 + 0.00062 × 0.005 × 3]). Thus, any case of AML among the exposed Service members would be highly unlikely to have resulted from military exposure. The AF associated with military service lasting 30 years is higher, at 3 percent. In contrast, Service members with a 3-year tour of duty who were exposed to 10 ppm during work hours, or a daily average of approximately 5 ppm, have an

AF of 76 percent: $AF = (0.00062 \times 5 \times 3)/(0.003 + 0.00062 \times 5 \times 3)$. This simple example illustrates the importance of segregating groups in terms of the magnitude and duration of exposure when those data are available. It also illustrates the importance of identifying those most heavily exposed in determining whether disease caused by an exposure to a given factor deserves compensation.

As illustrated below, it is occasionally possible to classify or otherwise identify individuals or groups of individuals in terms of their exposure duration, age at exposure, exposure intensity, as well as other factors to derive exposure group-specific AFs and hence more refined estimates of PCs for individuals.

Refining Estimates in the Presence of Multiple Known Causes of Disease

Many illnesses considered for compensation have multiple causes. For example, lung cancer has many known causes in addition to smoking, including asbestos, arsenic, radiation, and environmental tobacco smoke (NCI, 2006). Some lung cancers occur in individuals without significant exposures to any known cause. The proportion of disease that is attributable to military service exposure can be estimated when there are valid RR estimates for (1) the military service-related exposure in the absence of the other known causes (RR_E), (2) other known causes that individuals in the group were subjected to (such as smoking—RR_S), and (3) the joint exposure of both military service and other specific known causes (RR_{both}).

As an illustration, the proportion of disease attributable to military exposure and smoking, separately and jointly, is estimated for the hypothetical case described in Chapter 7. This is derived for two cases below, with smoking and military exposure interacting either additively or multiplicatively. In the additive model, smoking adds a constant RR over background ($RR_S - 1$) regardless of whether there is military exposure. Thus, in the presence of both exposures, the RR is $RR_{both} = RR_E + RR_S - 1$. In the multiplicative model, $RR_{both} = RR_E \times RR_S$.

We introduce new terminology to aid in the derivation of AFs for the joint and separate effects of these multiple known causal exposures. The population attributable fraction (PAF) is the proportion of disease in the entire population attributable to an exposure or any other factor. (The relation of the PAF to the AF will be discussed below.)

Assume that all disease in the population is attributed either to the background or to the two identified causes. PAF_0 is the proportion of disease attributable to background factors unrelated to smoking or military exposure. PAF_{both} is the proportion of disease attributable to smoking and military exposures. The two sum to unity $1 = PAF_0 + PAF_{both}$. Analogous to the AF, the PAF_{both} is given by

$$PAF_{both} = \frac{\left(RR_{both} - 1\right)}{RR_{both}}.$$

Thus PAF_0 is given by

$$PAF_0 = 1 - PAF_{both} = 1 - \frac{\left(RR_{both} - 1\right)}{RR_{both}},$$

which reduces to

$$PAF_0 = \frac{1}{RR_{both}}.$$

PAF_E, the proportion attributable to military exposure alone, is simply the proportion of disease attributable to background factors multiplied by the excess RR above the background ($RR_E - 1$):

$$PAF_E = \left(RR_E - 1\right) \times PAF_0,$$

which reduces to

$$PAF_E = \frac{\left(RR_E - 1\right)}{RR_{both}}.$$

Similarly PAF_S, the proportion attributable to smoking acting alone, is

$$PAF_S = \frac{\left(RR_S - 1\right)}{RR_{both}}.$$

The additional proportion attributable to the two factors acting in combination (i.e., interacting), PAF_{Int} is

$$PAF_{Int} = \frac{\left(RR_{both} - RR_E - RR_S + 1\right)}{RR_{both}}.$$

PAF_0 = proportion of disease attributable to background factors unrelated to smoking or military exposure
PAF_{both} = proportion of disease attributable to smoking and military exposures
PAF_E = proportion of disease attributable to military exposure alone
PAF_S = proportion of disease attributable to smoking acting alone
PAF_{Int} = the additional proportion of disease attributable to the two factors acting in combination
RR_E = RR estimates for military service-related exposure in the absence of the other known causes
RR_S = RR estimate for other known causes that individuals in the group were subjected to (e.g., smoking)
RR_{both} = RR for the joint exposure of both military service and other specific known causes

Table 9-1 provides the parameter values for the hypothetical case described in Chapter 7 for the two different cases—when smoking and military exposure interact multiplicatively and when they interact additively.

The calculations of AFs to the separate and joint exposures for this hypothetical example are laid out in Table 9-2. For the multiplicative example, one might be tempted to conclude that the contribution of military exposure was very small, since in the absence of the smoking interaction, the AF is only 6.7 percent. However, due to its interaction with smoking, the total contribution of military exposure is 66.7 percent (Table 9-2). (Note that this is the same PAF_E as for nonsmokers, [3 – 1]/3 = 67 percent [Table 9-1], revealing that under a multiplicative model, the total PAF_E

TABLE 9-1 Hypothetical Example of Risks from Multiple Causal Exposures

Military Exposure	Smoking Habit	Number at Risk	Cancer Cases		Relative Risk
No	Never	1,000	10		1
No	Current	1,000	100		10
Yes	Never	1,000	30		3
Yes	Current	1,000	Multiplicative	300	30
			Additive	120	12

TABLE 9-2 Hypothetical PAFs Due to Smoking and Military Exposure

PAF Due to	Multiplicative Model	Additive Model
Background only, PAF_0	1/30 = 3.3%	1/12 = 8.3%
Military exposure only, PAF_E	2/30 = 6.7%	2/12 = 16.7%
Smoking only, PAF_S	9/30 = 30%	9/12 = 75%
Military exposure and smoking interaction, PAF_{Int}	(30 – 3 – 10 + 1)/30 = 60%	(12 – 3 – 10 + 1)/12 = 0%
Total: $PAF_0 + PAF_E + PAF_S + PAF_{Int}$	3.3 + 6.7 + 30 + 60 = 100%	8.3 + 16.7 + 75 = 100%
SAF: Disease preventable by eliminating military exposure, $PAF_E + PAF_{Int}$	6.7 + 60 = 66.7%	16.7 + 0 = 16.7%

does not depend upon smoking.) Of course, the same calculation applied to smoking would yield an estimate of 90 percent for the total fraction attributable to that factor. If one were naively to add these two figures, it would appear that more than 100 percent of the risk would be accounted for, but of course, this is simply because the interaction contribution has been counted twice. In terms of prevention, 66.7 percent of the cancer cases in this group could have been prevented had the military exposure not occurred (or 90 percent [30 percent + 60 percent] if they had not smoked or 96.7 percent [30 percent + 60 percent + 6.7 percent] if both causes were eliminated [Table 9-2]).

Under a purely additive model, there is no interaction, no proportion of disease is attributable to the interaction, and the term PAF_{Int} becomes zero (Table 9-2). Among smokers, then, the proportion attributable to military exposure is 16.7 percent, considerably lower than in the multiplicative case. Among nonsmokers, however, military exposure accounts for 67 percent of the cases (PAF_E = [3 – 1]/3 = 67 percent [Table 9-1]), revealing that under an additive model (or any less-than-multiplicative model), the PAF_E will be larger for nonsmokers than for smokers. This holds even if the relative effect of smoking is much larger than exposure.

Chapter 7 also considered a scenario where one of the two factors was an intermediate variable on a causal pathway from exposure to disease (the example was smoking resulting from an amputation and leading to lung cancer). In this case, one would not want to partition the AF in this manner, because the direct effect of smoking on lung cancer was itself a consequence

of the exposure (battle trauma) and is therefore part of the total lung cancer burden attributable to that trauma.

Turning to the concept of the AF that was introduced at the beginning of this chapter, as the fraction of disease in the population that would not have occurred had the exposure not occurred, the AF can be derived from PAFs computed in this manner. It is simply

$$AF = PAF_E + PAF_{Int}.$$

As before, the AF can be refined to provide estimates for individuals in specific subgroups, with the same caveats and cautions discussed earlier. For the multiplicative case in the hypothetical illustration above, the SAF is thus estimated to be 66.7 percent (Table 9-2). The elimination of exposure would have eliminated the excess cases due to exposure acting alone and those due to its joint action with smoking. Hence, both components are counted in deriving the SAF. For the additive case, with the interaction term (PAF_{Int}) equal to zero, the SAF estimate is 16.7 percent. This underscores the importance of understanding the potential for interaction among multiple causal factors when evaluating the SAF for specific subgroups to be applied to individuals.

Using Data on Susceptibility and Exposure to Refine an AF Estimate

People differ in their susceptibility to disease and predispositions toward certain disabilities. Some of these differences are within an individual's control (e.g., food choices and eating habits), while other differences (e.g., genetics, age, and gender) are not. Differences in susceptibility remain to a great extent unquantifiable for most diseases, and thus are a source of uncertainty that in turn cannot be quantified in estimating the PC for individuals. When the background risk (in the absence of the exposure in question) varies substantially among individuals in the group, or there are strong interactions between background factors and exposure, the PCs among individuals can vary substantially, even for the same exposure level, and these will be misestimated by the AFs calculated for specific subgroups that cannot incorporate information on background risk.

Epidemiologic data may provide the basis for refining estimates of the AF for subgroups to be applied to individuals. As illustrated above, data on smoking or other causes of a disease not related to military service may allow refinement of the SAF. A variety of susceptibility and other factors have been used to refine estimates of the AF for radiation-induced cancers. In 1985, a set of radioepidemiological tables was released that provided probability of causation estimates for radiation exposures in terms of a

person's gender, age at exposure, age of cancer diagnosis, dose, and other factors (DHHS, 2002; NIH, 1985) (see the case study on radiation in Appendix I for details). These tables have since been updated using mathematical models of risk incorporating the characteristics of the individual claimant. In addition to gender, age at exposure and diagnosis, and smoking status, the dose, type, and energy intensity of the radiation are addressed. These estimates can now be obtained using an interactive computer program. The program also explicitly accounts for uncertainty in model inputs to "help minimize the possibility of denying compensation to claimants under the Energy Employees Occupational Illness Compensation Program (EEOICPA) for those employees with cancers likely to have been caused by occupational radiation exposures" (NIOSH, 2007, p. 3). Few if any other exposures lend themselves to such precise adjustments of risk.

Other Complexities of the AF

Most of the above discussion treats RR of exposure as fixed. A typical assumption for cancers is that, following a latency period after exposure, d, there is an age-specific incidence $p(t,d)$ that is a fixed multiplicative factor above the nonexposed

$$p(t,d) = RR(d) \times p(t,0).$$

In other words, there is a constant RR at any age t. An alternative assumption—constant excess risk—is that a given exposure d increases the absolute risk in the exposed by a fixed amount $g(d)$, so that $p(t,d) = g(d) + p(t,0)$. Because background incidence of every type of cancer changes with age, the constant excess risk model is incompatible with the assumption of constant RR. Another aspect of this problem is that for some diseases there are ages at which an individual is more susceptible to certain diseases. For radiation carcinogenesis there are considerable data for evaluating dose-response relationships that account for exposure level and duration, and age at exposure, and still uncertainty remains regarding how best to model these relationships for the purpose of calculating AFs for individuals (DHHS, 2002). For other cancer causes and other diseases there is usually much greater uncertainty about these relationships.

AF AND COMPENSATION

Earlier in this chapter, the concepts of the AF and the SAF were further developed after being initially introduced in Chapter 6. The extension of these concepts to attempt to estimate refined AFs that could be applied to

individuals was then introduced and discussed. We now bring these concepts to bear on the issue of compensation.

Considerations in Assessing Alternative Compensation Schemes

Exposure-Based Schemes

Compensation can theoretically be based on any number of considerations, not all of which make use of the notion of causation. For example, compensation could simply be based on a determination that certain types of exposure are so hazardous or extreme that they merit compensation regardless of whether they cause a disease. The Prisoner of War (POW) experience could reasonably be a candidate for an experience worthy of compensation on the basis of exposure alone, regardless of whether any illnesses resulted from this "exposure," and with perhaps some consideration of the severity of the experience. Similarly, when an exposure strongly increases the risk of a specific disease or condition, compensation could be granted regardless of whether the disease actually occurs. This approach was considered by the Presidential Commission on Catastrophic Nuclear Accidents and discarded (Presidential Commission, 1990). These approaches to compensation will not be considered further here, as they are matters of policy. We restrict our discussion to the compensation of persons whose exposure was causally linked to a health outcome and who were actually diagnosed with the outcome of interest.

A Traditional Approach Using the PC

For most questions of compensation, the decision rests on whether a specific exposure has been established as the cause of a disease or condition. It is usually not possible to establish the fact of causation for individuals (also referred to as *causation in fact* or *individual causation*) because the exposed cases caused by the exposure cannot be distinguished from the exposed cases caused by something else (Presidential Commission, 1990, pp. 107, 110). Furthermore, it is often difficult, if not impossible, to reconstruct the past doses, or even the exposures, when the latency period is very long. One approach to establishing the fact of causation in these circumstances has been to use an estimate of the *probability of causation* (PC) to determine whether compensation should be provided (OSTP, 1988). This estimate of PC (which is itself sometimes also referred to as *PC*), as discussed above, is the AF refined to be applicable to subgroups of individuals and is used to assign group risk to exposed individuals with the condition. A minimum threshold value of this estimated PC is then selected to determine whether one is eligible for compensation. This PC can also then be

used to determine, in those below this threshold, what lesser degrees of compensation might be provided.

The Presidential Commission on Catastrophic Nuclear Accidents used this approach when it recommended, in the context of radiation exposure, that someone for whom PC was determined to be more likely than not (i.e., $PC > 0.50$) would merit full compensation (Presidential Commission, 1990). At the other end of the spectrum, those in which it was determined that "it is extremely unlikely that an illness results from" an exposure would receive no compensation. For those who fell in between those two extremes, a "proportional recovery" approach was recommended in which compensation was awarded in relation to the PC (Presidential Compensation, 1990, p. 10). This approach, then, uses PC at a threshold of 0.5 to determine full compensability, with PC being determined by estimated exposure dose. Information on dose is then again brought to bear in determining the amount of compensation for those who do not meet the threshold PC, but who have received a dose that could possibly have caused the disease. Some of these issues are developed in more detail below (see "Possible Applications of the AF in Determining Individual Compensation").

A cogent critique has been developed that argues against the use of PC for the purpose of determining compensation (Cox, 1984, 1987; Greenland, 1999; Greenland and Robins, 1988, 2000; Robins, 2004; Robins and Greenland, 1989a,b, 1991). This critique has important implications as to whether the AF itself should be used in compensation. We later summarize the relevant aspects of this critique in the context of promoting use of AFs for this purpose as it relates to veterans (see "Promoting the Use of AFs in Determining Compensation for Veterans").

Use of YLL, YLD, and DALYs in Compensation

As an alternative to the use of PC or AF, Greenland and Robins proposed an approach to compensation based on expected years of life lost (YLL) (Greenland and Robins, 2000) (see above, "Reconsidering the Assumptions of the AF and Alternatives," where YLL, YLD, and DALYs are defined). Compensation would then be based on some reasonably assessed amount per year of life lost. An important feature of such a scheme is that it takes into account *when* an exposure caused death rather than merely *whether* it caused death. A compensation scheme based on YLL, it is argued, is economically rational because the total compensation payable under such a scheme corresponds to the total health burden caused by an exposure (at least as reflected by mortality), a quantity that can be estimated from epidemiologic data. However, because YLL cannot be estimated for any individual from epidemiologic data, it is not possible to determine the correct apportionment of the total YLL among those exposed (Robins and Greenland, 1991).

Apportioning compensation among exposed individuals would still require a policy decision based on unverifiable, but—one hopes—realistic, assumptions. Because mortality is not as relevant for veterans' compensation as illness and disability, the above scenario can use YLD and DALYs instead.

Applying Concepts of Sensitivity and Specificity to Compensation Schemes

Criteria for determining compensation make both explicit and implicit assumptions. One set of assumptions involves sensitivity and specificity (see Chapter 6). Sensitivity in this context is the probability that someone whose condition (or disease) was caused by a specific exposure is identified as such. Specificity is the probability that someone whose condition (or disease) was caused by something other than the specific exposure is identified as such. Typically when one improves sensitivity, specificity deteriorates, and vice versa. By trying to provide compensation for everyone whose condition was caused by the exposure, we typically increase the likelihood of mistakenly compensating some whose condition was not caused by the exposure. Conversely, in trying to exclude from compensation those who do not warrant it, we increase the chance of excluding those whose disease was in fact caused by exposure.

It is difficult to maximize both sensitivity *and* specificity. Optimizing one or the other means making some kind of mistake: either we optimize sensitivity by compensating some whose disease was not caused by exposure or we optimize specificity by failing to compensate some whose disease was caused by exposure.

The closely related concepts of true positive (TP) and false positive (FP), and true negative (TN) and false negative (FN), describe making the right and the wrong decisions (Table 9-3). True positives are those correctly identified by some criteria. False positives are those mistakenly identified by the criteria. False negatives are those not identified by the criteria, but who should have been. True negatives are those who were correctly not identified by the criteria.

Sensitivity is $TP/(TP + FN)$—the proportion of those whose condition was in fact caused by the exposure ($TP + FN$) who are correctly identified

TABLE 9-3 True and False Positive and Negative Rates

		Disease Caused by Exposure	
		Yes	No
Compensation criteria	Met	TP	FP
	Not met	FN	TN

as such (*TP*). Specificity is *TN*/(*TN* + *FP*)—the proportion of those whose condition was in fact not caused by the exposure (*TN* + *FP*) who are correctly identified as such (*TN*).

The positive predictive value (PPV) and negative predictive value (NPV) are important related concepts that are also defined from Table 9-3. The PPV is the proportion of those who meet the criteria whose condition was caused by the exposure, namely, *PPV* = *TP*/(*TP* + *FP*). The NPV is the proportion of those who do not meet the criteria whose condition was not caused by the exposure, namely, *NPV* = *TN*/(*TN* + *FN*).

A hypothetical example using two alternative criteria for compensation will be used to help clarify these concepts. Consider a disease, *D*, caused by an exposure, *E*, and service in a theater, *T*, the only theater in which exposure to *E* was known to have occurred. First, criteria that would provide compensation to all veterans who are eventually diagnosed with *D* and who served in *T*, and who would therefore have potentially been exposed to *E*, are very sensitive criteria (Criteria A in Table 9-4). No veteran whose disease *D* was caused by exposure to *E* would be missed by using these criteria (i.e., sensitivity is excellent). However, because we have elected to make sure that all veterans whose disease *D* was caused by exposure to *E* are compensated, we likely mistakenly also compensate those individuals whose disease *D* had another cause (i.e., specificity is poor). The use of criteria in this case to make certain that everyone in whom the disease was caused by exposure to *E* is compensated results in compensating many with the disease in whom it was not caused by *E*.

In contrast, criteria that would provide compensation only to veterans with the disease *D* who, for example, also had documented exposure to *E* for a specified period of time and of a specified intensity, and who also were diagnosed with *D* within a specified number of years of their first exposure, would be very "specific" criteria (Criteria B in Table 9-4). One can be more certain that if any group of veterans got *D* from exposure to *E*, those who were provided compensation by these criteria would be most likely to

TABLE 9-4 Comparing Sensitivity and Specificity of Two Hypothetical Sets of Compensation Criteria

		Specificity			
		excellent	good	some	poor
Sensitivity	excellent				Criteria A
	good				
	some	Criteria B			
	poor				

belong to that group (i.e., specificity is excellent). However, these specific criteria could potentially result in not providing compensation to some of those in whom *D* was in fact caused by *E* (i.e., sensitivity is compromised). The use of *specific* criteria increases the likelihood of denying compensation to some whose disease was in fact caused by *E*.

Sensitivity and specificity are not affected by the AF (the proportion of those with the condition whose condition was caused by the exposure). However, PPV and NPV are strongly influenced by the AF. Because the PPV indicates what fraction (or percentage) of veterans compensated for a condition actually had their disease caused by the exposure, varying the AF will change the likelihood that those compensated will have had their disease caused by the exposure. The following tables illustrate how this works. It is assumed that the compensation criteria have fixed excellent sensitivity (0.90) and relatively poor specificity (0.20)—a realistic scenario. What happens when the AF is allowed to vary? In Table 9-5, we begin with a hypothetical scenario in which half of the veterans with the disease will have gotten it as a result of the exposure (*AF* = 0.50). Here the PPV is 9,000/17,000 = 0.53, or 53 percent of those who are compensated will have had the disease caused by the exposure.

In Table 9-6, a lower and in some instances a more realistic AF of 0.09 is assumed, produced here by decreasing the number of those whose disease was caused by the exposure 10-fold. Here the PPV is 900/8,900 = 0.10, which means only 10 percent of those compensated will have it caused

TABLE 9-5 Hypothetical Scenario 1: PPV When AF = 50 Percent

		Disease Caused by Exposure		
		Yes	No	Total
Compensation criteria	Met	9,000	8,000	17,000
	Not met	1,000	2,000	3,000
Total		10,000	10,000	20,000

TABLE 9-6 Hypothetical Scenario 2: PPV When AF = 9 Percent

		Disease Caused by Exposure		
		Yes	No	Total
Compensation criteria	Met	900	8,000	8,900
	Not met	100	2,000	2,100
Total		1,000	10,000	11,000

by the exposure, but 90 percent will have been compensated without the exposure having played a role. If the AF is even lower, say 0.02 (2 percent), then PPV falls to 0.02 and only 2 percent of those compensated will actually have had it caused by exposure while 98 percent will have been compensated without the exposure having contributed (Table 9-7).

The definition of *exposure* as used in these calculations plays a large role in determining whether the AF is large or small. For example, if exposure is defined precisely based on documented exposure to a specific agent, then a larger AF may be realistic. However, if a nonspecific exposure is used, such as presence in a given theater where relevant exposure to the agent is relatively uncommon, then the AF might be expected to be very small, meaning that the proportion of disease caused merely by being in a given theater would often most likely be small. As discussed above, while the AF can clearly vary depending on level of exposure, in this case, it is the definition of exposure that strongly influences the AF.

The Receiver Operator Characteristics Curve

A more flexible and informative way of displaying these concepts is by the use of the receiver operator characteristics (ROC) curve (Obuchowski, 2003). An ROC curve (Figure 9-1) can display similar features as Table 9-4, but allows sensitivity (the proportion of true positives) and specificity (in this case reflected by the proportion of false positives [1 – specificity]) to be expressed on a continuous scale. The straight line of identity indicates combinations of sensitivity and specificity for criteria that do no better than chance in distinguishing those with disease caused by the exposure from those with disease not caused by exposure; the ability of criteria along this line to distinguish the two is no greater than that of tossing a coin.

Points on curved lines that are displaced upwards and to the left of the line of identity indicate combinations of sensitivity and specificity corresponding to specific criteria (cut points) that perform better than chance. Points on a line are generated using different criteria and produce an empirical ROC curve. The resulting curve illustrates how sensitivity and the

TABLE 9-7 Hypothetical Scenario 3: PPV When AF = 2 Percent

		Disease Caused by Exposure		
		Yes	No	Total
Compensation criteria	Met	180	8,000	8,180
	Not met	20	2,000	2,020
Total		200	10,000	10,200

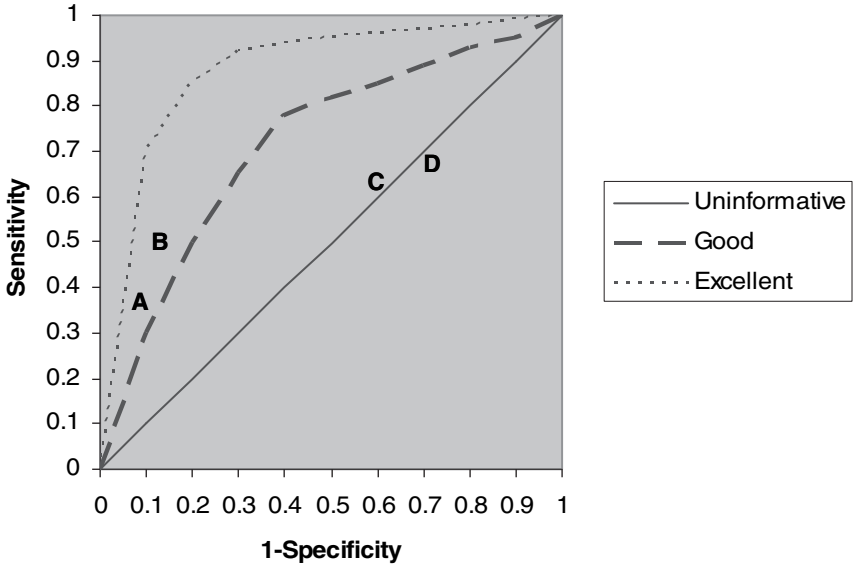

FIGURE 9-1 Example of ROC curves.
NOTE: Example of ROC curves. Different individual compensation criteria (A and B, and C and D) are displayed for different sets of criteria (dashed and dotted lines).

specificity vary together for different criteria. Each curved line corresponds to a different set of criteria for which varying the criteria within each set corresponds to different points along the line. Those curves displaced further upwards to the left than curves with lesser degrees of displacement generally perform better in distinguishing those with disease caused by exposure from those in which it was not caused by exposure. The point at the extreme upper left corner indicates largely unachievable criteria in which there is both perfect sensitivity and specificity—all those whose disease was caused by exposure receive compensation and none of those whose disease was not caused by the exposure receive compensation. The relevant advantages of an ROC curve over the table presented above are that the ROC curve (1) displays all possible criteria, (2) displays the relationship between sensitivity and specificity for different criteria, and (3) allows the performance of different sets of criteria (curves) to be directly compared.

The hypothetical example of disease *D* and exposure *E* can also serve to attempt to make ROC curve concepts clearer. A set of criteria were presented above in which compensation was provided only to veterans who developed *D* with documented exposure to *E* for a specified period

of time and of a specified intensity, and who also were diagnosed with *D* within a specified number of years of their first exposure. Using this set of criteria, alternative specific criteria can be considered. Criteria that favor specificity (A, Figure 9-1) might require cumulative exposure to *E* of at least 3 months of direct dermal or inhalational exposure and diagnosis of *D* within 10 years of first exposure (i.e., a latency of diagnosis of less than 10 years). Alternative criteria (B) that favored sensitivity might only require 1 week of direct dermal or inhalational exposure to *E*, with the same latency requirement. Each of these criteria would correspond to a specific point on an ROC curve, with corresponding sensitivity and specificity.

Another set of criteria could be considered that only uses information on exposure *E*, for example, but did not incorporate information on latency of diagnosis of *D*; this set of criteria would generate a new curve, with points corresponding only to different criteria for exposure. Another curve could be generated that only used information on time in theater *T*, for example 6 months (C) or 3 months (D), without any attempt to incorporate information either on exposure *E* or on latency. These criteria would be less specific, but probably more sensitive, than criteria A or B.

A feature shared by the ROC curve, and sensitivity and specificity, since the ROC curve simply displays sensitivity and specificity, is that there is no allowance for graded decisions. Compensation does not necessarily need to be an either-or decision, but instead could incorporate a mechanism (see below) that allows degrees of compensation. Sensitivity and specificity, and therefore the ROC curve, cannot accommodate such decisions.

In the earlier discussion pertaining to the AF and compensation ("A Traditional Approach Using the PC" in which PC terminology was used in place of AF terminology) it was noted that the level of the AF can be used to determine compensation. Note that selection of a specific AF for this purpose necessarily implies some sensitivity and specificity. Selection of a large AF would be less sensitive but more specific (i.e., with the more stringent criteria entailed by a larger AF, more people whose disease was caused by the exposure would not be compensated, but those compensated would be less likely to have had their disease caused by something besides the exposure), while a small AF would be more sensitive, but less specific.

Valuing Sensitivity or Specificity

Another feature of ROC curves, as was also noted above in discussing sensitivity and specificity, is that they are not affected by the proportion of a disease caused by the exposure (i.e., the AF) and therefore do not directly incorporate information on PPV and NPV. However, consideration of the AF can inform deliberations as to which criteria along an ROC curve are better than others. Specifically, the ROC curve does not tell us whether

we should place more value on improving sensitivity at the expense of specificity, or vice versa. The AF, by identifying the proportion of those with the disease that is caused by the exposure and thereby allowing us to calculate PPV, provides information that allows us to quantify the mistakes entailed in using different criteria.

The value (or cost) placed on these mistakes will play an important part in determining which mistake is least (or more) tolerable, and therefore whether it is better to optimize sensitivity or specificity. One could argue, using an analogy from the battlefield, that it is intolerable to think of leaving any wounded behind on the battlefield. In the compensation context, this sentiment might translate into optimizing sensitivity to make sure that no one whose disease was in fact caused by the exposure was denied compensation, even at the expense of mistakenly providing compensation to many whose disease was not caused by the exposure. Alternatively, if economic concerns were paramount (for example, if there were severe budgetary constraints on the total amount of money available to a compensation program), then it might be better to optimize specificity, making sure that only those whose disease was caused by exposure received compensation, even at the expense of mistakenly not providing compensation to some whose disease was in fact caused by the exposure.

Options for compensation criteria lie on the spectrum that ranges from complete sensitivity (top right corner of the ROC curve) to complete specificity (bottom left corner). Obviously, there is no universally correct choice from among the options along this spectrum. However, whether this is done explicitly, or whether this is merely implicit in the decisions (which is normally the case), a compensation policy chooses some combination of sensitivity and specificity. Typically such decisions favor one over the other. In the case of a common disease or illness, if there is a fixed budget available for compensation, then use of very sensitive criteria, such as motivated by the battlefield analogy, might result in many receiving only a small amount of compensation. If the budget is not fixed, use of very sensitive criteria would result in the total amount of compensation paid out becoming exceedingly large. These issues are further developed in the following section.

Developing a Basis for Compensation Based on AF

In earlier sections of this chapter, we discussed the properties of the AF, its underlying assumptions, and its inherent limitations. Here we discuss a critique of AF as a tool for determining compensation and propose justifications for its continued use in the context of veterans' compensation. We also explore options for the application of AF for this purpose.

Promoting the Use of AFs in Determining Compensation for Veterans

In the 1980s, Cox published an important critique of using epidemiologic data based on groups (and therefore the AF that is derived from these data) to draw conclusions about individuals, as is done in compensation settings (Cox, 1984, 1987). This theme was extended in a series of papers published from 1988 to 2004 by Robins and Greenland in which they developed their own critique of using probability of causation, and by implication, AF, as a basis for compensation or liability (Greenland, 1999; Greenland and Robins, 1988, 2000; Robins, 2004; Robins and Greenland, 1989a,b, 1991). There are at least three points in their critique that are relevant to the issue of AF and compensation.

First, compensation schemes based on AF alone allow consideration only of *whether* a disease occurs, not *when* the disease occurs. Although RRs, and the AFs derived from them, can vary by time in the sense that they can be estimated for different ages and for varying times since exposure, they do not reflect time lost due to disability or death. Those who live with a disease for a longer period of time, or had their life shortened by a longer period of time, presumably deserve more compensation. Approaches that use YLD or YLL (or DALYs) reflect when disease occurs and therefore provide an attractive alternative. (It should be recalled that the AF is a component of any calculation of YLD or YLL that tries to estimate the portion due to exposure [Steenland and Armstrong, 2006], and so any limitations inherent to the estimation of the AF itself will also apply to these extensions of the AF.)

Second, with an RR we cannot distinguish a situation where an exposure causes new disease *in a few* that would otherwise not have occurred from the extreme case where an exposure accelerates the onset of disease that would have occurred anyway *in all* of the exposed (Robins, 2004). In fact any RR, no matter how little elevated above a no-effect RR of 1.0, is as consistent with the exposure accelerating the onset of disease in all exposed as it is with the exposure causing the disease in the fraction of the exposed represented by the AF. One important implication is that an RR of 2.0 (and hence an AF of 0.5) does not equate to a 50 percent probability that exposure contributed to the disease in either the population or in an individual. That is, an RR of 2.0 does not make it *as likely as not* that the exposure caused the disease. It is important to understand that the distinction between accelerating the onset of a disease and causing disease that would not have occurred without the exposure is a blurry one. For example, because most men have latent prostate cancer by age 80 (Oh et al., 2003), it is often assumed that all men, if they were to live long enough, will get prostate cancer. Yet we have no hesitation in referring to exposures as potential *causes* of prostate cancer even though any exposure

would in reality have accelerated the onset in all who got it as a result of the exposure.

Third, when there is heterogeneity in baseline disease risks (i.e., when the risk of disease in the absence of exposure is different for different people, which is the usual situation), the AF does not necessarily equal the average of the probabilities that exposure caused the disease in each individual. This follows from the general principle that a nonlinear function (in this case a ratio) of averages does not in general equal the average of individual nonlinear functions (i.e., individual ratios). In the case here, the ratio of averages is the AF, and the average of ratios is the average of individual probabilities that exposure caused the disease. The greater the individual differences in the baseline probabilities, the greater the disparity between the AF and the average of individual probabilities.

In light of these compelling arguments, why would the AF continue to be recommended in compensation plans? Part of the answer relates to the features of a given compensation plan. A compensation plan that pays a lump sum to a veteran (or spouse/survivor) in direct proportion to the AF would be open to the criticisms of Robins and Greenland. VA compensation does not work in this way. VA compensation has many features of a compensation plan based on YLD or YLL. For diseases associated with disability only (which is common), monthly VA disability benefits begin when a case is approved for compensation and continue until death. VA compensation therefore accounts for the period of time a veteran lives with a disability.

Further, the amount of each monthly payment is intended to reflect the amount of disability, another feature incorporated in YLD (Steenland and Armstrong, 2006). Even though VA compensation does not directly account for YLL, spouse/survivor benefits for diseases that result in early mortality continue for the lifetime of the spouse/survivor. Thus, if the spouse/survivor outlives the veteran by many years because the veteran's life was shortened by many years due to the disease, the total payment would reflect this degree of life shortening. Although this might not be true in any individual case (if the spouse/survivor also dies early, for example) VA compensation nonetheless accounts for YLL at least indirectly.

Although we acknowledge the limitations, we also recognize the simplicity and transparency of the AF as a measure of disease burden. As others have deliberated similar issues of AF and assigned shares (NRC, 2000), we accept the utility of the AF as an input to compensation. In the following section we explore ways in which the AF might be applied for VA compensation.

Possible Applications of the AF in Determining Individual Compensation

There are several possible criteria for choosing among compensation plans. We focus here on two: economic rationality and fairness.

An economically rational basis for compensation is one in which the total compensation provided to the population is equal to the total burden of disease caused by exposure in the exposed group (as defined by the AF). Thus, the total compensation given to the exposed group is determined by the total disease burden caused by their exposure. For example, if the AF is 50 percent (and we make the simplifying assumption that half of the cases of disease among the exposed are due to the exposure), then the total economically rational compensation is the amount needed to compensate half of the afflicted persons. Unless the AF were 100 percent (a rare occurrence), the total economically rational compensation is always less than full compensation to every person with the disease.

One problem with the economically rational approach is that it says nothing about how to divide the total fairly among the eligible persons. The "correct" way would be to compensate each person according to his or her particular burden of disease caused by the exposure. We have discussed ways in which better information on exposure or individual susceptibility might improve estimates of individual PC. Ultimately, however, it is almost always impossible to determine which person's disease was caused by military exposure. This is because most disabilities and diseases have multiple causes, and each exposed person is also exposed to other causes of the condition. *Even with perfect research*, it is not usually possible to determine which case of the disease was caused by the military exposure and which was not. This is a central feature and problem of compensation for military exposure.

Given this problem, one approach would be to spread the total compensation evenly among all exposed persons who have the disease. For example, if half of the disease cases among the exposed were caused by the exposure (AF = 50 percent), then half compensation could be given to everyone. More generally, under this plan every exposed person with the disease would get a percent of compensation equal to the AF for their disease. This plan is illustrated in Figure 9-2. This approach has been used in class-action suits, but to our knowledge has not been used for military compensation.

A criticism of this approach is that even if we cannot identify them, we know there are probably some people whose disease was actually caused by their military exposure. Such people get only partial compensation, which can be construed as unfair. The only way to guarantee this never happens is to compensate everyone 100 percent, regardless of the likelihood that their disease was caused by their exposure (Figure 9-3). Such an approach achieves

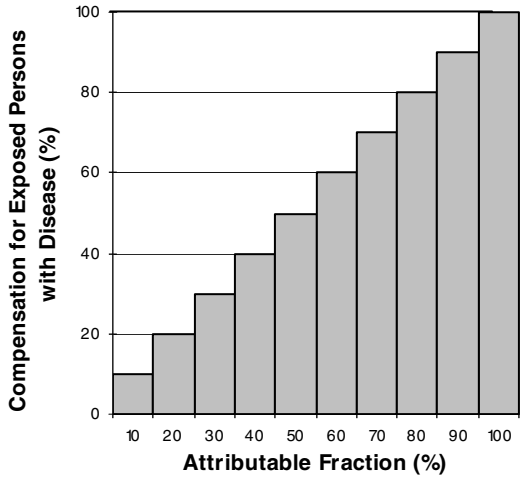

FIGURE 9-2 "Economically rational" compensation plan, based on the attributable fraction.

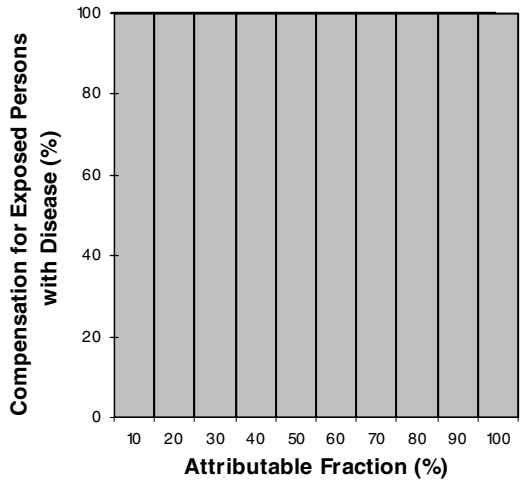

FIGURE 9-3 Complete compensation (100 percent) for all exposed persons with disease, regardless of attributable fraction.

extremely high sensitivity, but at high cost. This plan is not economically rational, in that it provides more compensation to the exposed population (in some cases, far more compensation) than the total disease burden would justify. It is worth noting that other criteria may legitimately be regarded by policy makers as more important than economic rationality.

The two plans described in Figures 9-2 and 9-3 define the boundaries of practical plans for compensation. The economically rational model provides the minimum rational compensation (Figure 9-2) and the compensation-to-all model provides the maximum possible compensation (Figure 9-3). All remaining plans discussed here fall somewhere between.

One in-between approach would be to establish a level of AF necessary for 100 percent compensation. The usual criterion is 50 percent—that is, the chance that the disease in an exposed person was caused by their exposure is at least 50:50. This approach is shown in Figure 9-4.

A criticism of the "50 percent criterion" is its all-or-none property. Because of uncertainty in the estimate of RR, there is little real difference between an RR of 2.1 and 1.8 (producing AFs of 52 percent and 44 percent), and yet a disease with the first AF might get 100 percent compensation, and a disease with the other might get none. By the criterion of economic rationality, the plan in Figure 9-4 undercompensates persons when the AF is less than 50 percent, and overcompensates them when it is 50 percent or greater.

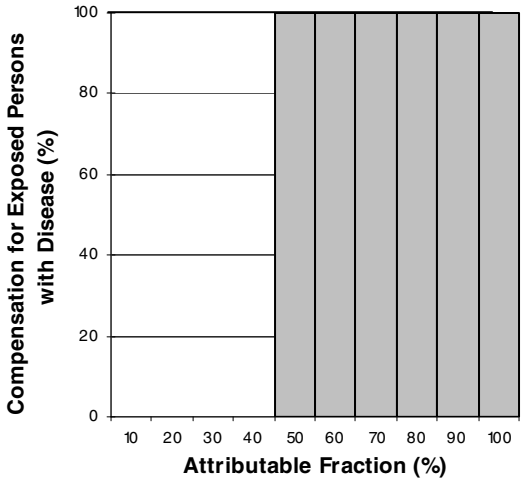

FIGURE 9-4 Complete compensation for all exposed persons only when attributable fraction is 50 percent or more.

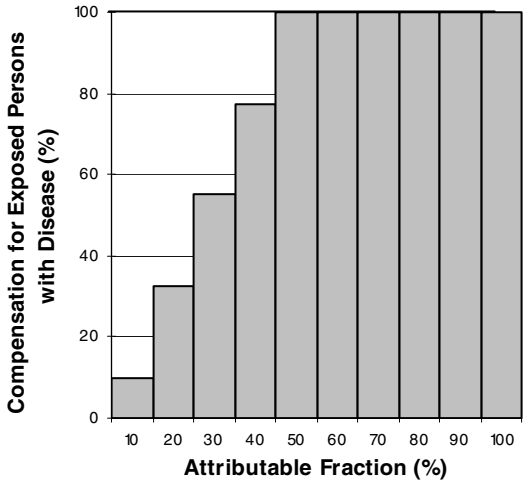

FIGURE 9-5 Complete compensation for an AF of 50 percent or more, plus graduated compensation below 50 percent.

This problem of all or none has been addressed in an alternative compensation scheme. The 1984 NRC Oversight Committee (NRC, 1984) suggested that when the AF was 50 percent or greater, compensation should be 100 percent, and when it is less than 50 percent, it should be linearly scaled down to 10 percent. This is shown in Figure 9-5.

A graded strategy of compensation (such as Figure 9-5), is more fair than an arbitrary cutoff of 50 percent and comes closer to achieving economic rationality—although at any given AF, it still provides total payouts much larger than the total burden of disease.

In the past, there has been a policy not to compensate individuals at levels less than 10 percent. Such a threshold would be relevant if any these models generated estimated compensations under 10 percent.

INTEGRATIVE SYNTHESIS: ROLES FOR PRESUMPTIONS

In this chapter the factors that can serve as information inputs to the decision-making process underlying the determination of veterans' compensation have been identified and discussed. These factors and the point(s) in the process at which they come into play are displayed in Figure 9-6. Additional inputs to the compensation process that are not strictly informational in nature are also displayed. These consist of ethical, political, and economic considerations that in practice can be critical determinants of the

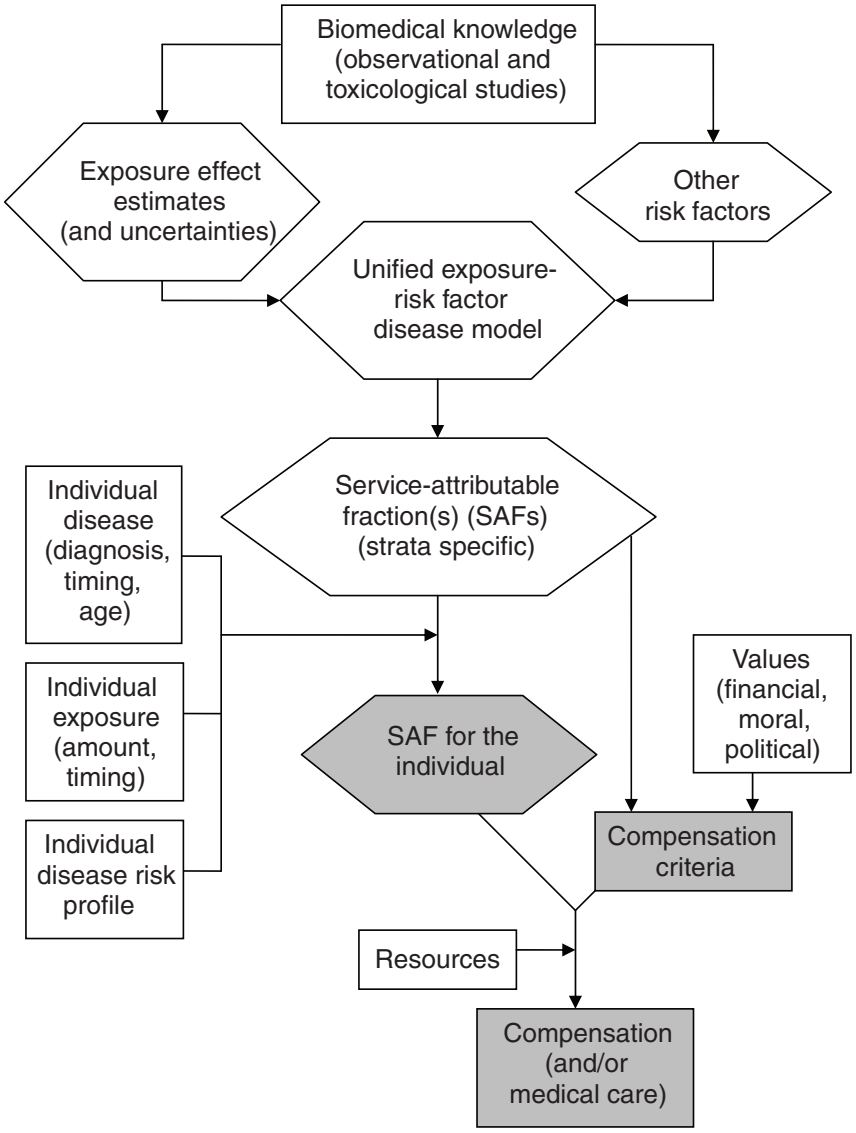

FIGURE 9-6 A rational process for determining veterans' compensation.

outcome of the process, but do not lend themselves to the type of exploration that has been undertaken in this chapter.

A Rational Compensation Determination Process

The compensation determination process for veterans displayed in Figure 9-6 is, we argue, a scientifically based and rational scheme, albeit necessarily somewhat idealized for most situations. Scientific findings here form the foundation for compensation. These scientific findings are more typically observational in nature, although toxicological or other experimental findings, depending on the specific exposure or disease, can either complement the observational findings or occasionally comprise the bulk of the findings. However, to be useful in this scheme, science must provide estimates of exposure effect that can be used to derive estimated AFs, and such effect estimates are best derived from observational data. Measures of uncertainty in the effect estimates could potentially play a role in some compensation schemes, although we have not here presented applications of how this might work. Toxicological findings, or the lack of them, could be reflected in the measures of uncertainty.

The size of effect estimates are affected by the extent of exposure and, by definition, effect modifiers. These, then, also affect the SAFs. Moreover, as we have seen, the SAF can be affected by how other risk factors interact with the exposure in causing disease, being affected not at all if they interact multiplicatively, but potentially dramatically if they interact additively (see Table 9-2 and corresponding discussion). To make use of these influences on the AF in the compensation process, science must not only provide information on how exposure and effect modifiers influence effect estimates, but also provide information on the form of interactive effects of other disease risk factors.

Armed with a host of exposure SAFs that correspond to levels (strata) of exposure, to states (strata) of the modifying factors, and to states of other risk factors if their interactions with the exposure are other than additive, individual SAFs can be estimated. Assuming that this information on exposure and these factors are also available for a given veteran seeking compensation, a corresponding SAF can be assigned to the veteran in lieu of our ability to know any individual's PC.

A compensation scheme for a specific exposure-disease combination that is economically rational (i.e., one that provides a total award reflecting the total disease burden of the exposed group) is formulated. A compensation scheme can potentially incorporate features relating to the certainty of the scientific information that is used in estimating the SAF, although we have not provided examples as to how this might be done. Criteria that define who is eligible for some form of compensation

implicitly assume some sensitivity and specificity, and for the population of concern, corresponding false positive and false negative rates. The AF, as shown above (Tables 9-5 to 9-7), has a great impact on both of these rates for a fixed sensitivity and specificity, and therefore could influence the selection of compensation criteria apart from its role in determining the individual SAF. Because of the trade-offs involved in choosing one set of criteria over another, the choice will always entail invoking values of some sort, for example, ethical, political, or financial (i.e., resource) values.

For many cases, including those involving veterans, this version of a compensation process may seem farfetched. It is unlikely that any single instance involving determination of compensation for veterans has features that look exactly like this. Nevertheless, it is instructive to consider how individual processes differ from this version. First, by identifying how actual cases differ from this framework, insight can be gained into some not so obvious assumptions that have been made in these cases. Second, this framework might help pinpoint or clarify the critical influences on any given compensation process. Finally, this framework can serve to identify information needs that, if met, would improve the specific presumptive disability decision-making process.

One way of viewing presumptions is as compromises necessitated by either poor or absent information on one or several of the inputs to the veterans' compensation determination process. For example, absent information on exposures of Service members in a specific theater, a presumption could be used to make the determination that any Service member who served in that theater was exposed. As another example, epidemiologic and other evidence about the association between a specific exposure and disease may be inadequate for estimating the AF. A presumption could be used to determine that any veteran with the disease who had been exposed most likely had the disease caused by the exposure. Or, there may be no information on how risk factors other than the exposure of interest influence the risk of disease, or how timing of disease occurrence influences the likelihood that the exposure was relevant. Even if this information existed, there may be no reliable way of obtaining this information for a veteran. A presumption might be used to determine that all exposed veterans, regardless of gender, age, the time since exposure, or exposure to other suspected disease risk factors, have the same AF.

Some Case Studies Revisited

It is instructive to again examine some of the case studies in light of this view of presumptions, and to assess characteristics of presumptions pertaining to sensitivity and specificity, and positive and negative predictive

value. The contrasting cases of Agent Orange and type 2 diabetes and of radiation and lung cancer will be used for this purpose.

With Agent Orange and type 2 diabetes, much of the information needed to apply our proposed process is unavailable or of poor quality (see Agent Orange and type 2 diabetes case study in Appendix I). First, scientific information that can be used to estimate an SAF indicates that the SAF is small, at best, and uncertain. Consequently, it is difficult based on this information to provide meaningful SAFs that correspond to different levels of exposure, or SAFs that correspond to different strata of possible modifying factors. There is information on the effect of several diabetes risk factors, but none is available on how any of these interact with Agent Orange exposure to influence diabetes risk.

Assuming that meaningful SAFs could be estimated, information about the veteran to make use of the SAFs is needed. First, information on exposure to Agent Orange is needed, including first and foremost whether exposure occurred, and the intensity and duration of exposure. Although there has been little attempt to make use of possible sources of exposure information for Agent Orange in Vietnam veterans for the purpose of compensation, attempting to characterize exposure based on current information will nevertheless be difficult. Information on the time of onset of diabetes, the certainty of diagnosis, and diabetes risk factors, while not perfect, is comparatively good.

Compensation schemes for Agent Orange and type 2 diabetes could take several forms, any of which might require some type of presumptions. We assume that the scientific findings indicate that exposure to constituents of Agent Orange causes type 2 diabetes, with some degree of certainty. With the SAF being small, even among those with well-documented exposure, the total disease burden is relatively small. This is true whether total disease burden is estimated directly from the SAF or using the SAF to modify a YLD or DALY. For compensation to be economically rational, the total compensation award to the veterans affected would then also be relatively small. Alternatively, if the overall cost of compensation for Agent Orange and type 2 diabetes is not relevant, then economic rationality is also not pertinent. With a small SAF, it is also likely that the proportion of those who would receive compensation under any scheme whose diabetes was actually caused by Agent Orange exposure would also be small (i.e., the false positive rate would be high). With crude measures of exposure that would include large numbers of veterans without the degree of exposure needed to cause disease, the SAF would be smaller still, with a correspondingly high proportion mistakenly compensated.

Any available information on the above inputs to the compensation process could restrict the scope of presumptions needed for Agent Orange and type 2 diabetes. Clearly the use of some information on exposure to

Agent Orange would reduce the effect on reduction of the SAF caused by including unexposed veterans. In the absence of better scientific information on Agent Orange exposure and type 2 diabetes, it will not be possible to utilize veteran information on potential modifying factors such as age of exposure, age of disease onset, or latency period to provide strata of SAF, although assumptions might have a role. For example, a hypothetical case could be made to limit the number of years allowable between exposure to Agent Orange and onset of diabetes. Regarding the presence of other diabetes risk factors that modify baseline risk, in the absence of good information on the form of interactions with Agent Orange, an assumption of additivity of risks might be made that could make it possible to provide stratified SAFs. A later age of diabetes onset in this case, for example, would increase baseline risk and reduce the SAF.

The current presumption for Agent Orange and type 2 diabetes has implicit assumptions as to sensitivity and specificity. With a presumption that requires service in Vietnam and diagnosed type 2 diabetes, sensitivity, $TP/(TP + FN)$, is nearly 1.0 as there are essentially no FNs. That is, any Vietnam veteran who got diabetes from Agent Orange exposure will receive compensation. On the other hand, specificity, $TN/(TN + FP)$, is 0 since there are no TNs. That is, no Vietnam veterans whose diabetes was caused by something other than Agent Orange will not be compensated. The positive predictive value of compensation, $TP/(TP + FP)$ is very small because FP is exceedingly large due to the small SAF. That is, only a small fraction of those who receive compensation will actually have had their diabetes caused by exposure. The negative predictive value, $TN/(TN + FN)$, is almost meaningless because both TN and FN are essentially nonexistent. These characteristics of this particular presumption are therefore quite extreme.

The case of radiation and lung cancer presents distinct contrasts to that of Agent Orange and type 2 diabetes. As detailed earlier (see radiation case study in Appendix I), here the case for causation is strong, uncertainty is relatively well estimated, and there is extensive information on dose-response relationships. Information on the effects of other factors, principally smoking and age, is also relatively extensive. However, even in this case there are deficiencies in the state of the information that invite presumptions. These deficiencies include (1) poor individual person-dose estimation; and (2) inadequate information on the form of the radiation interaction model for other risk factors, again principally smoking.

Based on the above information it is clear that the estimated SAF is relatively large for radiation and lung cancer and has less associated uncertainty than most exposures. As noted before, the radioepidemiological tables (NIH, 1985) provide estimated PCs for radiation in lung cancer by exposure dose, age at exposure and at cancer diagnosis, latency, and cigarette smoking history. However, there is little agreement on the form of the

radiation-smoking interaction in lung cancer, with initial evidence favoring additive effects and more recent interpretations favoring multiplicative (or submultiplicative) effects (see radiation case study in Appendix I). Because the form of the interaction has a large impact on estimation of the SAF, uncertainty about the form complicates use of an SAF even for lung cancer (see discussion on effects on the positive predictive value below).

The current presumption for radiation and lung cancer also has implicit assumptions as to sensitivity and specificity. Sensitivity, $TP/(TP + FN)$, is good as there will only be a few FNs. That is, most radiation-exposed veterans who get lung cancer from radiation exposure will receive compensation, at least when based on a presumption of exposure. Specificity, $TN/(TN + FP)$ is also good because those with low radiation risk, such as those with low estimated exposure, are less likely to receive compensation, although because of inaccuracies in the estimated exposure, some will (these will be FPs). The positive predictive value of compensation, $TP/(TP + FP)$, is very good because FPs are relatively uncommon because of the large AF. That is, a large fraction of those who receive compensation will actually have had their lung cancer caused by exposure. The negative predictive value, $TN/(TN + FN)$, is also very good because FNs are relatively uncommon. These characteristics of this particular presumption therefore seem to be reasonable.

However, even for the case of radiation and lung cancer, the above assessment of these characteristics is dependent on the way other disease risk factors, for example smoking, are determined to interact with the effect of radiation. For nonsmokers the above assessment is reasonable and does not depend on the form of the interaction. For smokers the assessment varies depending on whether smoking is determined to interact additively or multiplicatively with radiation exposure. With a multiplicative interaction, exposure RR and therefore AF is the same regardless of smoking status. In the additive case, the RR and the AF can vary dramatically by smoking status (see Tables 9-1 and 9-2, above). This will have no effect on sensitivity or specificity, as these are unaffected by the AF. However, positive and negative predictive values will be affected as both change as a function of the AF. Because the AF is substantially smaller in smokers than nonsmokers under an additive model, the positive predictive value is likewise smaller, indicating that for smokers a substantial percentage of those receiving compensation will not have gotten lung cancer as a result of exposure to radiation. The AF (and the PC derived from it) in the radioepidemiological tables is therefore critically dependent on the form of the interaction that is determined to be the case. Therefore, even with better scientific information than is available for any other military exposure, there is still room for presumptions. However, the better the information, the more focused and limited in scope the presumptions can be.

Science and Compensation Presumptions

The inability to identify the disease role of specific military exposures in any *individual* veteran partly motivates the need for compensation presumptions. The scope of a presumption is, in turn, partly determined by the available scientific information and corresponding information on any given veteran. The more scientific information available on the causal relationship between a service exposure and disease, and the more information available on an individual veteran's exposure and disease risk, the more narrow in scope the presumption needs be. The contrasting cases of Agent Orange and type 2 diabetes, and radiation and lung cancer, discussed above serve to make these points.

It is likely that there will be substantial advances in our ability to quantify exposure and other disease risks in individual veterans, perhaps through the use of specific biomarkers of exposure or disease for example, and by exploiting findings from toxicogenetics and toxicogenomics. These advances could possibly refine the scope of presumptions or conceivably do away with the need for some presumptions.

Earlier chapters laid out a framework for determining when a compensation presumption may be considered based on the state of scientific information. The intent in this chapter has been to identify concepts and tools that can be utilized in making decisions as to the form and content of a compensation presumption. These include (1) a set of SAFs that is as refined as the science permits; (2) features of alternative presumptions, such as sensitivity, specificity, and positive predictive value, that characterize and quantify the relative strengths and unavoidable mistakes (and therefore costs) implicit in each presumption; and (3) an appreciation of the relationship between the SAFs and some of these features, namely the positive and negative predictive values.

It has not been the intent here to determine whether a specific presumption and its form are justified or sensible or to identify better alternatives. These are issues on which VA and Congress deliberate. It is hoped, however, that the framework outlined can be used in these deliberations to allow for more rational, science-based decisions about the content of specific presumptions than may have been the case in the past.

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10

Health and Exposure Data Infrastructure to Improve the Scientific Basis of Presumptions

INTRODUCTION

This chapter addresses the implementation of a system of data collection to support surveillance and research, as well as to track the exposures of individual military personnel. The long-term goal is a system that would improve or complete many of the evidence gaps that now lead to presumptions. Information on exposure is needed to conduct studies that will provide data for calculating attributable fractions and for determining exposure groups of particular individuals.

Once a causal relationship has been established or presumed between a specific disease and a type of exposure, it becomes crucial to establish whether the Service member was exposed during military service. When data are not sufficient to describe a specific Service member's service-exposure history, presumptions are needed to give guidance about what to assume as exposure magnitude is considered. One clear path toward reducing the need for presumptions in decision making is to accurately document and provide Service member-specific exposure and health data to those making decisions regarding that Service member's case. Thus individuals determined by an adequate exposure surveillance system not to be exposed to an agent of concern would not be at risk for the particular health outcome(s) caused by that specific exposure. The availability of exposure data would provide evidence to support a veteran's claim that the exposure occurred while in military service. The availability of exposure data will allow more informative epidemiological studies to be performed and a more accurate determination of service-attributable fraction (SAF).

The need for having better exposure data has been recognized repeatedly in numerous external reviews of Department of Defense (DoD) and Department of Veterans Affairs (VA) activities regarding Service member health protection and veteran health care and disability determination (GAO, 1999, 2000a,b, 2005a,b, 2006; IOM, 1996a, 1999b, 2000c).

Detailed health status data collected throughout a Service member's active duty and veteran experience, coupled with individual exposure data collected during that period, would provide the data needed to make better decisions about an individual's likelihood of service-related disease causation and thus minimize the need for presumptions. As the Institute of Medicine (IOM) noted in 1996,

> The DoD, the branches of the armed services, and the DVA should continue to work together to develop, fund, and staff medical information systems that include a single, uniform, continuous, and retrievable electronic medical record for each [S]ervice member. The uniform record should include each relevant health item (including baseline personal risk factors, every inpatient and outpatient medical contact, and all health-related interventions), allow linkage to exposure and other data sets, and have the capability to incorporate relevant medical data from beyond DoD and DVA institutions (e.g., U.S. Public Health Service facilities, civilian medical providers, and other health-care institutions). . . . (IOM, 1996a, p. 10)

DoD and VA have been working together since 1998 to improve sharing of medical information for active-duty military personnel and veterans. The agencies have developed a short-term plan to improve their existing health information systems and a long-term plan to create a modern health information system based on computable data. However, as GAO points out, DoD and VA lack a detailed project management plan to guide their efforts (GAO, 2007).

In 1997, President Clinton issued a directive to DoD and VA "to create a new Force Health Protection Program. Every soldier, sailor, airman, and Marine will have a comprehensive, life-long medical record of all illnesses and injuries they suffer, the care and inoculations they receive, and their exposure to different hazards. These records will help us prevent illness and identify and cure those that occur" (DoD, 2006a, p. 2).

Also in 1997, coincident with the presidential directive described above, DoD issued an instruction describing the "Implementation and Application of Joint Medical Surveillance for Deployments." This document defined initial expectations for more detailed medical surveillance and exposure assessment data collection systems for both deployment and in-garrison or nondeployment settings. This plan laid the groundwork for systems that would "eventually be capable of linking deployment and nondeployment

environmental and occupational exposure and data to health hazard and/or health risk assessments to individual medical records and medical outcome databases" (DoD, 1997, p. 5).

The vision for a more comprehensive and continuous surveillance system was articulated in DoD Directive 6490.2 issued in 2004. It proposed that

> Health surveillance systems shall be continuously in effect throughout each [Service member]'s career, capturing data about individual health status; instances of disease and injury; medical interventions such as immunizations, treatments, and preventive medications; and exposures to potential and actual health hazards associated with occupation, deployment, and lifestyle. (DoD, 2004, p. 3)

It also dictated policy that "[s]urveillance data collected on individual [Service member]s during their careers shall be provided to VA upon their separation or retirement from the military" (DoD, 2004, p. 4).

Defining and developing the mechanisms and systems to implement these goals has been an iterative process that has taken years—largely due to the magnitude and complexity of the issues being addressed. Those efforts are now bringing action as a series of systems and expectations are being implemented. DoD Instruction 6490.03 of 2006, which replaced the 1997 DoD Instruction 6490.3, sets clear expectations that deployment exposure assessment and monitoring data be submitted to individual health records and to a DoD-wide database (DOEHRS—the Defense Occupational and Environmental Health Readiness System) (DoD, 2006c, p. 21).

The remainder of this chapter reviews the current state and future plans for DoD and VA collection and use of health and exposure data throughout a Service member's span of service. The availability of such data would enable studies to better understand potential linkages between service-connected exposures and future health status and would reduce reliance on presumptions in decision making.

DOD HEALTH AND EXPOSURE ASSESSMENT DATA COLLECTION

DoD Health Assessment and Medical Surveillance

Overview

Opportunities for health assessments of Service members on active duty occur at obvious service milestones throughout the Service member's span of service. These milestones include the initial medical evaluation at accession, or entry into the service, and subsequent periodic health assessments

that continue until separation or retirement from the service. These milestones are displayed in Figure 10-1. Additional surveillance may precede or follow specific deployments with assessments tailored to the particular hazards of a deployment.

Routine Health Assessments Throughout the Span of Service

Elements of the health data collected for each of the assessments performed over the span of a Service member's service are found in Table 10-1. They may include responses to a health history questionnaire, physical examination findings, and laboratory test results. The degree of detail and areas of emphasis in each assessment vary based on the specific point in the span of service or on the purpose of each individual assessment. Generally, a self-completed questionnaire contains a core set of questions regarding physical and mental health, and history of environmental and occupational exposures and stressors. This is intended to follow the recommendations of the U.S. Preventive Health Services Task Force's *Guide to Clinical Preventive Services* (AHRQ, 2006). Data are collected in a combination of written and electronic formats.

All new recruits and enlisted Service members undergo an initial evaluation at the time of accession. This is the most comprehensive of the assessments and provides the baseline set of data that is updated at the time of each future assessment. As in all assessments, the nature of the responses and test results partly determine what additional evaluation or screening is performed. At this time, data from this evaluation are generally saved only in a hard copy format. The Health Assessment Review Tool (HART) is an electronic and standardized implementation of the self-reporting questionnaire that is currently being pilot tested at Ft. Jackson (Army) and San Diego (United States Marine Corps); the HART-A (the accession version) is expected to be more generally available in the next few months (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006).

The periodic health assessments (PHAs) are episodic (generally annual) follow-up evaluations primarily employing self-completed questionnaires. Positive responses on this questionnaire, or additions to previously collected information, trigger a more detailed assessment. In following the U.S. Preventive Health Services Task Force recommendations, the PHAs are ideally targeted based on gender, age, disease risk factors, medical history, and exposure history (DoD, 2006d). The PHA is currently being instituted by the Army, but it has been established in the Navy and Air Force for several years.

The separation, retirement, or deactivation assessment is the final routine evaluation that all Service members undergo. Whereas previously a

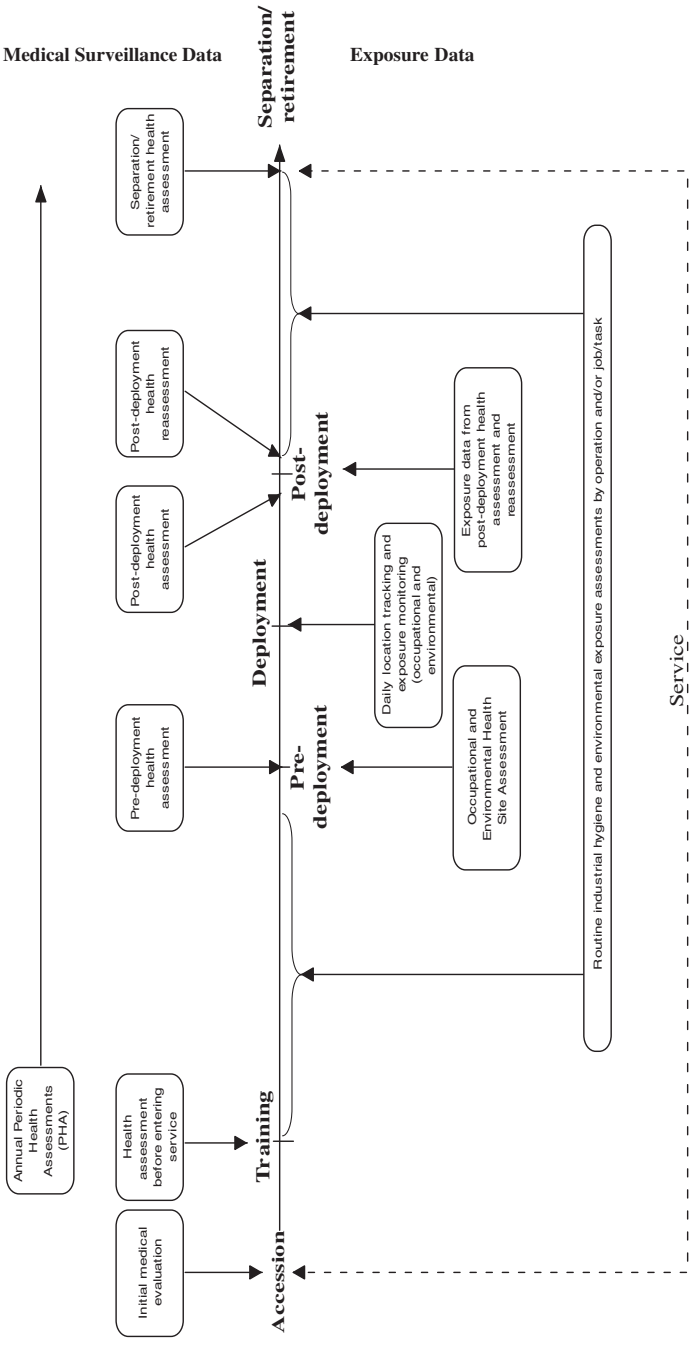

FIGURE 10-1 Timeline for medical surveillance and exposure data collection.

TABLE 10-1 Timeline for Medical Surveillance and Exposure Data Collection

			In Service					
	Accession	After Training Before Service	Throughout Service	Pre-Deployment	Deployment	Post-Deployment	Post-Deployment Reassessment	Separation/ Retirement
Routine Medical Surveillance Data[a]								
Self-Administered Questionnaire								
Family history of chronic diseases	X		X					
Personal habits	X							
Past medical history	X							
Medications	X			X		X		X
Allergies	X							
General health status			X	X		X	X	
Significant events since last periodic health assessment				X				X
On a profile, light duty, or undergoing a medical board				X				
Medical or dental problems				X				X
Pregnancy				X				
Counseling or care for mental health in past year				X				
Questions or concerns about health				X				
Health changes during deployment						X	X	
In sick call during deployment						X	X	

Nights spent as a patient in a hospital during deployment	X	X		X
Vaccinations	X			
Symptoms now or developed anytime during this deployment[b]	X	X		
See anyone wounded, killed, or dead during this deployment	X			
Engaged in direct combat where discharged weapon	X			
During deployment, feel like in great danger of being killed	X			
Interested in receiving help for a stress, emotional, alcohol, or family problem	X	X		X
Little interest or pleasure in doing things	X	X		
Feeling down, depressed, or hopeless	X	X		
Thoughts that you would be better off dead or hurting yourself in some way	X			
Nightmares due to an experience so frightening, horrible, or upsetting	X	X		
Constantly on guard, watchful, or easily startled	X	X		
Numb or detached from others, activities, or your surroundings	X	X		

continued

TABLE 10-1 Continued

			In Service					
	Accession	After Training Before Service	Throughout Service	Pre-Deployment	Deployment	Post-Deployment	Post-Deployment Reassessment	Separation/ Retirement
Self-Administered Questionnaire (continued)								
Concerns of serious conflicts with spouse, family members, or close friends						X	X	
Concerns of hurting or lose control with someone						X		
Having problems if wounded, injured, or assaulted during deployment							X	
Alcohol use							X	
Difficulty working, taking care of things at home, or getting along with other people							X	X
Illnesses or injuries that caused you to miss duty for longer than 3 days								X
Treated by a healthcare provider, admitted to a hospital, or had surgery								X
Injuries or illnesses while on active duty for which you did not seek medical care								X
Other questions or concerns about your health								X

Intend to seek Department of Veterans Affairs disability								X
Laboratory Tests								
Urinalysis (albumin, sugar, HCG)	X	X	X					
H/H	X	X	X					
Blood type	X	X	X					
Drugs and alcohol	X	X	X					
Serum sample	X		X	X		X		
HIV testing	X		X					
CBC	X							
Hemoglobin	X							
Hematocrit	X							
Vaccination status	X							
Clinical Screening and Measurements								
Height	X	X	X					
Weight	X	X	X					
Temperature	X	X	X					
Pulse	X	X	X					
Blood pressure	X	X	X					
Distant vision, near vision	X	X	X					
Refraction by autorefraction or manifest	X	X	X					
Heterophoria	X	X	X					
Color vision	X	X	X					
Depth perception, field of vision, night vision	X	X	X					

continued

TABLE 10-1 Continued

	Accession	After Training Before Service	In Service: Throughout Service	In Service: Pre-Deployment	In Service: Deployment	In Service: Post-Deployment	Post-Deployment Reassessment	Separation/ Retirement
Clinical Screening and Measurements (continued)								
Intraocular tension	X	X	X					
Audiometer	X	X	X					
Pap smear	X	X	X					
Allergies			X					
Tobacco use			X					
Alcohol abuse and stress management			X					
Chronic illnesses			X					
Medications			X					
Cholesterol			X					
Breast exam, mammogram			X					
Fecal occult blood			X					
Sigmoid			X					
Colonscopy			X					
Immunizations			X					
Clinical Evaluations								
Head, face, neck, and scalp	X	X	X					
Nose, sinuses	X	X	X					
Mouth and throat	X	X	X					
Heart	X	X	X					

Lungs and chest, vascular system	X	X	X
Anus and rectum	X	X	X
Abdomen and viscera	X	X	X
External genitalia	X	X	X
Upper and lower extremities	X	X	X
Spine, musculoskeletal system	X	X	X
Body marks, scars, tattoos	X	X	X
Skin	X	X	X
Neurologic and psychiatric disorders	X	X	X
Pelvis	X	X	X
Endocrine system	X	X	X
Routine Exposure Data[a]			
Industrial Hygiene Exposure Assessment of Operations, Jobs/Tasks			X
Qualitative Exposure Judgments			X
Occupational Exposure Monitoring			X
Routine Environmental Health Programs			X

continued

TABLE 10-1 Continued

			In Service					
	Accession	After Training Before Service	Throughout Service	Pre-Deployment	Deployment	Post-Deployment	Post-Deployment Reassessment	Separation/ Retirement
Environmental Health Site Assessment (EHSA)[c]								
Current use of site, adjoining properties, and surrounding area				X				
Past use of site, adjoining properties, and surrounding area				X				
Geologic, hydrogeologic, hydrologic, meteorologic, and topographic conditions				X				
General description of structures				X				
Roads				X				
Potable water supply				X				
Sewage disposal system				X				
Hazardous materials in connection with identified use				X				
Storage tanks				X				
Odors				X				
Pools of liquid				X				
Drums				X				

Hazardous materials and petroleum products containers	X			
Unidentified substance containers	X			
Heating and cooling	X			
Stains or corrosion	X			
Drains and sumps	X			
Pits, ponds, and lagoons	X			
Stained soil or pavement	X			
Stressed vegetation	X			
Solid waste	X			
Waste water	X			
Well	X			
Septic systems	X			
Daily Location Tracking		X		
OEHS Site Assessments		X		
Environmental Monitoring		X		
Exposure Incident Response		X		
Self-Administered Questionnaire				
DEET insect repellant applied to skin			X	X
Pesticide-treated uniforms			X	X

continued

TABLE 10-1 Continued

	Accession	After Training Before Service	In Service: Throughout Service	In Service: Pre-Deployment	In Service: Deployment	In Service: Post-Deployment	Post-Deployment Reassessment	Separation/ Retirement
Self-Administered Questionnaire (continued)								
Environmental pesticides (like area fogging)						X	X	
Flea or tick collars						X	X	
Pesticide strips						X	X	
Smoke from oil fire or burning trash or feces						X	X	
Vehicle or truck exhaust fumes						X	X	
Tent heater smoke						X	X	
JP8 or other fuels						X	X	
Fog oils (smoke screen)						X	X	
Solvents						X	X	
Paints						X	X	
Ionizing radiation						X	X	
Radar/microwaves						X	X	
Lasers						X	X	
Loud noises						X	X	
Excessive vibration						X	X	
Industrial pollution						X	X	
Sand/dust						X	X	
Depleted uranium						X	X	
Days wear MOPPS over garments						X		

Times put on gas mask because of alerts and not because of exercises		X
Ever enter or closely inspect any destroyed military vehicles		X
Exposed to chemical, biological, or radiological warfare agents during deployment		X

[a] Non-routine medical surveillance and exposure data are event driven.

[b] Includes chronic cough, runny nose, fever, weakness, headaches, swollen, stiff or painful joints, back pain, muscle aches, numbness or tingling in hands or feet, skin diseases or rashes, redness of eyes with tearing, dimming of vision, chest pain or pressfainting, lightheadedness, difficulty breathing, still feeling tired after sleeping, difficulty remembering, diarrhea, frequent indigestion, vomiting, ringing of the ears.

[c] This information is used to develop a conceptual site model and may be summarized into a preliminary hazard assessment; SOURCE: ASTM, 2003. SOURCE: For medical surveillance data: Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006; DoD Form 2808 "Report of Medical Examination"; DoD Form 2795 "Predeployment Health Assessment Form"; DoD Form 2796 "Post-Deployment Health Assessment Form"; DoD Form 2900 "Post Deployment Health Reassessment Form"; DoD Form 2697 "Separation and Retirement Medical Assessment." For exposure data: ASTM, 2003; DoD Form 2796 "Post Deployment Health Assessment Form"; DoD Form 2900 "Post Deployment Health Reassessment Form."

retirement evaluation of a career Service member was optional, this has become mandatory since 2005 (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006). The final assessment is performed to document any history of a "limiting" condition. This is determined by a medical evaluation board and may describe the need for "alternative duty" in subsequent employment because of a disability suffered while in the service. The determination of this board addresses the service connectedness of a condition that a Service member may have and thus that Service member's eligibility for VA services.

Nonroutine Health Assessments

Event-driven assessments Health evaluations are also performed in the event of acute health problems or worsening of preexisting conditions. These are focused evaluations that address the specific concern at hand.

Deployment-specific health assessments The predeployment assessment occurs within 60 days of deployment and builds on the PHA. This brief evaluation focuses on interval changes since the most recent PHA, highlighting medications used and any limited duty or short-term disability given. A serum sample is archived and any theater-specific or occupation-specific testing is performed. An HIV test is required if none has been done in the previous 12 months. For deployments lasting less than 30 days, the predeployment assessment is optional as determined by the deployment health authority. Combatant command determines whether additional specific tests will be required, such as cholinesterase levels if deployed into pest management activities or zones, or G6PD enzyme levels. Although not all Service members undergo this assessment, at least 90 percent do (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006).

During deployment there are no generic health assessments. Evaluations are triggered by specific exposures or events, and there may be theater-specific assessments. Also, follow-up may be indicated when environmental sampling suggests a hazard, such as poor water quality. Patient-encounter data are often in electronic format and are captured by the Armed Forces Health Longitudinal Technology Application (AHLTA); sites that are currently not using an electronic data record are planned to have their data entered in the future. Depending on the circumstance, exposures to documented excursions of ambient air, water, or soil concentrations, are also theoretically entered into individual records. Under a new requirement, environmental summaries for all permanent and semi-permanent base camps will be generated according to time and location (Personal

communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006).

Postdeployment evaluations must occur within 30 days of redeployment, although most take place before actually leaving the deployment arena, or while in transit from theater. This evaluation uses a self-reported questionnaire, but also includes a personal interview with a care provider who determines the need for further follow-up. A serum sample is typically obtained when a Service member is at "home." There is documentation of environmental and occupational exposures. Rosters of specific exposure- or event-defined cohorts are assembled based on professional judgment; these are used for purposes of health follow-up or risk communication. Examples include lung function testing following sulfur dioxide exposures or follow-up of those exposed to depleted uranium (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006). Though the impact of combat related stressors on mental health may be significant, structured assessments on symptoms related to emotional stressors, depression, anxiety, posttraumatic stress disorder, and interpersonal difficulties, including hurting someone or losing control, are brief and only assessed at postdeployment period.

HEALTH DATABASES

The above-described assessments generate data that are stored in several databases or formats, thus requiring record linkage, and data entry, for analysis. One primary database is the Defense Medical Surveillance System (DMSS). The DMSS is a relational database that currently contains up-to-date Service member data for all in- and out-patient in-garrison health encounters including acute health events and exposures. It currently has some in-theater encounters provided by AHLTA, but not all. As noted above, HART-A is only now being implemented, so much of the accession evaluation is only present in hard copy form. Also, while standardization is the goal, data collection is not completely standardized across the service branches. AHLTA is the new DoD automated medical records system and clinical data repository; this includes all laboratory data and electronic PHAs. Integration of medical records is clearly a goal in DoD. This is manifested in the current process of establishing an Armed Forces Health Surveillance Center to integrate DMSS, AHLTA, and personnel data (from the Defense Manpower Data Center). Although much of the surveillance health data present in the DMSS are relevant to AHLTA (for example, reportable medical conditions), there is no need for complete overlap (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006).

Troop Tracking and Linking of Individual Exposure and Health Data

Improvements in tracking of troop location are underway, reflecting in part an awareness of the need to perform troop tracking to allow reconstruction of exposure scenarios. A new tracking software, the Defense Theater Accountability Software, which is in limited use, currently requires data entry by hand at the unit level. The Defense Manpower Data Center can currently query records in the DMSS. There is no capability to resolve location within a 24-hour period, as only one 24-hour entry is currently used (Personal communication, Col. K. Cox and C. Postlewaite, Department of Defense, November 1, 2006).

The need to link exposure data with health outcomes is appreciated, but this capability is currently not fully developed. The current situation is driving efforts to construct environmental monitoring summaries for various theaters and locales, and to assign surveillance exposure data to individual health records.

DOD EXPOSURE ASSESSMENT

Overview

Occupational and environmental exposures occur throughout the span of a Service member's service career. In summarizing the exposure assessments needed to cover that experience, we can use the same milestones as were used to describe health assessments. They begin with exposure opportunities in the first months of service immediately following service entry and also proceed in a longitudinal manner through routine garrison experiences through multiple deployments and on through separation or retirement (see Figure 10-1).

Exposure Assessments Throughout the Span of Service

Exposure assessment elements collected for each milestone of the Service member's span of service are summarized in Table 10-1 and may include qualitative exposure judgments, occupational exposure monitoring, and environmental monitoring results. As in the case of health assessments, the degree of detail and areas of emphasis vary based on the specific point in the span of service or a specialized reason for the assessment. Data are collected in a combination of written and electronic formats, but there is significant activity moving DoD toward fully integrated electronic records.

Exposure assessments are made so that appropriate exposure controls can be planned and implemented. In the case of routine operations or low-risk combat scenarios the implementation of these controls is straight-

forward. Under high-risk combat scenarios, however, it may be difficult or impossible to consistently implement controls for environmental agents as the risks posed by implementing those controls under severe combat conditions may be higher than those posed by the exposures. In each case, however, there is a need to characterize and document exposures to agents from occupational and environmental sources.

Nondeployment Military Bases

The individual services within DoD have had traditional industrial hygiene and environmental health programs in place for many years in military base or installation settings. These programs conduct occupational and environmental exposure risk assessments for routine and nonroutine operations and document results in a variety of service-specific paper and electronic data repositories.

Predeployment

In support of deployment occupational environmental health and safety (OEHS) measures for information/intelligence preparation of the environment, a phase I deployment OEHS assessment is produced for military location(s) of interest that assesses known and/or potential deployment OEH hazards and threats ranging from industrial chemicals, historical contamination, radiation, infectious disease, entomological risks, weapons of mass destruction, and specified intelligence based threats. These assessments are quantitative and also identify any preventive medicine measures and counter-measures and deployment OEH surveillance activities to ensure force health protection measures for deployments. For deployments less than 30 days, some of these activities are performed at the discretion of the operational commander as it is recognized that for special operations and very short deployments they may not all be feasible (DoD, 2006c).

Deployment

OEHS site assessments, exposure assessments, environmental monitoring, exposure incident response (and reports), and daily individual troop locations as determined by global positioning system (GPS) or other means are performed during deployment (see Figure 10-2) (DoD, 2006c). The content and detail included in these assessments vary depending on the length of deployment, the location of deployment, the intensity of combat operations, the number of deployed personnel, and the training of deployed personnel (DoDI 6490.03 2006 [DoD, 2006c]).

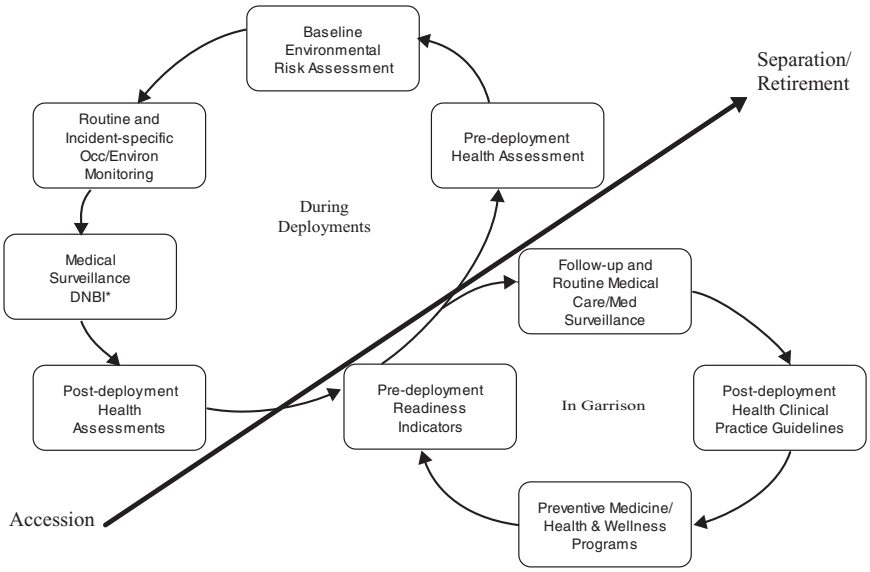

FIGURE 10-2 DoD's deployment health surveillance elements.
*DNBI (disease and nonbattle injury).
SOURCE: Adapted from Postlewaite, 2006.

Postdeployment

Postdeployment assessment activities primarily involve data and report cleanup and submission for central documentation—including documentation of health and exposure data and incidents in individual health records.

EXPOSURE DATABASES

Service Specific

The Army and Navy maintain collected exposure data at their respective occupational health and preventive medicine headquarters, the U.S. Army Center for Health Promotion and Preventive Medicine and the Navy Environmental Health Center respectively. The Air Force retains its data at each individual Air Force base (Table 10-2). Although the Army and Navy have a central headquarters database maintenance system, they also have individual activity databases for exposure data. These individual activity databases are rolled into the headquarters system but are also maintained at

TABLE 10-2 Service-Specific Databases for Exposure

Service	Database	Data Maintenance	Health Hazard Inventory Database	Quantitative Exposure Data	Deployment Exposure Data	In-Garrison Data
Army	HHIM	CHPPM	HHIM	Yes	No	Yes
Army	DESS	USACHPPM	DESS	Yes	Yes	No
Navy	IHIMS	NEHC	NOED	Yes	Yes	Yes
Air Force	CCS	AF Bases	AF-EMIS/ HMMS	Yes	No*	Yes

NOTE: Table conveys the service-specific databases available and where the data are stored.
ABBREVIATIONS: AF-EMIS = Air Force Environmental Management Information System; CCS = Command Core System; CHPPM = U.S. Army Center for Health Promotion and Preventive Medicine; DESS = Deployment Environmental Surveillance System; HHIM = Health Hazard Information Module; HMMS = Hazardous Material Management System; IHIMS = Industrial Hygiene Information Management System; NEHC = Navy Environmental Health Center; NOED = Navy Occupational Exposure Database.
*Some deployment exposure data are currently stored in the Air Force's Global Expeditionary Medical System (GEMS).
SOURCE: Adapted from DoD, 2006a.

the respective individual activities. All data will eventually be consolidated into the DOEHRS program, but individual activity data are also retained at the respective individual sites. Services have indicated that they will retain some of their legacy systems after inclusion of data into DOEHRS. Industrial hygiene exposure data consolidation into DOEHRS is expected to be completed by 2010 with all exposure data entry completed by 2013.

DOEHRS—DEFENSE OCCUPATIONAL AND ENVIRONMENTAL HEALTH READINESS SYSTEM

Overview

DOEHRS is an automated information system designed to replace existing service-specific database collection and storage systems. It supports reduction in redundant data entry between worksites and occupational health clinics. DOEHRS also eliminates redundant exposure data collection through interfaces with clinical, environmental, safety, and personnel automated information systems. The DOEHRS structure is outlined in Figure 10-3.

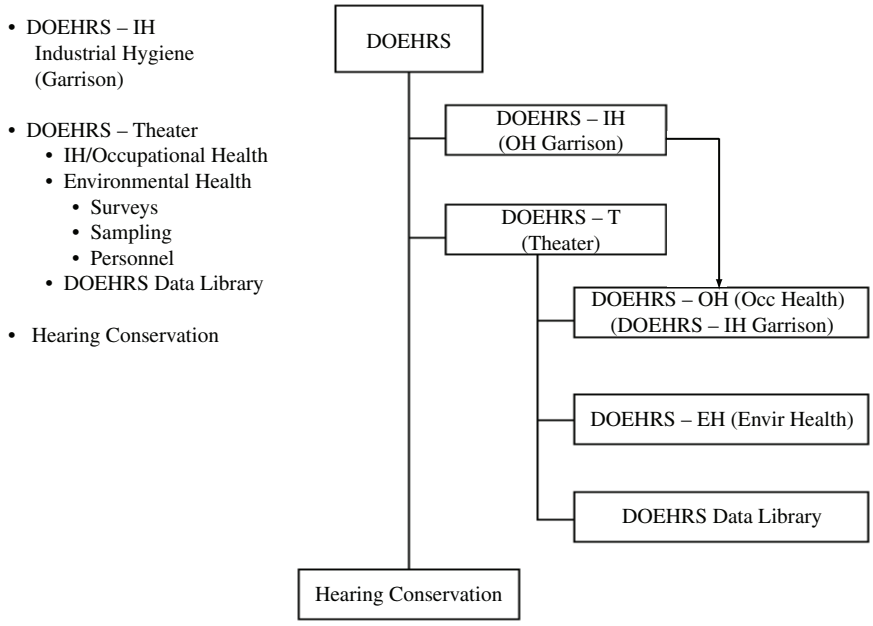

FIGURE 10-3 National Defense Occupational and Environmental Health Readiness System (DOEHRS).
SOURCE: Adapted from Heller, 2006.

According to the DOEHRS student guide,

> The Industrial Hygiene module of DOEHRS, DOEHRS [sic] is a key enabling technology within the presidentially mandated FHP and is further supported by Public Law 105-85. DOEHRS is a comprehensive, automated information system for assembling, comparing, using, evaluating, and storing occupational personnel exposure information, workplace environmental monitoring data, personal protective equipment usage data, observation of work practices data, and employee health hazard educational data. DOEHRS provides information needed by occupational health staff and command surgeons for reporting options to commanders regarding the reduction of health threats. (DoD, 2006b, ch. 1, p. 2)

DOEHRS supports the prevention of illness and injury in DoD military members and civilian employees from exposure to chemical, biological, or physical hazards. Exposures can occur throughout the continuum of military operations, such as industrial maintenance facilities, administrative offices, hospitals, aboard ship, while operating weapon systems in training

> exercises, and while deployed in war fighting or other military operations. DOEHRS prevents illness by identifying potential health hazards; providing and documenting exposures and provides recommendations to commanders, supervisors, and personnel to minimize adverse health effects; and monitoring effectiveness of procedures followed. Interface with other DOEHRS occupational health programs provides medical surveillance for early identification of exposure, treatment, rehabilitation, and follow-up to ensure that no repeated illnesses occur. (DoD, 2006b, ch. 1, p. 3)
>
> DOEHRS maintains longitudinal exposure records for individual workers in DoD. Longitudinal exposure records contain a history of predeployment, deployment, and postdeployment exposure. These records provide a baseline to facilitate postdeployment follow-up. (DoD, 2006b, ch. 1, p. 2)
>
> DOEHRS is scheduled to interface with each service's hazardous material tracking system and laboratory information management systems. DOEHRS is the occupational medicine answer for DoD's medical records system (AHLTA). . . . DOEHRS will be deployed on a Defense Information Systems Agency (DISA) platform in the DISA Defense Enterprise Computing Center Detachment in San Antonio, Texas to support the Army, Navy, Coast Guard, and other agencies. (DoD, 2006b, ch. 1, p. 3)

Initial implementation of this system includes the DOEHRS industrial hygiene module, which supports the DoD industrial hygiene exposure assessment model based on the American Industrial Hygiene Association's "Strategy for Assessing and Managing Occupational Exposures," a state-of-the-art approach developed through consensus of government, industry, and academic industrial hygienists (DoD, 2006b). The approach is applicable to assessing and managing occupational and environmental exposures associated with routine and nonroutine operations that may be encountered in-garrison and during deployment. Core to the approach is the appropriate grouping of individuals into similar exposure groups and the characterization, assessment, and control of exposures common to individuals in those groups (DoD, 2006b).

DOEHRS Implementation and Continuous Improvement

DODI 6490.3 (DoD, 1997, p. 9) set the original intent to integrate exposure records with medical records. DODI 6490.03 (DoD, 2006c, p. 28) directed that exposure data records will be integrated into individual medical records and commits DoD to accomplish the integration. DoD personnel acknowledge that this integration will be a continuous improvement effort as functionalities of DOEHRS are developed (Personal communication, C. Postlewaite et al., Department of Defense, November 21, 2006).

The current version of DOEHRS, version 1.0.5.0, includes the first iterations of the industrial hygiene and theater-focused environmental health sample management capabilities. Many additional requirements were addressed in the DoD planning and programming budget for fiscal year (FY) 2013 (POM 2008-2013).

Because DOEHRS is a platform information system for all services, DODI 6490.03 specified how integration would occur and provided standardized definitions and exclusions for compliance. Recording exposures occurring during deployment is a crucial part of the database with *deployment* defined here as "[t]he relocation of forces and materiel to desired operational areas. Deployment encompasses all activities from origin or home station through destination, specifically including intracontinental United States, intertheater, and intratheater movement legs, staging, and holding areas" (DoD, 2006c, p. 2). This definition allows for home station (in-garrison) delineation of exposure data distinct from deployment data. The use of the term *deployment* for the Navy has different connotations and consequently this instruction addresses that issue: "[s]hipboard operations that are not anticipated to involve operations ashore are exempt from the requirements of this instruction *except* for recording individual daily deployment locations or when potential health threats indicate actions necessary beyond the scope of shipboard occupational health programs or per the decision of the commander exercising operational control" (DoD, 2006c, p. 2).

DOEHRS Current Functionality

DOEHRS is being implemented step-by-step, phasing in each of its functional elements. The hearing conservation portion of DOEHRS has been functional since 1997, as directed by the DoD Instruction 6490.3. (DoD, 1997). Some industrial hygiene exposure data have been collected and entered into the system through the DoD Industrial Hygiene Exposure Assessment Model released in January 2000 (DoD Industrial Hygiene Working Group, 2000). The Navy and Air Force plan to fully implement the industrial hygiene (in-garrison) function by the end of FY 2008. This implementation includes the downloading of currently stored exposure data as applicable. The use of the DOEHRS industrial hygiene functionality for currently collected exposure data will be deployed to all Army installations by March 2007. While deployment data are currently being collected and archived, the deployment exposure data function has not been fully developed or implemented. The Army serves as the DoD lead for deployment occupational and environmental health surveillance data archives (DODI 6490.03, 2006; CJCS Memorandum MCM-0006-02, 2002, under revision). This deployment data with DOEHRS is expected to be fully completed and online in FY 2010 (POM 2008-2013).

As set out in the DoD POM 2008-2013 for DOEHRS, all anticipated requirements and functionalities for the project have been addressed. Funding support is anticipated on a fiscal year basis with new functionalities being developed and implemented on the same fiscal year basis. If fully funded as anticipated, all DOEHRS functionalities will be completed and online by the end of FY 2013. As presented by DoD representatives (Postlewaite, 2006; Personal communication, C. Postlewaite et al., Department of Defense, and reiterated during the teleconference on November 21, 2006), DOEHRS has full funding support by DoD, and DoD is fully committed to DOEHRS full implementation and triservice functioning by the end of FY 2013.

DOEHRS Effectiveness

As proposed and defined, DOEHRS will be a highly effective system for coordinating collected exposure data from both home station (in-garrison) and deployment locales. Combining the Service member's medical records with the consolidated environmental monitoring and personal exposure data in DOEHRS is key to enabling VA to provide necessary health care to these future veterans. A major problem encountered in the current VA health-care provision system is a lack of exposure data. The DOEHRS program has the potential to alleviate this lack of data. However, the data must be provided to VA to be of any use. Currently, there is no avenue to transfer these data from DoD to VA. This avenue of data transference must be developed and supported by both DoD and VA for DOEHRS to fully benefit the veteran. An agency-to-agency coordinating board between DoD and VA would be a starting point. VA is at a distinct disadvantage if it must consistently request the data from DoD.

One barrier to implementation of this system of shared exposure data is the concern that sharing some of these data may compromise the secrecy of troop locations or other combat-specific or national security issues. Although DoD classification for security purposes must be considered, there remains a need to work through this challenge for the benefit of the veteran. Although secrecy is a necessary requirement for the protection of Service members during conflict, a rapid declassification of the collected exposure data is also necessary to provide health care to Service members when needed. Furthermore, if exposure studies are conducted involving secrecy classification, VA must make their health-care providers aware of the possible adverse health effects so that presenting veterans can be properly treated.

DOEHRS, as envisioned, is a project that can greatly benefit DoD and VA when used effectively and competently by both agencies. Full funding to complete development and implementation of DOEHRS is necessary to

provide and deliver to VA the exposure data needed for the provision of health care for our nation's veterans.

USE OF HEALTH AND EXPOSURE DATA BY VA

Veteran Care and Disability Support

Overview

The Veterans Health Administration (VHA) is the largest of the three operational administrations of VA and comprises more than 200,000 employees who provide medical, surgical, and rehabilitative care via a system of over 150 hospitals and 1,000 outpatient clinics nationwide. Close to 8 million veterans were enrolled in the VA hospital system in 2005; of those, more than 5.3 million sought and received care (VA, 2006a, pp. 2, 3, 6).

The vast majority of care provided by VHA is through its network of outpatient clinics, which registered more than 57 million visits in 2005. Close to 600,000 inpatients were also treated in hospitals (VA, 2006a, p. 2).

Eligibility

Eligibility for VHA care has been codified into an elaborate hierarchy of eight levels with the first level being the highest priority for care. In this level are veterans with service-connected disabilities rated 50 percent or more or veterans determined by VA to be unemployable due to service-connected conditions (VA, 2007a, p. 2). Lower priority levels of eligibility for VHA care are a function of degree of service-connected disability and income. Importantly, by FY 2005, it was estimated that close to 80 percent of all disabled and low-income veterans had enrolled with VHA for care, and 65 percent sought care and were treated (VA, 2006a, pp. 2-3).

It is also important to note that while incurring a disability during military service is one pathway to eligibility for VA care, the care provided is not limited to that required for the qualifying disability, but rather, that needed for the total care the veteran requires. Following entry into the VA health-care system, a veteran may request an appointment with a primary care physician who can conduct a comprehensive assessment of the veteran's health-care needs.. For veterans in the first level of eligibility, the wait time for this initial appointment is supposed to be less than 30 days (VA, 2007d).

Military Service and Special Eligibility for VA Health Care

On the application form for health benefits required for entry into the VA health-care system, veterans record their service branch, dates of service, and type of discharge. Veterans are also queried about history of injury (Purple Heart awarded), presence of a service-connected disability, percentage of impairment, and a host of questions on specialized exposure opportunities including Agent Orange, radiation, and presence of illness from Gulf War service or spinal cord injury (VA, 2005b).

Seamless Transition

There has been an increased effort on the part of VA to publicize to Service members who are preparing for discharge their eligibility for VA benefits and health care (VA, 2007b). This is true for both those who have not incurred a service-related disability and those who have. A network of field-based VA employees has been sent to the larger military transfer facilities to act as onsite liaisons and offer counseling on benefit eligibility to Service members. Currently, under the seamless transition effort, VA has employees staffed at Landstuhl, Germany, and major military transfer facilities, such as Walter Reed and Eisenhower medical centers. These VA employees assist with disability claims and Service members' transfer to enrollment in the VA system. The VA Secretary also notifies every new veteran by mail of his or her potential eligibility. There is also an attempt, again in the field, when large groups of Service members are separating, to have onsite VA counselors on hand to help with the transition. However, the "seamless transition" appears to be more about communicating eligibility for care and benefits than about the transfer of medical and exposure records. With the exception of Service members who are being discharged from a military transfer facility to a local VA facility with significant residuals of traumatic injuries, the likelihood that a Service member's medical record, much less an exposure record (if one existed), seamlessly passes from DoD to the VA health-care system is remote at best.

Seamless Transfer of DoD Data to VA

The medical records system of the DoD (AHLTA) does not interface easily with VA's (VISTA) systems. Some transfer to VA of both physical and electronic records takes place, but this is generally on a case-by-case basis.

The reports from medical evaluation boards dealing with a Service member's health conditions that render him or her unfit for regular duty or requiring restricted duty (e.g., asthma, insulin-dependent diabetes) are

currently relatively crude, impairing their usefulness for decision making regarding service connectedness for VA care. This directly affects the ability of VA to determine care and benefit eligibility assessments and disability evaluations. A postdeployment electronic form—the Health Assessment Form—is under development and uses the Federal Health Information Exchange to transfer information in one direction, between DoD and VA. The plan is to use the Federal Health Information Exchange (FHIE) to allow two-way data transfer (Do, 2006), though currently it provides only for unidirectional flow of information from DoD to VA. The plan is for the FHIE to evolve into the Clinical Health Data Repository (CHDR).

EPIDEMIOLOGIC STUDIES OF VETERANS

Introduction

Epidemiologic studies on the adverse health effects of military service in veterans have covered exposures that have occurred in essentially every war in which U.S. Service members have been deployed, beginning with World War I. Although the largest group of these studies has been carried out in some fashion through VA, some have been supported through the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and other funding organizations. In this section, we review the breadth of these studies with a view to understanding the sources of data and the sources of funding. In this way, it is hoped that insights can be gained that might recommend preferred, or even alternative, approaches to carrying out epidemiologic studies on the health of veterans to inform the compensation and disability decision-making process. It is not the primary purpose of this chapter to review these studies with a view to assessing the validity of their findings.

VA has carried out and been involved in many epidemiologic studies addressing the health of veterans. Here we provide an overview of studies that specifically deal with veterans' health in relation to actual or suspected exposures that occurred while they were serving in the U.S. military.

Department of Veterans Affairs Epidemiologic Studies

Veterans Health Administration (VHA) Studies

The VHA funds research studies through its Office of Research and Development. A broad range of health-related studies is supported, including clinical, basic science, and epidemiologic studies. Epidemiologic studies include those on the effects of wartime exposures on veterans' health, including studies on recently returning Service members. For example, in

2005 the Office of Research and Development announced an invitation for research proposals on combat casualty neurotrauma (VA, 2005a), and in 2006 it announced an invitation for research proposals on health studies of veterans returning from Afghanistan and Iraq (VA, 2006b). Other research surveillance activities sponsored by VA include the establishment of several registries. In 2003, the Office of Research and Development created a national registry of veterans with amyotrophic lateral sclerosis to track the health status of veterans with the disease and help recruit research participants (VA, 2003). Strategic planning for VHA-funded research is carried out by the Field Research Advisory Committee.

Two centers for the study of war-related illnesses were established in VA medical centers in 2001, one in Washington, D.C., and one in East Orange, New Jersey. Initially known as the Centers for the Study of War-Related Illnesses, these were subsequently renamed the War-Related Illness and Injury Study Centers (WRIISC). Both have clinical and research responsibilities (VA, 2006c).

The largest and undoubtedly the most substantial body of research on health effects of returned veterans has been carried out by Dr. Han K. Kang and his colleagues at the Environmental Epidemiology Service at the VHA in Washington, D.C., which is now part of the Washington, D.C., WRIISC. Dr. Kang has carried out studies of veterans in the following broad areas: mustard gas exposure, prisoners of war, radiation exposure, Vietnam veterans, Gulf War veterans, and women veterans. A bibliography of Dr. Kang's epidemiologic studies is included in Appendix K-1, organized by these subject areas.

Twin Registry Studies

In 1958, the Medical Follow-Up Agency, with funding by NIH and VA, began a project to identify white male twin pairs who had been in military service during World War II (The National Academy of Sciences [NAS]/National Research Council [NRC] Twin Registry of WWII Military Veteran Twins [SOURCE: http://www.iom.edu/CMS/3795/4907.aspx]). Using state birth records, searches were made by hand against VA files to determine veteran status. Eventually, nearly 16,000 twin pairs were identified. Baseline data were abstracted from VA and military records and a baseline questionnaire was mailed to the twin pairs. Anthropometric and fingerprint data were used to determine zygosity (IOM, 2004b).

A bibliography of research studies based on this NAS/NRC twin registry can be found at http://www.iom.edu/CMS/3795/4907/17038.aspx. A total of 308 published research studies and 7 research reports are based on this registry.

The Vietnam Era Twin (VET) Registry The VET registry was created by VA in the mid-1980s in response to concerns regarding the health effects specifically of exposure to Agent Orange (Goldberg et al., 2002). The registry was built using DoD computerized records and consists of 7,369 male-male twin pairs born between 1939 and 1957, who served from 1965 to 1975 (VA, 2007e). It is now housed in the Seattle Epidemiological Research and Information Center, a joint venture of the Department of Epidemiology at the University of Washington's School of Public Health and Community Medicine and VA (VA, 2007c). Approximately half of the twins are monozygotic, and half are dizygotic (Henderson et al., 1990). Table 10-3 details the research studies that have been completed using the VET registry, or are currently underway.

National Academies' Monographs on Veterans' Health by Theater or Exposure

The National Academies has produced a large number of monographs on veterans' health dealing with exposures during military service dating back to WWI (Table 10-4). These provide useful summaries, assessments, and updates of scientific findings based on studies completed before the publication of each monograph. It is evident that the more recent the exposure, the larger the number of monographs devoted to it.

Non-VA Epidemiologic Studies of Veterans' Health

The Millennium Cohort Study

The Millennium Cohort Study is the largest prospective study of military personnel ever conducted. Sponsored by DoD, and recommended by the IOM Committee on Measuring the Health of Gulf War Veterans (IOM, 1999a, p. 6), the study was initiated in 2001 to evaluate the long-term health effects of military service, particularly operational deployment. More than 110,000 people are enrolled currently, and a total of 140,000 are expected to be enrolled by the end of study recruitment in 2007. Study participants will complete a paper or Web-based questionnaire assessing demographics, medical conditions and symptoms, and health-related behaviors once every 3 years until 2022. Survey data will be linked with data from other military databases on deployment, occupation, vaccinations, health-care utilization, and disability. It is hoped that the cohort data will serve as a foundation upon which additional epidemiologic studies of military personnel might develop, in addition to revealing trends in veterans' health over time (Gray et al., 2002; The Millennium Cohort Study, 2007).

TABLE 10-3 Summary of VET Registry Projects

Study Name	Method of Recruitment	Recruitment Period	Number of Participants	Twin Pairs
Registry construction				
Military Records	Record abstracts	1983-1986	14,750	7,375
Studies of the full registry				
Survey of Health	Mail/telephone follow-up	1987	10,979	4,774
NHLBI VET Study of Cardiovascular Disease	Mail/telephone follow-up	1990	8,169	3,698
Harvard Twin Study of Drug Abuse and Dependence	Telephone	1991-1993	10,979	3,698
Male Health Survey	Mail	1999	5,349	1,615
Studies of selected twins				
Impulsivity and aggression	Mail/telephone follow-up	1992	796	314
Consequences of drug abuse	In-person	1995-1996	254	127
Alcohol and health services use	Telephone	1995	2,936	
Biologic markers for	In-person	1995-1998	322	161
posttraumatic stress disorder (PTSD)	Telephone	1995-1996	2,003	322
Alcohol vulnerability	In-person	1997-1999	760	380
PTSD Sleep study	In-person	Ongoing	11/22	9
	Telephone		207/248	248
Twin-family study of health behaviors	Telephone and mail	Ongoing	533	214
PTSD MRI study 1	In-person	Ongoing	48	45
PTSD MRI study 2	In-person	Ongoing	52	
New studies of selected twins pathological gambling				
Spirituality and PTSD	Mail	Newly funded 2006	510	255
Cardiovascular disease and depression	Mail	Newly funded 2006	320	160
Twins as parents	Telephone and mail	Newly funded 2006	1,060	530

SOURCE: Adapted from VA, 2007c.

TABLE 10-4 National Academies' and VA Medical Monographs on Veterans' Health by Theater or Exposure

Mustard gas exposure	IOM. 1993. *Veterans at risk: The health effects of mustard gas and lewisite.*
Prisoners of war	VA Medical Monographs. 1954. *A follow-up study of World War II prisoners of war* (Cohen and Cooper, 1954). IOM. 1992. *The health of former prisoners of war: Results from the Medical Examination Survey of Former POWs of World War II and the Korean Conflict.*
Other WWII	VA Medical Monographs. 1955. *Tuberculosis in the Army of the United States in World War II.* (Long and Jablon, 1955). VA Medical Monographs. 1961. *A follow-up study of head wounds in World War II* (Walker and Jablon, 1961).
Radiation exposure	NRC. 1985. *Studies of participants in nuclear tests* (Robinette et al., 1985). IOM. 1995a. *Adverse reproductive outcomes in families of atomic veterans: The feasibility of epidemiologic studies.* IOM. 1996b. *Mortality of veteran participants in the CROSSROADS nuclear test.*
Vietnam veterans	IOM. 1994. *Veterans and Agent Orange: Health effects of herbicides used in Vietnam.* IOM. 1996b. *Mortality of veteran participants in the CROSSROADS nuclear test.* IOM. 1997. *Characterizing exposure of veterans to Agent Orange and other herbicides used in Vietnam: Scientific considerations regarding a request for proposals for research.* IOM. 1999c. *Veterans and Agent Orange: Update 1998.* IOM. 2000d. *Veterans and Agent Orange: Herbicide/dioxin exposure and type 2 diabetes.* IOM. 2001b. *Veterans and Agent Orange: Update 2000.* IOM. 2002. *Veterans and Agent Orange: Herbicide/dioxin exposure and acute myelogenous leukemia in the children of Vietnam veterans.* IOM. 2003a. *Characterizing exposure of veterans to Agent Orange and other herbicides used in Vietnam: Interim findings and recommendations.* IOM. 2003b. *Characterizing exposure of veterans to Agent Orange and other herbicides used in Vietnam: Final report.* IOM. 2003d. *Veterans and Agent Orange: Update 2002.* IOM. 2004c. *Veterans and Agent Orange: Length of presumptive period for association between exposure and respiratory cancer.* IOM. 2005b. *Veterans and Agent Orange: Update 2004.*

TABLE 10-4 Continued

Gulf War veterans	IOM. 1995b. *Health consequences of service during the Persian Gulf War: Initial findings and recommendations for immediate action.*
	IOM. 1996a. *Health consequences of service during the Persian Gulf War: Recommendations for research and information systems.*
	IOM. 1998a. *Adequacy of the VA Persian Gulf Registry and Uniform Case Assessment Protocol.*
	IOM. 1998b. *Measuring the health of Persian Gulf veterans: Workshop summary.*
	IOM. 1999a. *Gulf War veterans: Measuring health.*
	IOM. 2000a. *The five series study: Mortality of military participants in U.S. nuclear weapons tests.*
	IOM. 2000b. *Gulf War and health, volume 1: Depleted uranium, pyridostigmine bromide, sarin, vaccines.*
	IOM. 2001a. *Gulf War veterans: Treating symptoms and syndromes.*
	IOM. 2003c. *Gulf War and health, volume 2: Insecticide and solvents.*
	IOM. 2004a. *Gulf War and health: Updated literature review of sarin.*
	IOM. 2005a. *Gulf War and health, volume 3: Fuels, combustion products, and propellants.*
	IOM. 2006. *Gulf War and health, volume 4: Health effects of serving in the Gulf War.*
	IOM. 2007. *Gulf War and health, volume 5: Infectious diseases.*

CDC-Funded Studies

The CDC and its National Center for Environmental Health has supported studies on veterans of Vietnam (SOURCE: http://www.cdc.gov/nceh/veterans/default1.htm) and the Gulf War (SOURCE: http://www.cdc.gov/nceh/veterans/default2.htm). Relating to Vietnam, CDC supported the following studies:

- Vietnam Experience Study
- Postservice Mortality Among Vietnam Veterans Study
- Agent Orange Validation Study
- Selected Cancers Study

On the Gulf War, CDC funded the following studies:

- Health Effects of Exposure to Smoke from Oil Well Fires
- Birth Defects
- Air Force Study
- Health Assessment of Gulf War Veterans from Iowa
- Iowa Asthma Follow-Up Study
- Cognitive Function and Symptom Patterns in Gulf War Veterans

- Defining Gulf War Illness
- Epidemiologic Study of the Occurrence of Amyotrophic Lateral Sclerosis (ALS) among Gulf War Veterans
- Deployment to the Gulf War and Subsequent Development of Cancer

Of these CDC-funded studies, the Vietnam Experience Study was arguably the most influential. A random sample of 7,924 men who enlisted in the period from 1965 to 1971 and who served in Vietnam, and 7,364 non-Vietnam veterans, were interviewed by telephone. Vietnam veterans reported more health problems than non-Vietnam veterans, including less fertility and more health problems in their children. An in-person, comprehensive health evaluation was done on a random subsample of 2,490 Vietnam veterans and 1,972 non-Vietnam veterans. Although the vast majority of comparisons showed no differences, results of this examination showed more hearing loss, lower sperm concentrations, and more depression, anxiety, and PTSD in Vietnam veterans. Offspring of Vietnam veterans did not show increased birth defects (see Appendix K-3) (CDC VES, 1989).

NIH-Funded, Individual Investigator Studies

The NIH has funded a large number of health studies involving veterans through its several research funding mechanisms, and has also collaborated with VHA and CDC in providing funding for research on veterans. Relatively few NIH studies focus on investigating the role of military exposures in disease. Many use a population sample of veterans to gain mechanistic insight into diseases affecting the general population. Others evaluate effectiveness of disease treatment. NIH-funded studies that are relevant to the assessment of military exposure effects are listed in Appendix K-4 by title and year funding was begun.

Observations and Recommendations on Epidemiologic Studies of Veterans

Clearly a large number of epidemiologic studies on health effects of military exposure in veterans have been completed over the years. Many continue to be performed, reflecting the ongoing military engagements in Iraq and Afghanistan. There has been a near-exponential increase in the number of completed health studies and IOM reports in relation to the proximity in time of the specific engagement.

Although the scientific information on military exposures and subsequent health status is extensive, some exposures of concern remain inadequately studied or the relevant studies on these exposures have yielded findings that are inconclusive. It is acknowledged that there may be obsta-

cles to performing rigorous observational studies on the veteran population. Nevertheless, there are at least three other potential reasons for some of the inadequacy in the scientific information: (1) there has been no effective organized approach to setting research priorities; (2) exposure information and exposure metrics are relatively crude for most exposure-disease combinations of interest; and (3) there is no standardized, comprehensive, universal, and accessible source of information on veteran's health outcomes.

Two complementary options for improving the utility of this health research in strengthening the scientific foundations for veterans' compensation are (1) establishing a body that is responsible for strategically managing the research agenda on veterans and military exposures, and (2) developing and maintaining a repository of research on veterans' health to allow an overview of research supported by various funding agencies. Suggestions to facilitate carrying out these studies and to allow more rigorous study of exposure health effects center on exploiting the exposure and health information systems described above. This would require more centralized data storage and improved data access.

VA REGISTRIES

Another public health surveillance tool that can be used to collect and organize health status data of a specific population is a registry. "A registry is an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects" (SOURCE: From FAQ on Public Health Registries: www.ncvhs.hhs.gov/9701138b.htm).

Registry data offer a number of valuable uses in public health and medicine, "including estimating the magnitude of a problem," "determining the incidence of disease," "examining trends of disease over time," "identifying groups at high-risk," estimating health service needs, and "conducting research" (SOURCE: www.ncvhs.hhs.gov/9701138b.htm). For some groups of veterans, surveillance could be extended to intermediate markers, such as indicators of physiological functioning, so that adverse effects of exposures could be detected before the level of impairment became sufficient to produce a diagnosed disease. For example, in personnel exposed to respiratory hazards, lung function could be tracked over time to detect a rate of loss beyond that expected on the basis of aging alone.

Registries collect data on individuals who share certain characteristics, typically a specific disease or condition. This information includes demographic and medical information. Registries often seek validation of the

data by collecting detailed test results (such as a pathology report from a biopsy or a specific blood test result).

More recently, the registry concept has been applied to follow groups of people who do not share a common disease, but rather, a common exposure history. Examples here would include the National Exposure Registry operated by the Agency for Toxic Substances and Disease Registry (ATSDR), part of CDC. This registry identifies and enrolls persons likely to have been exposed to hazardous environmental toxicants, usually due to the location of the person's residence near a contaminated Superfund site. The registry establishes a pool of persons, potentially at increased risk of health harm, and allows tracking of this group. This tracking enables subsequent contact of the registered persons by health authorities, who may offer health information, opportunities for study participation, or care recommendations. The course of the registrant's health may also be followed over time through periodic surveys performed by the registry (ATSDR, 2003).

VA has used the public health registry concept to identify and track several different groups of veterans. It operates registries that are both disease based, such as the multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) registries, and those that are exposure based, such as the Agent Orange and Gulf War registries (see Table 10-5).

Summary of Important Findings and Recommendations

DoD and VA are clearly intent on improving the breadth, depth, and availability of health and exposure data. In addition, there are numerous examples of those data being used to better understand Service member and veteran health and its relationship to exposures. Suggestions follow for ensuring that the data improvements are fully realized and the data fully utilized in Service member–veteran disease prevention and treatment in well-conceived and coordinated surveillance and research efforts and in compensation adjudication and presumptive decision-making. Many of these recommendations are also found in the Committee's overall recommendations in Chapter 13. The Committee presents these suggestions here to tie back into the specific lessons learned from an assessment of the military personnel's and veterans' health and exposure data infrastructure.

1. Ensure that DOEHRS is implemented as planned.

DOEHRS is a major undertaking that has potential for dramatically increasing the availability of exposure data. However, DoD has many important priorities and short-term funding pressures have the potential to delay implementation activities. Due to the importance of these efforts for both DoD and VA, we recommend that additional steps be taken to ensure that DOEHRS is fully implemented as planned. In addition, due to the

importance of adequately trained individuals to the success of DOEHRS, we further recommend that these steps specifically include detail on the training of individuals needed to make the accurate professional judgments and generate appropriate exposure data critical to DOEHRS. These additional steps are as follows:

1. Include a specific DoD budget line item for DOEHRS that includes funding for system development and enhancement, system implementation, and training of personnel.
2. Develop clear metrics for tracking the effective deployment and utilization of DOEHRS throughout DoD.
3. Require an annual status report to Congress on DOEHRS development and implementation progress and related training activities.

2. Improve the interface between the electronic health record data systems used by DoD and VA—including capabilities for handling individual exposure information that is included as part of a Service member's health record.

While there are efforts underway to electronically transfer Service member health records from DoD to VA, these efforts are moving slowly and the timeline for completion of a seamless interface is unclear. DoD and VA should increase attention to this effort with a clear integration plan, timetable for implementation, metrics for tracking implementation progress, and annual reporting of metric results.

To date, there has been little discussion regarding the electronic transfer of Service member exposure information to VA. As the inclusion of exposure data in employee health records is a key DoD strategy for ensuring that exposure information is available for individual Service members, this seems a major disconnect. DoD and VA should explicitly include the integration of these individual exposure data into the health record transfer integration plan, implementation timetable, metrics, and annual reporting. Reports on progress of these plans should be included in the annual report to Congress on DOEHRS progress.

3. Develop an interface that allows the VA to access the electronic exposure data systems used by DoD.

DoD is investing heavily in DOEHRS and other improved exposure data systems that are standardized across the various armed services. In our interviews with people responsible for development and deployment of these systems we did not encounter anyone with knowledge of activities by DoD or VA to develop a VA interface with these systems that will allow use of the Service member-specific and longitudinal exposure data by VA.

TABLE 10-5 VA Health Registries

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
Agent Orange Registry[a] (Started in 1978) Managed by the Environmental Agents Service To identify medical problems associated with Agent Orange exposure	408,811 400,849 men 7,962 women	Service in Vietnam, Korea, or otherwise exposed	Dates, areas of service, possible Agent Orange exposure, birth defect data	Purely voluntary; data from Agent Orange Registry exams; veterans are well informed of the existence of registry exams

Data Collected	Selected Publications from Registry
Demographics: Race/ethnicity; martial status; gender; current military status; branch of service; service in either/or Vietnam or Korea; dates of last two periods of service if other than Vietnam or Korea; full medical history, including information about the family, occupation, social history noting tobacco, alcohol, and drug use; civilian exposure to possible toxic agents; psychosocial history	Bullman TA, Kang HK. 1994. Posttraumatic stress disorder and the risk of traumatic deaths among Vietnam veterans. Journal of Nervous and Mental Disorder 182:604-610. Bullman TA, Watanabe KK, Kang HK. 1994. Risk of testicular cancer associated with surrogate measures of Agent Orange exposure among Vietnam veterans on the Agent Orange Registry. Annals of Epidemiology 4:11-16.
Medical history: Assessment of own health; date of registry examination; complaints/symptoms (coders are asked to enter ICD-9 codes on form); chest X ray (if determined to be medically necessary); complete blood count; comprehensive metabolic panel or blood chemistries and enzyme studies; urinalysis; hepatitis C screening	Bullman TA, Kang HK, Thomas TL. 1991. Posttraumatic stress disorder among Vietnam veterans on the Agent Orange Registry: A case control analysis. Annals of Epidemiology 1:505-512.
Exposure: Exposure to Agent Orange (definitely yes, not sure, definitely no); handling or spraying Agent Orange; not directly sprayed but in a recently sprayed area; exposed to herbicides other than Agent Orange; directly sprayed with Agent Orange; ate food/drink that could have been sprayed with Agent Orange	

continued

TABLE 10-5 Continued

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
Gulf War Registry[b] (Started in 1992) Managed by the Environmental Agents Service To identify medical problems associated with exposures in the Persian Gulf	97,002 87,074 men 9,928 women	Service in SW Asia (1990 to present) Operation Enduring Freedom (OEF) veterans not included because they are in Afghanistan	Exposures of concern, combat experiences, birth defect data	Purely voluntary; data from Gulf War Registry exams

Data Collected	Selected Publications from Registry
Demographics: Race/ethnicity; marital status; gender; occupation; current military status; branch of service; military service in Persian Gulf area; dates and MOS of last two periods of service	Miller R, Costigan, Young H, Kang H, Salager N, Crawford H, Page W, Thaul S. 2006. Patterns of health care seeking of Persian Gulf War Registry members prior to deployment. Military Medicine 171:370-375.
Medical history: Family history; occupational history; social history including tobacco, alcohol, drug use; civilian exposure(s) history to possible toxic agent; psychosocial history; military service in Persian Gulf area; dates and military occupational specialty (MOS) of last two periods of service	Gray GC, Gackstetter GD, Kang HK, Graham JT, Scott KC. 2004. After more than 10 years of Gulf War veteran medical evaluation, what have we learned? American Journal of Preventive Medicine 26:443-452. Hallman WK, Kipen HM, Diefenbach M, Boyd K, Kang H, Leventhal H, Wartenber D. 2003. American Journal of Public Health 93:624-629.
Medical history: Psychosocial conditions; review of systems; complaints and symptoms (coders asked to include ICD-9 codes on form); time of onset of the symptoms or conditions; intensity; degree of physical incapacitation; details of any treatment received; complete blood count; blood and serum screening tests; urinalysis; pulmonary function, sperm counts, or other diagnostic studies if medically indicated	Smith TC, Smith B, Ryan MA, Gray GC, Hooper TI, Heller JM, Dalager NA, Kang HK, Gackstetter GD. 2002. Ten years and 100,000 participants later: Occupational and other factors influencing participation in US Gulf War health registries. Journal of Occupational and Environmental Medicine 44:758-768. Murphy FM, Kang HK, Dalager NA. 1999. The health status of Gulf War veterans: Lessons learned from the Department of Veterans Affairs health registry. Military Medicine 164:327-331. Kipen HM, Hallman W, Kang HK, et al. 1999. Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry veterans. Archives of Environmental Health 54:313-318.

continued

TABLE 10-5 Continued

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
Gulf War Registry (continued)				
Ionizing Radiation Registry[c] (Started in 1986) Managed by the Environmental Agents Service To identify medical problems associated with ionizing radiation exposure	23,624 23,472 men 152 women	Set up for WWII and Cold War veterans Service in Hiroshima and Nagasaki, gaseous diffusion plants, and area K25 in United States; nuclear weapons testing	Receipt of nasopharyngeal treatment, birth defect data, diagnoses if possible radiogenic-related diseases, disability claims	Purely voluntary; data from Ionizing Radiation Registry exams
ALS Registry Managed by the Epidemiologic Research and Information Center in Durham, NC To identify and characterize veterans with ALS	1,602	Diagnoses of ALS within VA health-care system and self-referrals	Health-care utilization, ALS Functional Rating Scale every 6 months	Data from existing VA files and self-referrals; a consecutive registry

Data Collected	Selected Publications from Registry
Exposure: Exposure to environmental factors (smoking cigarettes, years of smoking cigarettes, number of packs smoked per day, years smoked); while in the Gulf exposure to smoke from oil fires, fumes from tent heaters, cigarette smoke (passive from others), diesel and/or other petrochemical fumes, and burning trash/ feces; skin exposure to diesel; chemical agent-resistant compounds; other paint or solvent and/or petrochemical substances; depleted uranium; microwaves; personal pesticide use; nerve gas or other nerve agent	Gray GC, Hawksworth AW, Smith TC, Kang HK, et al. 1998. Gulf War veterans' health registries. Who is most likely to seek evaluation? American Journal of Epidemiology 148:343-349. Blanck RR, Hiatt J, Hyams KC, Kang HK, et al. 1995. Unexplained illnesses among Desert Storm Veterans: A search for causes, treatment, and cooperation. Archives of Internal Medicine 155:262-268.
Demographics: Family; occupation; tobacco, alcohol, and drug use	
Medical History: Psychosocial conditions; time of the onset of the veteran's symptoms or conditions; intensity of symptoms or conditions; degree of physical incapacitation; details of any treatment received; chest X ray (if medically necessary), complete blood count; basic metabolic panel and comprehensive metabolic panel or equivalent blood chemistries and enzyme studies; urinalysis	
	Kasarkis EJ, Dominic K, Oddone EZ. 2004. The National Registry of Veterans with Amyotrophic Lateral Sclerosis: Department of Veterans Affairs Cooperative Studies Program (CSP). Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders 5(Supplement 1):129-132.

continued

TABLE 10-5 Continued

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
MS Registry (Started in 1998) Managed by the MS Center of Excellence East in Baltimore, MD, and the MS Center of Excellence West in Portland, OR, and Seattle, WA, to identify and characterize veterans with MS	31,946	Diagnoses of MS within the VA health-care system	Health-care utilization, health economic data	Data from existing VA files; a consecutive registry
Cancer Registry (Started in 1995) Managed by the Program Office for Oncology in Washington, DC To identify and characterize veterans with cancer, analysis of specific therapies and outcomes, and resource allocation	356,174	Diagnoses of cancer within the VA health-care system	Possible cancer risk factors, cancer identification, prognosis factors, treatment data, follow-up, and recurrence	Compilation of cancer registries at each VA facility; a consecutive registry

Data Collected	Selected Publications from Registry
	Culpepper WJ, Mhrmantraut M, Wallin MT, Flannery K, Bradham DD. 2006. Veteran Health Administration multiple sclerosis surveillance registry: The problem of case-finding from administrative databases. Journal of Rehabilitation Research and Development 43(1):17-24.

continued

TABLE 10-5 Continued

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
HIV Registry (Started in 1983) Managed by the Center for Quality Management in Public Health in Palo Alto, CA To track overall trends in HIV-related outcomes, health-care utilization planning, quality improvement of care	54,000	Diagnoses of HIV within the VA health-care system	Possible risk factors, lab results, pharmacy use	Data from existing VA files; a consecutive registry
Hepatitis C Registry (Started in 1996) Managed by the Center for Quality Management in Public Health in Palo Alto, CA To track overall trends in hepatitis C-related outcomes, health-care utilization planning, quality improvement of care	253,160	Diagnoses of hepatitis C within the VA health-care system	Liver biopsy data, lab results, pharmacy use	Data from existing VA files; a consecutive registry

Data Collected	Selected Publications from Registry

continued

TABLE 10-5 Continued

Registry Management Purpose	Number of Veterans	Basis for Enrollment	Source of Data	Type of Data
Depression Registry (Started in 2001)[d] Managed by the Serious Mental Illness Treatment, Research, and Evaluation Center in Ann Arbor, MI To identify and characterize veterans with depression; monitor and evaluate care	690,867 (in FY 2005)	Diagnoses of depression within the VA health-care system	Health-care utilization, Global Assessment Functioning Scores, medication use, health-care costs	Data from existing VA files; an annual registry
Psychoses Registry[e] (Started in 1988) Managed by the Serious Mental Illness Treatment, Research, and Evaluation Center in Ann Arbor, MI To identify and characterize veterans with psychoses; monitor and evaluate care	239,304 (in FY 2005)	Diagnoses of psychoses within the VA health-care system	Healthcare utilization, Global Assessment Functioning Scores, medication use, health-care costs	Data from existing VA files; a consecutive registry

[a] More information can be found at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=77.
[b] More information can be found at http://www.vethealth.cio.med.va.gov/Pubs/1303.2GWHB-05.pdf.
[c] More information can be found at http://www1.va.gov/irad/docs/IRADHANDBOOK012006.PDF.

Data Collected	Selected Publications from Registry
Demographics: Age, gender; race/ethnicity; marital status; VISN analyses; service connection; VERA patient class, homelessness, access to medical care Medical History: Inpatient and outpatient services uses; medication and services use; health-care costs; primary care treatment; mortality; psychiatric comorbidities (depression alone or depression with an anxiety disorder other than PTSD); depression and substance abuse; depression and PTSD; other complicated depression; medical comorbidities (peripheral vascular disease, chronic obstructive pulmonary disease, diseases of the digestive system, liver disease, genitourinary symptoms, arthritis, injury and poisoning); Global Assessment of Functioning (GAF)	
Demographics: Age, gender, race; martial status Medical History: Pharmacy and medical services use; cost; diagnoses (total, schizophrenia, bipolar, other); GAF scores; mortality; VERA patient class; homelessness; service connection; access to health care; inpatient psychiatric care; inpatient rehabilitation; inpatient domiciliary care; inpatient nursing home care; outpatient care	

[d] More information can be found at http://www.hsrd.ann-arbor.med.va.gov/documents/2002NARDEP.pdf.
[e] More information can be found at http://www.hsrd.ann-arbor.med.va.gov/documents/3rdAnnual_psychosisVHA.pdf.
SOURCE: Derived from [a] DoD/VHA, 2000; [b] DoD/VHA, 2005; [c] DoD/VHA, 2006; Kang, 2006; [d] SMITREC, 2002; [e] SMITREC, 2001.

VA should move quickly to develop plans for interfaces to these new DoD exposure data systems. This should not require massive new data systems within VA but instead consist of appropriate interfaces and views to the data within DoD systems that are accessible by the VA. The first step would be a VA team embedded with DoD implementation team at the Army's CHPPM where they can examine the system capabilities and data structures so that appropriate interfaces can be defined and developed to meet the needs of VA.

Recommendation: Conduct a critical evaluation of Gulf War troop tracking and environmental exposure monitoring data so that improvements can be made in this key DoD strategy for characterizing exposures during deployment.

Characterizing exposures during intense combat deployment scenarios is the most challenging aspect of DoD's efforts to characterize Service member exposures throughout their military service. An important part of the current strategy is a combination of troop tracking and environmental monitoring such that overlaying of troop location with the location of environmental monitoring results will enable the characterization of troop exposures. The success of this approach depends directly on the detail of both the troop tracking and the environmental monitoring. More frequent measurement and recording of troop location coupled with more frequent (e.g., time and location) environmental exposure monitoring will allow more accurate characterization of individual exposures. The current goal is to record troop location at least once every 24 hours. Minimal environmental monitoring requirements are less clear. In particular, monitoring during shorter deployments (less than 30 days) may be sporadic as requirements vary depending on the predeployment risk assessment, the availability of appropriate medical personnel, and the commander's discretion (DOD Instruction 6490.03 [DoD, 2006c]).

DoD should undertake a detailed review of this strategy using data from the Gulf War and subsequent deployments in Afghanistan and Iraq to determine limitations to the current approach and identify opportunities for improvement. The review should consist of the formation of exposure matrices for a group of randomly selected Service members who served in that theater using data available on troop location, environmental measurements, and exposure data in individual health records. Gaps in those exposure matrices should then be examined to identify data limitations so that strategies can be developed for future approaches that minimize those limitations.

4. Develop DoD policy to ensure that classification/declassification (secrecy) issues are managed appropriately for both DoD and the veteran.

There are clearly times when national security or mission success depends on maintaining secrecy regarding certain aspects of a Service member's military experience. However, every effort should be made to find mechanisms for characterizing Service member exposure and health histories in manners that do not interfere with the broader issues of national security or mission success. DoD should develop procedures that ensure full or partial declassification of sensitive information for the timely provision of that Service member's or veteran's health care. When such declassification is not possible, DoD should establish procedures whereby blinded data relevant to the Service member's health and exposure history are provided.

In some instances where national security and secrecy issues cannot be resolved, DoD and VA may need to establish mechanisms involving experts with appropriate security clearances to monitor affected registry cohorts for potential health outcomes and define surveillance or research activities that may need to be conducted within appropriate secrecy clearances. An interagency agreement could be developed between DoD and VA addressing the secrecy issue. Since both agencies have used the classification system in the past this agreement would address the policy development process and the exchange of classified information between the two agencies. The process would include establishment of a joint DoD-VA board comprised of individuals who have sufficient security clearance to discuss classified data. The access to classified information process would be contained in a written document outlining a mechanism to identify, monitor, track, and medically treat individuals who were part of research activities involving human subjects and whose research design and results have been classified.

Recommendation: Establish registries of Service members and veterans based on exposure, deployment, and disease histories.

Recommendation: DoD and VA should establish and implement mechanisms to identify, monitor, track, and medically treat individuals involved in research and other activities that have been classified and are secret.

5. Strengthen the assessment of psychological stressors and symptoms.

Psychological and combat-related stressors may detrimentally impact the long-term mental and emotional well-being of military personnel and should be thoroughly assessed at key points during the military career of men and women. Currently, basic clinical evaluations for neurological and psychiatric disorders are made at accession, after training, and throughout

the service career. Very brief structured assessments for some psychiatric symptoms occur during the post-deployment periods only.

Assessment of exposure to combat and of psychological stress during deployment is a particularly challenging element of the Committee's proposed approach to tracking factors influencing the health of veterans. Scales have been developed to assess exposures during combat and the validity and reliability of these instruments has been assessed (Friedman et al., 1986; Janes et al., 1991; Keane et al., 1989; Laufer et al., 1984; Lund et al., 1984; Wessely et al., 2003). These instruments have been used in investigations of Vietnam veterans (Buydens-Branch et al., 1990; Frueh et al., 2005; Green et al., 1989; Yehuda et al., 1992) and more recently for personnel deployed in Iraq and Afghanistan (Hoge et al., 2004). A 2004 study carried out by military investigators addressed mental health problems and combat duty in personnel deployed to Iraq and Afghanistan (Hoge et al., 2004). This study demonstrates the feasibility of investigations directed at troops in relation to combat deployment. A follow-up study of Vietnam veterans, the National Vietnam Veterans Readjustment Study, incorporated an exposure measure based on military records (Dohrenwend et al., 2006). Onset of posttraumatic stress disorder (PTSD) was associated with combat exposure, with evidence for a positive close-response relationship.

These studies show that combat exposure and related stress can be measured. They also show the feasibility of informative research on neuropsychiatric disorders among veterans. Further development will be needed to achieve the type of surveillance proposed by the Committee.

Psychiatric disorders, particularly PTSD, depression, and alcohol abuse and dependence are common. More data systematically collected using validated and structured instruments pre- and post-deployment will aid DoD and the VA to better identify stressors that may predispose individuals to develop these disorders, identify Service members to whom early intervention should be provided, and track individuals exposed to emotional trauma and with psychiatric symptoms in specialized registries.

A number of brief validated instruments are available for PTSD, major depression, and alcohol abuse and dependence—three common psychiatric disorders experienced by veterans. A dedicated, face-to-face interview by an experienced clinician, recognized to be the most valid method of assessing PTSD, is likely not feasible in the post-deployment or separation/retirement medical evaluations. While a host of instruments are available for assessing PTSD, realistically the only feasible instruments that might be useful in this context would be one of several available screening questionnaires. These include (1) the 4-question Primary Care PTSD Screen (Prins et al., 2003), (2) a 7-question scale keyed to the DSM-IV criteria for PTSD (Breslau et al., 1999), (3) the 17-question PTSD Symptom Scale Self-Report (Coffey et al., 1998), (4) the Screen for Posttraumatic Stress Symptoms (Carlson, 2001),

and (5) the PTSD subscale of the large Psychiatric Diagnostic Screening Questionnaire (Zimmerman and Mattia, 2001). Only the first of these, the Primary Care PTSD Screen, has been validated on combat veterans. Also, while these screening instruments may be useful in identifying veterans who may have PTSD, they are not adequate for diagnosing PTSD.

There are also a host of screening instruments for major depression including the 2 item Prime-MD, the 9 item Patient Health Questionnaire, and the 20 item Centers for Epidemiological Studies Depression (CES-D) scale, among others. Alcohol abuse and dependence can be screened with a number of instruments including the RAPS-QF, the AUDIT, and the CAGE, among others. These instruments vary in length and sensitivity and specificity in different populations.

Studies that employ these screening instruments for prospective research will need to account for some degree of misclassification of the health outcome. In spite of these shortcomings, data from a screening instrument on an unselected population of veterans obtained in a systematic manner would be very valuable for the type of prospective studies envisioned in this report to better understand service-related morbidity.

6. Establish registries of Service members and veterans based on exposure, deployment, and disease histories.

The Committee recommends that VA and Congress consider the initiation and prospective follow-up of specific veteran populations who may share a common exposure history as a viable surveillance tool. Creating a registry that may include initial demographic, exposure, and health information is a reasonable interim response to veterans with unexplained or underexplained health complaints that are temporally but not scientifically related to military service.

A registry would allow the formation of a pool of veterans who are linked by some shared attribute of military service, such as combat campaign, theater location, or catastrophic event (e.g., Khamisiyah, Iraq), to be identified and actively followed forward through regular follow-up contacts from the registry staff. Trends in health of the registrants could be followed forward, and communication with registrants about new health information or treatment recommendations could be facilitated. As well, the registrants could be invited to participate in scientific studies to elucidate the cause or proposed mechanism of health harm they may have experienced. Such a model is being used to follow the World Trade Center responders, workers, and neighborhood population. This model differs somewhat from existing VA registries (e.g., Gulf War or Agent Orange) in that these tend to be cross-sectional assessments, with little regular follow-up or interaction with staff.

Although registry costs can be high, so are the costs of presumptions. Enrollment in a registry may offer the veteran access to some of the medi-

cal services a presumption provides, but under a different mechanism that could allow time for the clinical and epidemiologic evidence to accumulate so as to make a more evidence-based decision about a presumption.

Recommendation: Develop a plan for an overall integrated surveillance strategy for the health of Service members and veterans.

It is critical that DoD and VA work together to define a common strategy for integrated health surveillance of Service members and veterans. Fully leveraging the Service member-veteran exposure and health data is critical to the full understanding of disease etiology and causation, the establishment of relative risk, the adjudication of disability claims, and the treatment of disease. It is also critical to appropriate deliberations regarding presumptions in disability decision making.

The need for surveillance can be identified at any point in a Service member's or veteran's experience history. Surveillance studies begun during a Service member's service career may need to extend into his or her post-service experience. Data needs for the specific surveillance activity may have been generated during either the Service member experience or the veteran experience or both. Therefore this activity must be jointly well managed by DoD and VA. A strong central organization, staffed jointly by DoD and VA with external expert advisors, should be given responsibility for the ongoing evaluation of health and exposure data quality, the regular review of registry and surveillance activities, the definition of surveillance and research strategies, and the coordination of surveillance and research projects. This joint DoD-VA Service member and veteran exposure and health surveillance organization would have broad responsibility for oversight of all DoD and VA surveillance and research activities whether they are conducted internally or externally by those organizations.

Recommendation: Improve the data linkage between the electronic health record data systems used by DoD and VA—including capabilities for handling individual Service member exposure information that is included as part of the individual's health record.

Although there are efforts underway to electronically transfer Service member health records from DoD to VA, these efforts are moving slowly and the timeline for completion of a seamless interface is unclear. DoD and VA should increase attention to this effort with a clear integration plan, timetable for implementation, metrics for tracking implementation progress, and annual reporting of metric results.

To date there has been little discussion regarding electronic transfer of Service members' exposure information in their health records to VA. As the

inclusion of exposure data in employee health records is a key DoD strategy for ensuring that exposure information is available for individual Service members, this appears to be a major weakness in the system. DoD and VA should explicitly include the integration of these individual exposure data into the health record transfer integration plan, implementation timetable, metrics, and annual reporting. Reports on progress of these plans should be included in the annual report to Congress on DOEHRS progress.

Recommendation: Ensure implementation of the DoD strategy for improved exposure assessment and exposure data collection.

The DOEHRS program is a major undertaking that has potential for dramatically increasing the availability of exposure data. However, DoD has many important priorities, and short-term funding pressures have the potential to delay implementation activities. Because of the importance of these efforts, not only to DoD but to VA as well, we recommend that additional steps be taken to ensure that DOEHRS is fully implemented as planned. In addition, because of the importance of adequately trained individuals to the success of DOEHRS, we further recommend that these steps specifically include detail on the training of individuals needed to make the accurate professional judgments and generate appropriate exposure data critical to DOEHRS. These additional steps are as follows:

1. Include a specific DoD budget line item for DOEHRS that includes funding for system development and enhancement, system implementation, and training of personnel.
2. Develop clear metrics for tracking the effective deployment and utilization of DOEHRS throughout DoD.
3. Require an annual status report to Congress on DOEHRS development and implementation progress and related training activities.

Recommendation: Develop a data interface that allows VA to access the electronic exposure data systems used by DoD.

DoD is investing heavily in DOEHRS and other improved exposure data systems that are standardized across the various armed services. In the Committee's interviews with people responsible for development and deployment of these systems, we did not encounter anyone with knowledge of activities by DoD or VA to develop a VA interface with these systems that will allow use of the Service member-specific and longitudinal exposure data by VA.

VA should move quickly to develop plans for interfaces to these new DoD exposure data systems. This should not require massive new data

systems within VA but instead consist of appropriate interfaces and views to the data within DoD systems that are accessible by VA. The first step would be a VA team embedded within the DoD implementation team at the Army's Center for Health Promotion and Preventive Medicine where the VA team can examine the system capabilities and data structures so that appropriate interfaces can be defined and developed to meet the needs of VA.

Recommendation: Consider interim interventions for affected veterans while data are collected or more thoroughly analyzed to resolve scientific uncertainty.

It can take significant time to collect and analyze data needed to adequately resolve scientific uncertainty in establishing causal relationships between exposure and disease. VA should consider interim interventions in instances where veterans are severely affected during the time it takes to conduct the needed research. These measures might consist of provisional health care for affected veterans during the interim period.

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11

Governmental Classification and Secrecy

BACKGROUND

Secrecy surrounds many facets of homeland security issues and, in general, is of concern to national security. Many scientific studies conducted during the two world wars through the Cold War were classified, and many are still not declassified. Studies dealing with warfare gases and radiation were classified during the time of the studies and remain classified today. This classification makes appropriately informed treatment of the involved veterans with adverse health effects difficult, if not impossible, and impedes research on the consequences of exposures. The recent declassification of mustard gas and lewisite studies conducted during World War II and numerous radiation studies documented that classification greatly deterred treatment of health effects affecting the volunteers who played key roles during these studies. To many citizens, the idea of secrecy in government is linked with "national security secrets" or "classified information." The system of classification occupies a special place in governmental secrecy. Classified information is accessible only to those who have been "cleared" following investigation and who agree to abide by the rules regarding access to this information; violation of these rules can result in severe criminal penalties. These rules can greatly hinder medical treatment of individuals who have been exposed during classified activities.

The authority to classify information derives from legislation and from Presidential executive order. In 1917, Congress passed the Espionage Act to address wartime spying (SOURCE: http://www.firstworldwar.com/source/espionageact1918.htm; Gathering, Transmitting or Losing Defense Informa-

tion. 2007. 18 U.S.C. § 793; Gathering, or Delivering Defense Information to Aid Foreign Government. 2007. 18 U.S.C. § 794), and further legislation providing for military secrets was enacted in 1938 (Photographing and Sketching Defense Installations. 2007. 18 U.S.C. § 795; Use of Aircraft for Photographing Defense Installations. 2007. 18 U.S.C. § 796; Publication and Sale of Photographs of Defense. 2007. 18 U.S.C. § 797; Quist, 2002). In 1940 President Franklin D. Roosevelt issued the first executive order on classification, which was based on the authorization of the 1938 law enacted to protect military installations and equipment (Truman, 1950). The regulations that interpreted the World War I law declared that secrets could be kept not only for national security reasons but also for other reasons. In 1936, for example, the Army issued rules that provided for Secret, Confidential, and Restricted information. The definition of Confidential provided that

> A document will be classified and marked "Confidential" when the information it contains is of such nature that its disclosure, *although not endangering our national security,* might be prejudicial to the interests or prestige of the Nation, an individual, or any governmental activity, or be of advantage to a foreign nation. (Classification, 1936; emphasis added)

Similarly, data could be classified Secret if release "might endanger the national security or cause serious injury to the interests or prestige of the Nation, an individual, or any government activity"(Classification, 1936).

The use of classification and secrecy by the government is detailed exquisitely by the history of the formation of the Atomic Energy Commission and the development of the atomic bomb during World War II. The Advisory Committee on Human Radiation Experiments (ACHRE) Report (ACHRE, 1995) provides an extremely detailed chronology of the development of the classification scheme and the use of secrecy by the government as it relates to any aspect of radiation work. The history of use of the secrecy classification for radiation studies is outlined in Appendix L-1.

Especially during times of national crisis the general public and the government take security seriously. The concern about national security has evolved considerably over the evolutionary period of classification. During World War II and the development of the atomic bomb under the Manhattan Project, considerable emphasis was placed on wartime secrecy. Secrecy and the oath of secrecy were extended not only to the actual participating scientists and staff but to families of these individuals. Appendix L-1 provides an overview of the secrecy concerns surrounding these projects. During this developmental time period, considerable emphasis was placed on secrecy surrounding the use of human volunteers, and that empha-

sis remains today. Some materials still remain classified today under the umbrella of national security.

The historical development of the classification systems used during the atomic bomb era revealed that more than national security was a concern for classifying some material as secret. Concerns revolving around prestige, public relations, and governmental embarrassment were also used to invoke the secrecy umbrella. In public, some officials stated that national security was the paramount concern, while in private they endorsed the concerns involving prestige, public relations, and embarrassment (ACHRE, 1995). Declassification of materials has been slow, and many documents are still being withheld because of these expressed concerns.

Although Appendix L-1 addresses the history of classification in relationship to the birth of the Atomic Energy Commission (AEC), the recent declassification of some of the World War II mustard gas and lewisite studies reveals that radiation studies were not the only studies classified for national security concerns (IOM, 1993). A more current example of this classification usage is the recent declassification of some of the SHAD (Shipboard Hazard and Defense) Project data, studies that were conducted and classified in the 1960s (SOURCE: http://www.deploymentlink.osd.mil/shad/factSheets.jsp). In view of these two chemical examples, concern arises as to how many other studies were classified secret and have not yet been declassified, leading potentially to the withholding of needed medical care from human participants in the studies.

Although the written history addresses the experiences of the AEC (see Appendix L-1), the issues of secrecy and classification obviously could be extrapolated to other areas of research that would involve human subjects. Pertinent areas of concern in this regard would involve the use of chemical warfare agents for both prevention of injuries and possible use in tactical defense. The use of mustard agents and lewisite in studies addressing protective measures during and following World War II is a prime example of human subject use that was classified and remains partially classified today. Results from some of these studies were not declassified until the early 1990s at the insistence of an Institute of Medicine (IOM) study (IOM, 1993), and some studies remain classified today.

The use of chemical warfare agents and simulants in the 1960s is a further example of retaining human studies under the umbrella of secret classification. In a series of tests under the project list of SHAD, Navy ships were exposed to chemical or biological agents or simulants to establish protective measures and decontamination efficiency for machinery and personnel (SOURCE: http://www.deploymentlink.osd.mil/shad/index.jsp; http://www1.va.gov/shad/; Brown, 2003). The numerous tests were classified as secret and have only been recently partially declassified, again at the insistence of an IOM study (IOM, 1993). In this example, the Department

of Defense (DoD) allowed IOM and the Department of Veterans Affairs (VA) personnel who possessed sufficient security clearance levels to review the documents and release selected pieces of information. It must be noted, however, that not all of the classified SHAD data have been declassified; only those parts that identify personnel involved, for which records were kept by DoD, and the agents or simulants they were potentially or actually exposed to have been declassified. These examples then bring to the forefront: How many other human use studies have been, or are being, conducted and are classified secret? In an August 2006 information letter released by the Veterans Health Administration (VHA) (VHA, 2006, p. 2), more than 250 chemicals were identified as chemicals of potential concern related to human use studies.

DoD classification authority derives primarily from Presidential order. Currently the DoD Information Security Program (DoD, 1997) is the program used for classification and is based on Executive Order 12958 (Clinton, 1995) and its subsequent amendment Executive Order 13292 (Bush, 2003) addressing classified national security information. The current national security classification system is "designed primarily to protect the confidentiality of military, foreign policy, and intelligence information. It deals with only a small slice of the government information that requires protection although it drives the government's security apparatus and most of its costs . . . the classification system, largely unchanged since the Eisenhower administration, has grown out of control. More information is being classified and for extended periods of time. Security rules have proliferated, becoming more complex yet remaining unrelated to the threat" (Pike, 2002).

Today's classification system "starts with three levels of classification (Confidential, Secret, and Top Secret), often referred to collectively as collateral national security information. Layered on top of these three levels are at least nine additional protection categories. These include DoD Special Access Programs, Department of Energy (DOE) Special Access Programs, Director of Central Intelligence Sensitive Compartmented Information Programs, and other material controlled by special access or bigot lists such as the war plans of the Joint Chiefs of Staff and the operational files and source information of the CIA Operations Directorate. Further complicating the system are restrictive markings and dissemination controls such as ORCON (originator controlled dissemination and extraction of information), WNINTEL (warning notice, intelligence sources and methods), NOFORN (not releasable to foreign nationals), and NOCONTRACT (not releasable to contractors)" (Pike, 2002).

LEVELS OF CLASSIFICATION

Policies governing DoD's classification program are implemented through the Information Security Program (DoD, 1997). This regulation implements Executive Order 12958 (Clinton, 1995), "Classified National Security Information," and has been codified at 32 CFR Part 159 (DoD Information Security Program. 2001. 32 C.F.R. § 159). "A security clearance is a determination that a person is eligible for access to classified information. 'Need to know' is a determination made by a possessor of classified information that a prospective recipient, in the interest of national security, has a requirement for access to, or knowledge, or possession of the classified information in order to accomplish lawful and authorized government purposes" (Pike, 2002). Current levels of classification are broadly contained under the headings of Unclassified, Limited, Confidential, Secret, Top Secret, Limited Dissemination (LIMDIS), Special Access Program (SAP), and Sensitive Compartmented Information (SCI) (Pike, 2002). Appendix L-2 provides a discussion of each of the categories of unclassified and classified information control.

> No person may have access to classified information unless that person has been determined to be trustworthy and unless access is essential to the accomplishment of lawful and authorized government purposes, that is, the person has the appropriate security clearance and a need to know. Further, cleared personnel may not have access until they have been given an initial security briefing. Procedures are established by the head of each DoD component to prevent unnecessary access to classified information. (Pike, 2002)

> There must be a demonstrable need for access to classified information before a request for a personnel security clearance can be initiated. The number of people cleared and granted access to classified information is maintained at the minimum number that is consistent with operational requirements and needs. No one has a right to have access to classified information solely by virtue of rank or position. The final responsibility for determining whether an individual's official duties require possession of or access to any element or item of classified information, and whether the individual has been granted the appropriate security clearance by proper authority, rests upon the individual who has authorized possession, knowledge, or control of the information and not upon the prospective recipient. (Pike, 2002)

SECRECY AND MEDICAL RESEARCH

Numerous aspects of medical research have been classified on the basis of national security and have only recently been brought to public light. The

ACHRE Report (ACHRE, 1995) enumerated numerous radiation studies conducted during and after World War II which were classified, and some still have not been declassified. Although the Espionage Act of 1918 really began the era of national security classification, more and more documents have been classified with each new Presidential administration (ACHRE, 1995; Quist, 2002). Today the system is complicated and burdensome to use as discussed above. Medical research is still conducted and classified under the aegis of national security. This secrecy classification can establish hindrances in the medical care provided to the participants in these studies. All institutions that participate in medical research have some degree of classification for their projects, depending upon funding sponsor, subject, and agents used. Much of the current research on modern nerve agents, for example, is classified at the secret and above levels, even though there are many unclassified documents on nerve agents available to the public (IOM, 1993). And while DoD participates extensively in classified medical research studies, VA has not been excluded from such activities. Chapter 13 of the ACHRE Report outlined VA participation in maintenance of "confidential" files regarding radiation studies:

> VA, similarly, was able to provide fragments of information that show that "confidential" files were kept in anticipation of potential radiation liability claims. However, neither the VA, nor the DOE and DoD (who evidently were parties to this secret record keeping), have been able to determine exactly what secret records were kept and what rules governed their collection and availability. (ACHRE, 1995, ch. 13)

(As explained in Chapter 10 of the ACHRE Report, VA concluded that a "confidential" division contemplated in relation to secret record keeping was not activated.)

> VA publications did contain lists of several thousand (nonclassified) human experiments conducted at VA facilities; however, the information was quite fragmentary, and further information could not be readily retrieved (if it still exists) on the vast majority of these experiments. Thus, in looking for answers to questions about the secrecy of data on human experiments and intentional releases, we find record-keeping practices that leave questions about both what secrets were kept and what rules governed the keeping of secrets. (ACHRE, 1995, ch. 13)

Medical research involving human subjects must follow certain ethical and standard practice guidelines such as those established by the Nuremberg Code of 1947 (Trials of War Criminals Before the Nuremberg Military Tribunals, 1949). The 10 key elements of the Nuremberg Code are outlined in Appendix L-3.

Some medical research studies conducted prior to the Nuremburg Code implementation might not have followed the precepts of the code. Congressional inquiries during 1975 and 1976 requested that the Army Inspector General review the use of human volunteers in chemical agent research (IOM, 1993). An excerpted summary of this review (Taylor and Johnson, 1975) is presented in Appendix L-4. While this report concentrated on psychochemical testing conducted during the period 1950-1975, it also addressed the history of chemical warfare testing using human volunteers and the degree of compliance with the Nuremberg Code (IOM, 1993). The overriding conclusion from this report was that the secrecy applied to research using human volunteers "left ample room for misinterpretation, lack of knowledge about [guidelines governing human volunteers] and outright disregard for established policies and guidelines" (Taylor and Johnson, 1975, as referenced in IOM, 1993, p. 379). Concern regarding these conclusions remains today.

The issue of secrecy hindering medical treatment for veterans is amply exhibited in the IOM report *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite* (IOM, 1993). Serious concerns were enumerated in the report over the secrecy issue demonstrated by DoD. These expanded concerns are presented in Appendix L-5.

CONCLUSIONS AND RECOMMENDATIONS FROM IOM'S *VETERANS AT RISK* REPORT

In *Veterans at Risk* (IOM, 1993), emphasis was placed on (1) the lack of exposure data, (2) the continuing dependence and reliance on secrecy by DoD, (3) serious ethical questions regarding the use of human volunteers, (4) total absence of long-term medical surveillance of participants, and (5) in some cases inadequate short-term follow-up even though medical knowledge was available as early as 1933 that exposure to mustard gas or lewisite could produce adverse health problems.

The oath of secrecy taken by participants, and enforced by potential punishment protocols if broken, resulted in continual and escalating cases of health impairment among the human volunteers in these chemical agent studies. The Taylor and Johnson report contains specific statements addressing the issue of secrecy and the participants who took the secrecy oath. An overarching conclusion stated in the report addressed future DoD research with human subjects. These future studies must be conducted following a set of ethical principles that mirror those that non-DoD researchers must follow. The 1975 Army Inspector General report (Taylor and Johnson, 1975) concludes that the mantle of secrecy gives implicit permission to researchers to stretch the boundaries of ethical guidelines in DoD human research under the guise of national security.

VA acknowledges that it must, at times, request exposure data from DoD in order to make a compensation decision. These exposure data may or may not be classified by DoD, and DoD has the option of releasing the data to VA. If the data are classified, DoD may not release them to VA citing national security issues (as stated during Do, 2006, and Freeman, 2006). This failure to release exposure data hinders medical treatment to the veteran. The potential for negative impact on the veteran population is demonstrated in the August 2006 VHA information letter released to health-care providers and the public (VHA, 2006). In this letter, VHA indicated that there may be in excess of 250 additional chemical agents that were used or tested in the chemical warfare arena. The Committee does not know if there are data available on each of these chemicals or if the data are unclassified. DoD is the only organization that can provide those answers. DoD has acknowledged that some 250 additional chemicals might fall under this concern (VHA, 2006). If chemical studies have been classified, DoD is not obligated to inform VA about the studies under the umbrella of national security concerns. As discussed above in the levels of classification, there are many levels under which exposure data could be classified. And, if DoD were to impose the restriction on VA that they must identify which data and under which level of classification the data fall before they release the data to VA, this would hinder access to important information useful for the care of veterans. Not withstanding national security issues, VA must have access to all exposure data to fully provide health care to veterans. A high level of cooperation between both agencies is necessary to provide maximum support to the veteran population.

SUMMARY

In view of the history of human subject use in various DoD and other agency studies, a mechanism is needed to protect the health of our veterans and their families. A joint effort between DoD and VA must be initiated to develop a mechanism to monitor human studies and provide health-protection measures to those individuals involved. Foremost would be the identification of all Service members involved in the studies. Secondly, the chemical, biological, infectious, and radiological agents used during the studies must be identified so that potential adverse health effects and treatments can be determined. Thirdly, accurate exposure assessment data must be collected and made available to appropriate scientists to be used in determining treatment regimens. As is the case in issues of this concern, the "dose makes the poison." Fourthly, national security concerns must be maintained while providing the necessary health support to veterans and their families.

These areas of concern should be addressed by the formation of, and

effective and intelligent use of, a joint DoD-VA board to develop and implement policy areas surrounding national security and human subject research. Paramount to the effectiveness of the board, would be membership of individuals with sufficient security clearance to address national security, DoD weapons and tactical areas, and medical concerns, including exposure assessment. The major undertakings of this board would be the following:

- Identifying any human-use study
- Developing a registry of Service members involved in the studies
- Developing a tracking mechanism to maintain contact with the Service members involved in the studies
- Providing periodic medical evaluations or surveillance of Service members involved in the studies
- Determining appropriate medical treatment if an adverse health effect is detected
- Developing a mechanism to make information public as necessary
- Keeping the veteran, and family as applicable, fully informed regarding potential health effects of the materials that were used in the studies

Recommendation

DoD and VA should establish and implement mechanisms to identify, monitor, track, and medically treat individuals involved in research and other activities that have been classified and are secret.

There are clearly times when national security or mission success depends on maintaining secrecy regarding certain aspects of a Service member's military experience. However, every effort should be made to find mechanisms for characterizing Service member exposure and health histories in manners that do not interfere with the broader issues of national security or mission success. DoD should develop procedures that ensure full or partial declassification of sensitive information for the timely provision of that Service member's or veteran's health care. When such declassification is not possible, DoD should establish procedures whereby blinded data relevant to the Service member's health and exposure history are provided.

In some instances where national security and secrecy issues cannot be resolved, DoD and VA may need to establish mechanisms involving experts with appropriate security clearances to monitor affected registry cohorts for potential health outcomes and define surveillance or research activities that may need to be conducted within appropriate secrecy clearances. An

interagency agreement could be developed between DoD and VA addressing the secrecy issue. As both agencies have used the classification system in the past, this agreement would address the policy development process and the exchange of classified information between the two agencies. The process would include establishment of a joint DoD-VA board composed of individuals who have sufficient security clearance to discuss classified data. The access to the classified information process would be contained in a written document outlining a mechanism to identify, monitor, track, and medically treat individuals who were part of research activities involving human subjects and whose research design and results have been classified.

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12

The Way Forward

INTRODUCTION

In previous chapters of this report, the Committee examined and described Congress' and the Department of Veterans Affairs' (VA's) past and present approaches to establishing presumptions. The case studies illustrate the application of the current approach, as well as approaches taken previously, and point to multiple points in the process of establishing presumptions that, in the Committee's view, should be modified by its participants (Chapter 5). The Committee set out principles related to evidence evaluation and causal inference as a foundation for setting in place an approach that is as firmly grounded as possible in the relevant base of scientific evidence for particular exposures and health outcomes (Chapters 6-9). The Committee also addressed the task of more comprehensively tracking the exposures of those serving in the military and prospectively monitoring military personnel and veterans for disease occurrence so that the risks of exposures can be assessed more systematically (Chapter 10) and so that exposures subject to secrecy can be considered (Chapter 11).

Based on the case studies and other information that was gathered, the Committee has concluded that there is a basis for making changes to the present approach. Building on the conceptual foundation developed in these earlier chapters, the Committee addresses the second part of its charge in this chapter and recommends a framework for establishing presumptions in the future.

The Committee suggests that its recommended framework be considered as a model to guide the evolution from the current approach toward

that proposed by the Committee. The Committee recognizes that specific elements of its proposal (e.g., the call for carrying out exposure assessments and making exposure estimates) are not fully practicable for all relevant exposures at present and would take time to develop and implement. However, feasibility of specific elements of its proposal should be enhanced with future methodologic developments. The Committee believes that its approach can be applied to the full range of factors (e.g., chemical, biological, infectious, physical, and psychological) that may adversely affect the health of military personnel and veterans. The Committee does not intend that its approach be applied retrospectively to existing presumptions. The Committee is aware that policy or other concerns could lead Congress or VA to modify or even reject some of the Committee's recommendations. Congress and VA may find alternative processes to achieve the overall objective of the Committee's recommendations: an evidence-based approach to making presumptive disability decisions. However, the Committee suggests that its proposal will prove feasible and practical over time, that many of the elements in its proposal can and should be implemented without delay, and that the Committee's proposal would significantly improve the presumptive disability decision-making process for veterans.

Out of necessity, the Committee also makes some recommendations related to the implementation of its proposed approach. The Committee makes specific recommendations with regard to proposed advisory and review committees that will likely require congressional authorization, and the Committee recommends that VA would need to make adjustments in its overall approach to the presumptive disability decision-making process in order to follow the Committee's recommendations.

The Committee's recommended approach (Figure 12-1) has multiple new elements: a process for proposing exposures and illnesses for review; a systematic evidence review process incorporating a new evidence classification scheme and quantification of the extent of disease attributable to an exposure; a transparent decision-making process by VA; and an organizational structure to support the process. In using the term "exposure," the Committee defines exposure in a broad manner to include chemical, biological, infectious, physical and psychological stressors. We also call for a comprehensive approach to tracking exposures of military personnel and monitoring their health while in service and subsequent to service. The tracking should cover the full spectrum of exposures relevant to future risk for disease, including chemical, biological, infectious, physical and psychological stressors. The Committee's recommendations are based in a framework that sets out this evidence-based process (Figure 12-1).

The proposed process includes the engagement of two panels: An Advisory Committee and a Science Review Board. The Advisory Committee would be advisory to VA and would consider proposals for the review

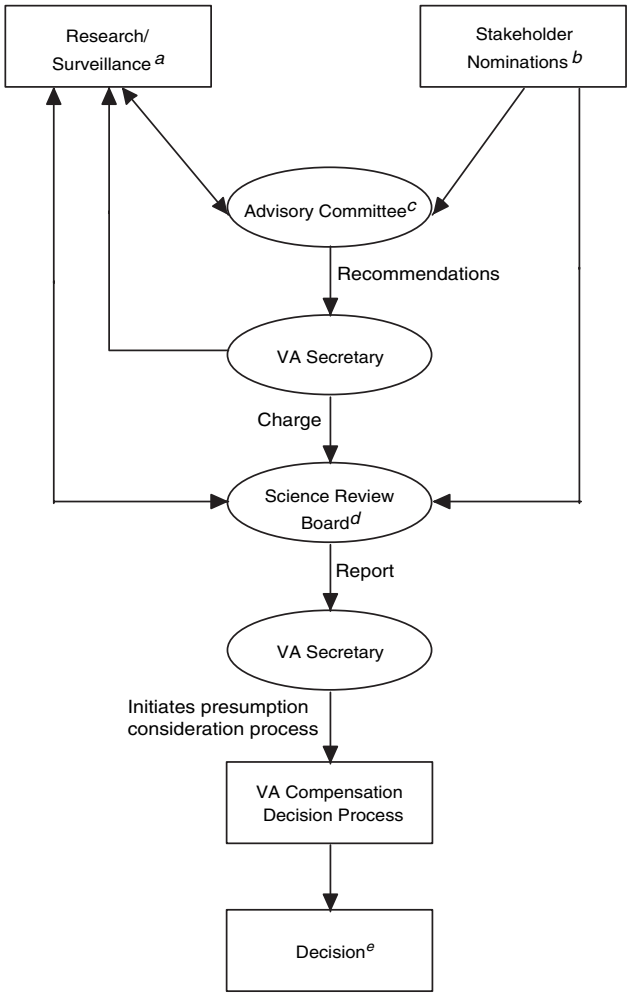

FIGURE 12-1 Proposed framework for future presumptive disability decision-making process for veterans.

[a] Includes research for classified or secret activities, exposures, etc.

[b] Includes veterans, veterans service organizations, federal agencies, scientists, general public, etc.

[c] This committee screens stakeholders' proposals and research in support of evaluating evidence for presumptions and makes recommendations to the VA Secretary when full evidence review or additional research is appropriate.

[d] The board conducts a two-step evidence review process (see report text for further detail).

[e] Final presumptive disability compensation decisions are made by the Secretary, Department of Veterans Affairs, unless legislated by Congress.

of exposures and illnesses that might be the basis for presumptions and recommend to the VA Secretary exposures and illnesses needing further consideration. The Science Review Board, which would be independent from VA, would conduct a comprehensive evaluation of the evidence for causation and, if warranted by the level of evidence in support of causation, estimate the service-attributable fraction of disease.

The Committee calls for the implementation of a health and exposure surveillance system such that veterans' health would be seamlessly tracked from entry into the service through retirement or separation and on to death. The resulting evidence on service-caused risks to health would be one critical component of the foundation of evidence for decision making, along with other sources of evidence, including studies of other populations, toxicologic studies, and other research. The accumulating evidence would undergo periodic review in a transparent and uniform fashion to gauge the strength of evidence in support of general causation and for determination of individual causation, drawing on the exposure data and perhaps other information. This review, carried out by the Science Review Board, would classify the strength of evidence for general causation in a standardized classification scheme as input into a compensation process by VA. VA, also deliberating in a transparent fashion based on established principles, would render a decision by the VA Secretary with regard to a presumption. The process includes a mechanism for stakeholders to propose exposures and illnesses for potential presumptions. These would be considered by the Advisory Committee.

GENERAL FRAMEWORK: THE ADVISORY COMMITTEE AND THE SCIENCE REVIEW BOARD

In the Committee's view, a change in the processes for the entities involved in the presumptive disability decision-making process is needed. In its recommendations for Congress, the Committee proposes the creation of an Advisory Committee and a Science Review Board.

The Advisory Committee would serve as an advisory committee to VA and consider the wide range of exposures and illnesses that might be a basis for presumptions. It would also consider research needs and assist VA in strategic research planning. The Science Review Board (independent from VA) would evaluate the evidence for causation and, if warranted, estimate the attributable fraction of disease in veterans due to exposure.

The role of the Advisory Committee would be to gather suggestions from all stakeholders (i.e., veterans service organizations, veterans, scientists, policy makers, and others) regarding specific exposures and illnesses that might be considered for comprehensive evaluation as potential presumptions, and to recommend to the VA Secretary those exposures and

illnesses worthy of further consideration. This committee would also advise on research to be carried out by various entities.

The role of the Science Review Board would be to weigh the evidence on general causation of disease (including data from a wide range of sources) and to provide recommendations to the VA Secretary regarding presumptions. One critical element in the deliberations of the Science Review Board would be evidence from monitoring the veterans themselves. The health of military personnel should be seamlessly tracked from entry into the service through retirement or separation and on to death. This accumulating evidence would undergo periodic review by the Science Review Board in a transparent and consistent manner. The Science Review Board would also consider evidence from studies of nonveteran populations, toxicological studies, and basic science research. The Science Review Board would provide VA with input for its presumptive decisions, including a summary report of the available scientific evidence in a standardized classification scheme. VA would then render its decision with regard to a presumption through a transparent process of deliberation for potential compensation.

PRINCIPLES FOR THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS FOR VETERANS

This section describes the principles that should be incorporated into this process at every level. VA's decision to make a presumption may involve weighing difficult and incomplete scientific evidence, in the context of veterans' concerns and society's obligations to the affected veterans as well as potential costs. Although the potential complexity of the presumptive disability decision-making process may make a complete codification difficult, the underlying principles can be clearly expressed.

Our country has long recognized that veterans make great sacrifices through their service, including being willing to risk their lives in combat. Historically, presumptions established by Congress and VA have acknowledged the special responsibilities of the government to injured veterans. Recent military conflicts have brought new concerns that extend beyond combat injury and that reflect the potential for delayed adverse consequences of complex combat exposures from chemical, biological, infectious, physical, and psychological stressors. The principles underlying presumptive disability decision making are critical for its success, and consequently the Committee calls for Congress and VA to affirm certain principles that underlie decision making around presumptions. The Committee recommends the following six principles as such a foundation:

1. Stakeholder inclusiveness
2. Evidence-based decisions

3. Transparency
4. Flexibility
5. Consistency
6. Causation, not just association, as the target for decision making

Each of these principles is discussed in detail below.

Stakeholder Inclusiveness

The Committee was impressed with the number of groups who expressed intense interest in the Committee's deliberations and in this report. The Committee's meetings were attended by representatives of veterans service organizations and by individual veterans. Optimal decision making has to include input from such stakeholders who will be affected by the process. Veterans and their families already have some input to VA through the political process. However, the Committee sees a need for more active solicitation of stakeholder input, not just into decisions on specific presumptions but more generally with regard to VA's overall process for making presumptions. It is with this principle in mind that the Committee recommends the creation of the Advisory Committee, separate from but advisory to VA, to consider exposures and diseases for which comprehensive scientific evaluation and possible presumptions may be warranted. Among others, this entity should consult with: representatives of veterans service organizations; veterans; veterans' families; medical personnel at VA who are engaged in the research, diagnosis, and treatment of conditions at issue; and personnel at the Department of Defense (DoD) who are knowledgeable about pertinent exposures and exposure data.

Evidence-Based Decisions

Over the last several decades, there has been a strong movement to ground clinical medicine and public health in an evidence-based framework for decision making. The systematic and consistent capture and analysis of all relevant evidence is central in this approach. Many previous IOM committees addressing scientific issues that would later be used by Congress or VA in establishing presumptions have followed structured approaches, typically evaluating all relevant observational studies on particular hazards faced by veterans and interpreting the findings in a broad biomedically grounded framework. However, while some of these reviews evaluated additional available toxicological or mechanistic evidence, they did not incorporate this evidence when reaching conclusions about the available scientific evidence for the relationship. The Committee recommends giving more consideration to toxicological investigation in general and to mecha-

nisms of action in particular. The overall presumptive disability decision-making process needs to be grounded in the full extent of the scientific evidence available.

Although previous IOM committees have appropriately considered all available epidemiologic evidence on veterans, both domestic and foreign, as well as relevant studies from civilian populations, the available studies may be limited for many agents. In spite of efforts over the years by VA, the Medical Follow-Up Agency at IOM, and other federal and non-federal organizations to address critical health matters for veterans, the array of studies and findings is lacking as a basis for establishing well-grounded scientific presumptive disability decisions for many health outcomes. With the principle of evidence-based decisions in mind, this Committee also recommends that veterans be more effectively monitored, both in their military exposures and in relevant health outcomes throughout their lifetimes.

Transparency

Transparency in decision making is critical to the perception of fairness. The Committee strongly recommends that more emphasis be put on assuring transparency at every stage of the presumptive disability decision-making process. There are multiple stakeholders concerned with every specific presumption, including veterans who are already ill, those potentially at risk of illness, veterans service organizations, and the general public. Transparency means that each step of decision making should have a clear and known basis; stakeholders should be able to fully understand how decisions about presumptions are made, and the basis for those decisions, with reference to documented details of the presumptive disability decision-making process. VA has expressed concern that transparency could compromise internal discussion and affect decision-making deliberations; any unanticipated, adverse consequences of transparency should be noted and implications considered.

Flexibility

Scientific evidence is not static, and it often is less than certain. Given that the scientific basis for presumptive decisions will change over time, the Committee recommends that VA should be able to adjust future decisions when such change is scientifically justified. This does not mean that the Committee recommends that benefits previously granted should be terminated. The Committee is aware that disabled veterans and their families are often dependent on such payments and that it could create a hardship to remove them, a matter that VA disability policy recognizes in other situations. There should be a process of ongoing data collection so that

relevant new findings are recognized and taken into account as quickly as possible. Differing approaches to assisting affected veterans might be used as evidence is accumulating. For example, when causation is very uncertain, a decision might be made by VA to award medical care to the veterans possibly harmed, leaving open the possibility of future financial compensation if the evidence strengthens over time.

Another aspect of flexibility is ongoing improvement of the decision-making process. At present, the Committee found little indication that VA assesses the performance of its own presumptive disability decision-making process or seeks to improve it. Even if VA were to adopt the decision-making structure recommended by the Committee (see Figure 12-1), it would also be necessary to set up mechanisms for evaluating VA's internal process over time. The Committee recommends that VA establish ongoing monitoring and evaluation to allow the decision-making process to be refined and improved. An information-gathering process would be needed for this purpose; consideration might also be given to appointment of an external committee to provide independent guidance on quality improvement, or the Advisory Committee could provide this function.

For the short term, as a new approach is implemented, careful review and evaluation may be particularly critical. Consequently, Congress may choose to be involved in the assessment and change the process as well, particularly as there is a transition from the current approach to a new process.

Consistency

One lesson from the case studies is that there is no firm consistency in the basis for presumptive decisions, possibly contributing to a perception by some of arbitrariness in the presumptive disability decision-making process. VA has offered a description of its internal processes as they have evolved over the last 15 years with regard to the receipt and consideration of IOM's Agent Orange and Gulf War reports. The materials from VA do not describe a standard protocol by which various internal groups respond to an IOM report. Although the Committee lacks full information on VA's processes, the Committee was left with the impression that better structure and documentation of its approach are needed. The Committee recommends that VA take steps to ensure that the bases for its internal decision making are explicit and applied consistently from case to case. To achieve consistency, consideration should be given to procedures for each element of the process within VA: evidence review, decision making, and implementation. For some elements of the process, models are already available, as in the instance of previous IOM Agent Orange and Gulf War committees.

Causation, Not Just Association

One of the most critical matters, in the Committee's view, is clarifying the basis for making a decision to compensate veterans for service-related disability. The Committee recommends that causation, not just association, should be the basis of presumptive compensation. The justification for this recommendation is provided below.

Presumptive disability decisions are based on two judgments: (1) that a group of veterans was *exposed* to a potentially harmful agent or condition during service, and (2) that the agent or condition *is able to cause* disease leading to disability. The second proposition states a causal association, and not merely an association for which causation has not been established. An association between an exposure and outcome can be good evidence for a causal claim, but it is not the same as a causal claim.

The history of presumptions for Agent Orange illustrates the need to be clear on this point. The Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984 (Public Law 98-542. 98th Cong., 2d Sess.) used language of both association and causation in describing the evidence required for presumptions. Initially, VA interpreted the law as requiring a certain threshold of evidence for causation, and as a result denied presumptions between Agent Orange and all diseases except chloracne. Veterans interpreted the intent of the law differently, and a district court sided with the veterans finding the Act ambiguous and interpreting *congressional intent* as establishing a threshold of evidence for an association (*Nehmer v. United States Veterans' Administration*, 1989. Henderson, T. E. United States District Court for the Northern District of California Case Number C86-6160 TEH).

The Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) led the VA to provide the following charge to IOM in making scientific determinations:

- whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
- the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
- whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

VA contracted with IOM to provide a biennial review of the scientific evidence, and VA provided each of the IOM Agent Orange committees (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) the 3-point charge con-

tained in the Agent Orange Act. IOM reports on Agent Orange (IOM, 1994, 1996, 1999, 2001, 2003b, 2005b) generally stated that the committees were unable to address the second point of their charge and did not use evidence from the third point of their charge to incorporate into the overall strength of evidence decision on association. The first IOM Agent Orange committee (IOM, 1994) established categories for the strength of evidence based on an *association* (sufficient, limited/suggestive, inadequate/insufficient, and no association) that have been used by subsequent IOM Agent Orange committees (IOM, 1996, 1999, 2000b, 2001, 2003b, 2005b).

Based in part upon IOM's categorization of limited/suggested evidence of an association between exposure to Agent Orange and a specific health outcome—without scientific research on increased risk in exposed veterans (second point of charge), or robust evidence for a plausible biological mechanism (third point of charge), VA has presumptively service-connected several health outcomes to Agent Orange since 1994. In the example of type 2 diabetes, the scientific basis for the presumption was not evidence of a causal connection, but far more limited evidence of an association. Of course, the Committee recognizes that Congress and VA may choose to presumptively service-connect health outcomes for which the evidence for causation is weak; however, the basis for making such a decision should be made explicit.

In recommending a shift from association to causation as the underlying basis for compensation decisions, the Committee notes that such a shift would not necessarily raise the bar for establishing a presumption. It should be noted here that previous IOM committees reviewing mustard gas and lewisite (IOM, 1993) and the Gulf War (IOM, 2000a, 2003a, 2005a, 2006, 2007) each used a causal categorization in their reports. A more thorough consideration of mechanistic evidence of causation could actually reduce the need for evidence of an association. For example, in *Gulf War and Health* (IOM, 2003a, p. 330) IOM found that "there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to benzene and myelodysplastic syndromes" in veterans even though many toxicologists and hematologists view the *overall* evidence as strongly supportive of a causal relationship in rodents.

The Committee recommends a scheme for the classification of evidence for causation in the following section.

STRUCTURE AND ACTIVITIES OF THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS

The Committee proposes a transparent, public process through which diseases or health conditions potentially caused or aggravated by military service and the putative causal agents (e.g., chemical, biological, infectious,

physical, and psychological stressors) would be nominated for review and, given sufficient information and numbers of veterans affected, formally evaluated to determine if the evidence for causality supports consideration of presumptive service connection by VA. The process would be fully transparent and the outcomes of the evaluation made available in a timely manner.

The Committee recommends that Congress create an Advisory Committee to VA. This Advisory Committee would be composed of scientific experts and veterans' representatives who would identify and recommend to the VA Secretary health conditions and agents (i.e., chemical, biological, infectious, physical, and psychological stressors) for referral to and comprehensive evaluation by the independent Science Review Board. In turn, the Science Review Board's findings and report would be provided to the VA Secretary for consideration in establishing presumptive compensation decisions.

The Advisory Committee

An Advisory Committee, chartered by Congress, is needed to identify potential exposures during military service, and related disabilities caused by these exposures, and to refer these topics for comprehensive review to the Science Review Board. This permanent committee would receive proposals for review, screen the available scientific information and research, and give priority to proposals based on the nature and extent of evidence supporting the relationship. The Advisory Committee would be composed of veterans' representatives and recognized and credible experts in relevant fields, for example epidemiology, industrial hygiene, toxicology, occupational medicine, public health, military surveillance and databases, and exposure assessment. The Advisory Committee would be supported by VA and other federal staff with appropriate backgrounds and expertise to assist the committee. The Advisory Committee would review the initial assessment, give priorities, and make recommendations for proceeding with the full, comprehensive scientific review to the VA Secretary. The VA Secretary would have the authority to select conditions and agents for comprehensive scientific review by the Science Review Board.

Open Proposal Process

Health conditions and causative agents or circumstances would be proposed for review based on evidence of a connection between the condition and military service, and evidence that a sizable or well-defined group of veterans is likely to be affected. Concerns as to the need for a presumption might arise from the health surveillance of veterans or active military

personnel, laboratory research discoveries, or findings from occupational studies of exposures and health effects (e.g., by the International Agency for Research on Cancer [see Chapter 8]). Proposals from any source on behalf of affected veterans (e.g., veterans, veterans' families, veterans service organizations, VA, DoD, other governmental bodies, researchers, or the general public) would be accepted. Proposals along with supporting information would be tracked and evaluated on a scheduled basis.

Screening of Proposals

An initial review of the evidence would be performed by professional VA staff in support of the Advisory Committee. The purpose of the screen would be to determine whether there is a minimum amount of evidence suggesting that the condition could have been caused or aggravated by military service, or of military exposure to the putative causal agent, and also to gauge the extent and nature of the evidence supporting the proposal. The process of proposal review would be structured to be responsive to stakeholders of varying expertise and capabilities, and include the gathering of additional evidence beyond that submitted with the proposal.

Prioritization

Those exposures found to, at a minimum, have some positive evidence of a relationship to health conditions and adequate data to initiate review would be candidates for full evaluation. Higher priority would be given to the conditions and causative agents or circumstances with the strongest evidence, affecting the largest numbers of veterans, and leading to the most severe health consequences.

Advisory Committee Review

The Advisory Committee would review materials assembled by the VA staff and other input from stakeholders and the general public to make recommendations to the VA Secretary for full, comprehensive scientific review by the Science Review Board. The process used by the Advisory Committee, which would be subject to the Federal Advisory Committee Act, and the rationale for recommendations would be documented and transparent. The process would also provide opportunities for input by stakeholders during the Advisory Committee's review of proposals. To assist the Advisory Committee in developing recommendations, it is important that VA improve its data collection processes to track claims filed by veterans for benefits so that environmental exposure issues connected with new claims can be identified quickly.

The VA Secretary

Ultimately, the decision regarding which topics deserve full, comprehensive scientific evaluation resides with VA. VA would take the Advisory Committee recommendations under advisement, and consider the nature and extent of evidence, number of veterans potentially affected, severity of the conditions, public comment, and potentially other factors to decide the topics that would proceed to the Science Review Board for full, comprehensive scientific evaluation. Transparency at this stage by VA is critical. The VA Secretary would be required to respond to the Advisory Committee's recommendations, providing an explanation for his or her decisions, a copy of which would be filed with Congress on an annual basis.

In the Committee's proposed presumptive disability decision-making process, VA would receive the full, comprehensive scientific evaluation, as described below, from the Science Review Board. We recommend that VA establish a uniform and transparent process for making decisions with regard to presumptions following receipt of such evidence reviews. The process should incorporate the principles embodied in this Committee's proposed approach. VA procedures should be established with input from the many concerned stakeholders. Its protocols should acknowledge who would be accountable for considering the reports of the Science Review Board and a description of how the reports would be used. A clear and comprehensive evidence-based rationale should be offered for all decisions and made public.

Science Review Board

For the process of comprehensive scientific review of the evidence to be successful, it must be regarded as credible by veterans, the general public, and the scientific community. It is essential that the process be objective, transparent, and of the highest scientific quality, reflecting scientific consensus among acknowledged experts at the time of the review. The Science Review Board is envisioned as following a transparently operated, adequately funded and staffed process in which outside experts, with various disciplinary backgrounds serving as needed, would conduct the full, comprehensive scientific evaluation. Rereview of cases would be conducted as new evidence would emerge, and further research would be encouraged when important hypotheses are unresolved by the available scientific evidence.

An independent Science Review Board would be authorized by Congress and funded by VA. The group would have expertise in the key disciplines needed to weigh the causal evidence and determine the service-attributable fraction. Ad hoc members could be added when specialized expertise was needed or issues of secrecy would need to be addressed. Members of the

Science Review Board would serve as independent experts, and without conflicts of interest. The Science Review Board would be housed in an organization or institution that would ensure its credibility, its sustained growth, and consistent efforts and products.

A staff of professionals with expertise in relevant disciplines would be needed to support the Science Review Board. Staff would seek out and compile relevant information, solicit input from outside organizations, and assist in report writing and in developing and finalizing recommendations from the Science Review Board.

Public and Other Requests for Relevant Data

VA would publicly announce in the *Federal Register* the health conditions and putative causal agents that would undergo full, comprehensive scientific review by the Science Review Board. In the initial preparations for the evidence review, a request for information on the evidence for and against causal relationship for the particular condition and agent or circumstance would be announced, for example in the *Federal Register* and on VA's website. Relevant data may also be requested from DoD, organizations within VA, or other knowledgeable organizations, by project staff or the Science Review Board.

Two-Step Process of Evidence Utilization

The Committee recommends a two-step process for evaluation of scientific evidence by the Science Review Board. Step one would involve a systematic review of relevant data to determine the strength of evidence for causation, using one of four categories as presented in Chapter 8:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

The scientific review would include all relevant evidence using existing systematic review models. The Science Review Board would develop standard operating procedures, which would be reviewed and updated on a regular basis, and outline the protocol by which evidence would be

reviewed and categorized. The evidence gathered and reviewed would be similar in nature to that supporting cancer or reproductive toxicity evaluations by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction, the National Toxicology Program's *Report on Carcinogens*, the International Agency for Research on Cancer, and the U.S. Environmental Protection Agency. The public and stakeholders would be encouraged to provide input into the scientific review process.

If the evidence for causation were categorized as *Sufficient* or at *Equipoise and Above*, then we anticipate that VA would consider a presumptive service connection based upon causal evidence categorization and the service-attributable fraction if available (to be estimated in the second step of the process, described below). As is current VA policy, if the evidence is at *Equipoise*, the benefit of the doubt would be given to the veteran, and a presumptive service connection would be considered. If the evidence were categorized as *Against*, then we anticipate that VA would not consider a presumptive service connection. If, however, the evidence were categorized as *Below Equipoise*, then we anticipate that VA would, after carefully considering the prospects and recommendations for future research, decide on an appropriate time frame for the subsequent scientific review of the evidence, with the expectation that the evidence would then be sufficient to resolve matters either for or against the causal claim at that time. Such information would be considered by the Advisory Committee serving in its capacity as overseer of the overall process and advisor to the VA Secretary.

If the VA Secretary were to decide that a presumption would not be established for evidence categorized as *Below Equipoise* or, for other reasons, for evidence categorized as *Equipoise and Above*, then during the period of further evidence development and gathering and prior to the subsequent scientific review of the evidence, VA should consider providing some support to potentially affected veterans, such as providing provisional access to medical care.

As evidence accumulates, the balance might move to strengthen or to weaken the case for causality. Importantly, the Science Review Board should be free to upgrade the level of evidence, to downgrade the level of evidence, or to leave it as the same categorization. For evidence that has reached the classification of *Sufficient*, we would not anticipate a potential lowering of the classification, if the original determination was correctly made and based on sound scientific evidence.

If the strength of the evidence reaches *Sufficient* or *Equipoise and Above*, then the evaluation would move to step two, the calculation of the service-attributable fraction of disease when required information and data are available. This calculation is independent of the classification of the strength of evidence for causation, and the magnitude of the service-attributable fraction is not considered in the application of the four-level

schema for categorizing evidence. Rather, the service-attributable fraction would be of value for decision making, giving an understanding of the scope of the population to be covered by a presumption.

In step two, the Science Review Board would consider the extent of exposure among veterans and subgroups of veterans, as well as dose-response relationships. When such information is available, the board would estimate the service-attributable fraction and its related uncertainty. The purpose of step two is to convey the impact of the exposure on veterans as a whole for the purpose of decision making and planning, but not to serve inappropriately as an estimate of probability of causation for individuals. Some exposures may contribute greatly to the disease burden of veterans, while other exposures (even with a known causal effect) may have a small impact overall. This additional information would be useful to VA in its decision making as to whether a presumption should be made for the veteran population in general, for subgroups, or not at all. When service-attributable fraction data are not available, the VA may consider presumptions on the information contained in step one.

Periodic Reevaluation of Evidence

All but the most conclusive evaluations would be subject to rereview and updating. Rereviews could follow a fixed cycle, for example every 5, 7, or 10 years. Rereview and updating could also be triggered by new compelling scientific information, in which case outside parties could make nominations to the Advisory Committee for reconsideration by the Science Review Board.

EXAMPLE OF APPLICATION IN CURRENT CONFLICTS

The Committee's framework is intended for prospective application during peace- and wartime and for in-garrison exposures as well as those experienced in wartime theatres. The potential utility of the recommended approach might be considered by applying it retrospectively to the case studies or prospectively to the current conflicts in Iraq and Afghanistan. For the purposes of this hypothetical illustration we use the current conflicts, although in establishing the framework we drew on lessons learned from the case studies regarding such matters as secrecy (e.g., mustard gas and lewisite), lack of ongoing epidemiological surveillance (e.g., cardiovascular disease in amputees), and insufficient exposure information (e.g., Agent Orange and Gulf War in 1990).

With regard to the current military actions in Iraq and Afghanistan, the conflicts have been marked by the hostility of the environments with ubiquitous threats to military personnel and widespread use of improvised

explosive devices (IEDs) bringing risk of maiming and death. The level of psychological stress has increased risk for posttraumatic stress disorder (PTSD) and the IEDs have led to high rates of limb loss and traumatic brain injury (TBI). Additionally, many of the deployed personnel are in the National Guard and Reserves and have faced unexpected disruption of their civilian lives from one or several deployments during the course of the current conflicts.

How might a full implementation of the Committee's proposed framework prove useful for the purpose of presumptive disability decision making for veterans of the current conflicts in Iraq and Afghanistan? We call for systematic and ongoing exposure assessment that would extend beyond chemical, biological, and physical stressors to psychological stress; with suitable instruments, exposures to stress would be estimated among samples of various at-risk groups of individuals, as the basis for future observation for onset of PTSD or other disorders in relation to exposure. For chemical exposures, industrial hygiene approaches could also be used for exposed groups of individuals, again as the basis for assigning exposures to various groups. Stored blood samples from pre- and post-deployment examinations could also be used to indicate and assess exposures to chemical agents, to assess immune responses to infectious agents, or to measure other biomarkers of exposure or of injury. For all deployed personnel, geographic location and duties could serve as the basis for assigning potential exposures to groups of individuals.

Information on future disease risks in relation to exposure could be obtained through follow-up via health status and exposure data records linkage to VA, DoD, and other data systems, including the National Health Index for mortality. Special cohorts (e.g., registries) could be constructed to identify and track particular exposed groups with greater intensity and focused outcome assessment. Service members with TBI should be identified and tracked, for example, for level of functioning and quality of life. Risk for PTSD might be monitored in groups with greater and lesser levels of stress.

A general consequence of the Committee's approach would be continuous monitoring of health outcomes among those who had been deployed to the zones of current conflict in Iraq and Afghanistan. Comparison of disease risks in those deployed to those not deployed in these areas could signal any potential increased risk and lead to more focused assessment and review of exposure and health outcomes concerns, including review by the Advisory Committee.

In the event that the Advisory Committee determined that an evidence evaluation was needed, the Science Review Board would be able to use the findings of the exposure and health tracking system. Evidence would be available directly from the tracking of veterans that would be

included in the review along with other relevant information. If indicated by the classification of strength of evidence, the service-attributable fraction should be estimable. The size of the exposed, and hence eligible, pool of veterans would be known with some degree of certainty. The evidence review conducted by the Science Review Board would be reported back to VA, so that the VA Secretary could make a determination as to whether a service-connection presumption would be established. These activities would follow the transparent process laid out by the Committee, possibly increasing confidence in the decisions made.

SECRECY AND THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS

Research involving individuals exposed to chemical, biological, or radiological agents is often classified for security reasons, and information related to clandestine missions is also classified. This classification can be detrimental to the long-term health status of our veterans, who maintain the oath of secrecy. So long as information remains classified—which can be for a long period of time—these veterans cannot openly investigate or inquire about the relationships between their disease or health condition and the exposures they received. Although secrecy must be applied and maintained for obvious homeland security and national defense reasons, this designation must not be used to deny or forestall necessary medical treatment for afflicted individuals. As made clear by the case study of mustard gas and lewisite (see Appendix I), veterans may be harmed by exposures from classified activities. It is absolutely necessary for DoD and VA to develop, implement, and maintain a policy program that addresses the issues of health maintenance and national security for our veterans. The case study of mustard gas and lewisite illustrates the opportunity for harm to occur in research volunteers because of secrecy (see Appendix I).

Regarding the processes for science review proposed here, review would be particularly challenging when classified or secret information is involved. Nonetheless, the Committee recommends that DoD and VA develop a process for ensuring that exposures sustained in the course of classified or secret activities are not excluded from the presumptive disability decision-making process. Our Committee can make only general comments on this matter. For some issues involving classified and secret information, consultants with appropriate expertise and security clearance might be added to the Advisory Committee and Science Review Board. They could review the classified or secret information and provide information or recommendations for the decision process in a format that would not violate the government's need for secrecy. This variation in process would be clearly and openly described.

Perhaps in some circumstances, no element of the relationship between military exposure and the condition could be divulged. This circumstance would call for a separate special process to protect government secrecy as well as provide fair treatment for affected veterans.

ADDITIONAL DATA FOR DECISION MAKING

To make the best possible decisions regarding compensation for veterans, it is necessary to go beyond the published literature. In this section we will consider several sources of data that would greatly enhance the presumptive disability decision-making process for veterans.

At present, research on the health of veterans is conducted in a variety of venues. Examples include the following:

- Intramural research of the War-Related Illness and Injury Study Center assesses the health consequences of deployment to a combat theater.
- The Medical Follow-Up Agency of IOM's Board on Military and Veterans Health carries out targeted epidemiologic research on health of military personnel.
- Extramural research related to the health of veterans may be funded by VA through its extramural research program or by the National Institutes of Health.

Although investigators at the War-Related Illness and Injury Study Center have a track record of productivity, the Committee anticipates that substantial additional capacity for multidisciplinary research will be needed as better surveillance methods are put into place and new hypotheses are generated.

The approach to research should be driven by a sustained and iterative planning process that strategically identifies and addresses emerging questions. Issues needing investigation might be identified through surveillance findings, stakeholder input, or findings emerging in research conducted beyond VA. VA needs a process that strategically addresses research needs to ensure that presumptions are evidence-based to the best extent possible. In the Committee's recommendations, we call for an Advisory Committee that would provide guidance to VA in developing and maintaining a targeted and strategic research planning process. The reviews carried out by the Science Review Board would also highlight gaps that need to be addressed through research.

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13

Recommendations

In meeting its charge, the Committee has heard presentations and received information from past and present congressional staff members as well as representatives of the Department of Veterans Affairs (VA), the Department of Defense (DoD), the Institute of Medicine (IOM), various stakeholder groups (e.g., veterans service organizations [VSOs]), individual veterans and the general public. The Committee has reviewed an extensive amount of information including (but not limited to): documents provided by the Veterans' Disability Benefits Commission, public laws and their supporting House and Senate committee reports, *Federal Register* notices, VA documents (i.e., cost estimates), DoD documents, and IOM reports that have been commissioned by VA and DoD. The Committee has completed case studies that analyze a wide variety of circumstances in which presumptions have been established by Congress and VA. Additionally, the Committee has considered how to use scientific evidence in guiding the process for making decisions that impact the compensation of veterans. It has covered the evaluation of evidence for inferring association and causation as well as the quantification of the contribution of an agent to disease causation in populations and the extension of this quantification to individuals.

Based on its extensive evaluation of the current process for establishing presumptive disability decisions and its consideration of alternative approaches, the Committee has a series of recommendations for an approach that is both more strongly grounded in scientific evidence and more responsive and open to veterans. Chapter 12 describes that process. We propose a transformation of the current presumptive disability decision-making process for veterans. We recognize that considerable time

will be needed to implement some of these recommendations and will require investment in tracking the exposures and health of current military service men and women as well as veterans. Progress depends on greater research capacity and changes in the evaluation and use of scientific evidence in making compensation decisions. The Committee finds that there are sufficient remediable shortcomings within the current process to warrant immediate action as Congress and VA move toward implementation of a new approach. The Committee concluded that improvements are needed throughout the presumptive disability decision-making process. The recommendations that follow are based on the Committee's proposed framework for making presumptive decisions (see Chapter 12). We list the recommendations in relation to the appropriate body. In recommending the organizational structure below, the Committee recognizes that Congress and VA might pursue alternative structures to achieve the Committee's overall goal of having an evidence-based presumptive disability decision-making process. However, the Committee believes that its proposal is feasible and practical over time, many of the elements in its proposal can and should be implemented without delay and that the Committee's proposal would significantly improve the presumptive disability decision-making process for veterans.

CONGRESS

Recommendation 1. Congress should create a formal advisory committee (Advisory Committee) to VA to consider and advise the VA Secretary on disability-related questions requiring scientific research and review to assist in the consideration of possible presumptions.

The investigation and evaluation of the relationships of exposures during military service and subsequent disabilities experienced by veterans have not been sufficiently prompt and comprehensive. To assure that research and review are timely and on target, the Committee recommends creation of an Advisory Committee to VA composed of veterans and recognized experts in disciplines such as epidemiology, toxicology, exposure assessment and biostatistics to identify and assess issues for referral to the VA Secretary and then to the Science Review Board, which would carry out the subsequent full, comprehensive scientific evaluation of the evidence (see Recommendation 2).

In the Committee's recommended approach, the Advisory Committee has two key roles: screening exposures and illnesses proposed for review for possible presumptive compensation, and providing guidance to VA on research needs and planning. The multidisciplinary Advisory Committee

should include stakeholder representatives and have a permanent staff to support its function.

The Advisory Committee would also receive the proposals for exposures and illnesses of concern made by stakeholders and other groups. With staff, the Advisory Committee would evaluate the candidates for potential presumptions and make recommendations to the VA Secretary as to whether a full, comprehensive scientific review by the Science Review Board should be carried out. Recommendations made to the VA Secretary and his or her responses thereto should be reported to Congress on an annual basis. To assist the Advisory Committee, a VA tracking system should be developed to identify filed disability claims that suggest the need for further investigation of the relationship linking exposures to health conditions during service. Additionally, claims filed and decided following the creation of a presumption should be tracked to validate previous estimates of case load and to project future claims arising secondarily from the primary condition for service connection.

Recommendation 2. Congress should authorize a permanent independent review body (Science Review Board) operating with a well-defined process that will use evaluation criteria as outlined in this Committee's recommendations to evaluate scientific evidence for VA's use in considering future service-connected presumptions.

Current statutory authority for independent evaluation of scientific evidence for potential service-connected presumptions has too often resulted from ad hoc responses to the pressing questions of the moment. Absent a permanent committee and staff to consider and evaluate the evidence relevant to particular potential presumptions, approaches to evaluation have not been uniform and have not always provided VA with evidence syntheses that fully used the available evidence. The implementation of the Science Review Board, or a comparable entity, is central to the Committee's recommended changes to the presumptive disability decision-making process.

The Science Review Board would implement a well-defined, consistent, and transparent evidence-based approach as described in this report. It should be housed within an organization or institution that can assure the highest level of credibility for its process and reports. The existence of a permanently staffed body would also allow it to be proactive rather than reactive to veterans' concerns.

Recognizing that the development of sufficient scientific evidence to warrant a positive presumptive decision does not always occur quickly, Congress should also consider granting VA discretionary authority to provide provisional medical treatment to veterans while research findings are pending.

DEPARTMENT OF VETERANS AFFAIRS

Recommendation 3. VA should develop and publish a formal process for consideration of disability presumptions that is uniform and transparent and clearly sets forth all evidence considered and the reasons for the decisions reached.

Pursuant to statute, VA is directed to make decisions concerning the establishment of service-connected presumptions for Agent Orange determined on the basis of sound medical and scientific evidence. In making such decisions, VA is required to consider pertinent reports from the National Academy of Sciences and "all other sound medical and scientific information and analyses available" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.).

The Committee found that VA (1) has no formal published rules governing this process, (2) does not thoroughly disclose and discuss what "other" medical and scientific information it considered, and (3) publishes abbreviated and insufficiently informative explanations of why a presumption was or was not granted.

The closed nature of VA practices does not foster public understanding of the reasoning behind the VA's decisions; the Committee believes that a move by VA to a more transparent process would better meet the expectations of the nation's veterans and of the public at large. The Committee recommends that VA promulgate, without delay, a more formal procedure for establishing presumptive disability decisions. The procedure needs to be transparent and consistent with the practices of federal regulatory agencies. The word "uniform" in the recommendation refers to a process that works in a consistent fashion with regards to its procedures and outcomes; in other words, given a similar body of evidence for different diseases, the end result of the process should be similar. Members of internal working groups should be disclosed; all evidence considered should be disclosed; and a thorough discussion of the weight attached to the evidence considered should be published so that veterans and the public have a clear understanding of the basis for the decision reached.

SCIENCE REVIEW BOARD

The recommendations that follow are directed toward the proposed, future Science Review Board, the entity to be established in the Committee's proposed approach.

Recommendation 4. The Committee recommends that the goal of the presumptive disability decision-making process be to ensure compen-

sation for veterans whose diseases are *caused by* military service and that this goal must serve as the foundation for the work of the Science Review Board. The Committee recommends that the Science Review Board implement its proposed two-step process.

Previous IOM Agent Orange committees have focused on strength of evidence for an association when causal language has also been included in their charge (IOM, 1994, 1996, 1999, 2000b, 2001, 2003b, 2005b). Agent Orange legislation calls for establishing the presence of an "association" between exposure and disease; however, the enabling legislation also called for consideration of study bias and biologic mechanisms, which address the underlying question of causation (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.). IOM Gulf War committees have established evidence categorizations based upon both causation and association (IOM, 2000a, 2003a, 2005a, 2006, 2007). The enabling legislation for Gulf War actions did not specify the strength of evidence to be used in scientific reviews (Veterans' Benefits Improvements Act of 1994. Public Law 103-446. 103rd Cong., 2d Sess., codified as Compensation for Disabilities Occurring in Persian Gulf War Veterans. 2006. 38 U.S.C. § 1117; Omnibus Consolidated and Emergency Supplemental Appropriations Act of 1998 (Part II). Public Law 105-277. 105th Cong., 2d Sess.). The IOM committee that evaluated mustard gas and lewisite based its evidence categorization solely upon causation (IOM, 1993). The Committee therefore recommends that the focus be shifted to the question most fundamental to presumptions, namely whether a military exposure is able to cause a disease.

Recommendation 5. The Committee recommends that the Science Review Board use the proposed four-level classification scheme, as follows, in the first step of its evaluation. The Committee recommends that a standard be adopted for "causal effect" such that if there is at least as much evidence in favor of the exposure having a causal effect on the frequency or severity of disease as there is evidence against, then a service-connected presumption will be considered.

The Committee recognizes that gathering and synthesizing the evidence necessary to prove a causal effect can be daunting, but expert groups have repeatedly done so using replicable approaches and standard classification schemes. The Science Review Board should adopt a written protocol for evidence review and apply the Committee's recommended four-level scheme:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and Above*: The evidence is sufficient to conclude that a

causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.

3. *Below Equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.

4. *Against*: The evidence suggests the lack of a causal relationship.

Using this scheme, the Committee recommends that the presumption of a causal effect be considered when an expert scientific evaluation finds the evidence considered in support of a causal effect to be at least as strong as the evidence against. We express this criterion as "*Equipoise and Above*."

Recommendation 6. The Committee recommends that a broad spectrum of evidence, including epidemiologic, animal, and mechanistic data, be considered when evaluating causation.

Past decisions on presumptions have sometimes been based largely on epidemiologic evidence. The Committee recommends that evidence to evaluate causation be derived not only from epidemiologic studies of veterans and other exposed groups, but also from toxicological studies of animals or tissue, mechanistic studies of biological mechanisms related to the exposure or the disease process, and any other relevant scientific evidence. There are a number of existing approaches used by other organizations that the Science Review Board should consider.

Recommendation 7. When the causal evidence is at Equipoise and Above or Sufficient, the Committee recommends that an estimate also be made of the size of the causal effect among those exposed.

In past evaluations, the primary question has been whether there is an association between an exposure and disease. The Committee recommends that future evaluations should, in addition, provide an estimate of the strength of this association. In the crudest setting, this may be a simple ratio of the risk among the exposed compared with the risk among the unexposed (the relative risk). More sophisticated estimates may also be made, for example when there are dose-response data that can be applied to levels of military exposure.

Recommendation 8. The Committee recommends that, as the second part of the two-step evaluation, the relative risk and exposure prevalence be used to estimate an attributable fraction for the disease in the military setting (i.e., service-attributable fraction).

The relative risk can be used to make a rough estimate of the fraction of diseased persons exposed in the military setting whose disease was actually caused by their military exposure. Although this number is only roughly approximate, it does provide an estimate of the burden of disease caused by the military exposure and could be useful for projecting future costs. This estimate may be useful to VA in its decision-making process and to the veterans themselves in assessing the need for a presumption.

DEPARTMENT OF DEFENSE AND THE DEPARTMENT OF VETERANS AFFAIRS

The following recommendations are intended to improve the evidence on exposures and health status of veterans:

Recommendation 9. Inventory research related to the health of veterans, including research funded by DoD and VA, and research funded by the National Institutes of Health and other organizations.

Recommendation 10. Develop a strategic plan for research on the health of veterans, particularly those returning from conflicts in the Gulf and Afghanistan.

Models are available for planning major long-term research agendas that are intended to identify critical gaps in the availability of evidence. For example, a National Research Council committee provided a national agenda for research on airborne particles (NRC, 1998) that was used by the Environmental Protection Agency to initiate and track a major research program.

Recommendation 11. Develop a plan for augmenting research capability within DoD and VA to more systematically generate evidence on the health of veterans.

Recommendation 12. Assess the potential for enhancing research through record linkage using DoD and VA administrative and health record databases.

Recommendation 13. Conduct a critical evaluation of Gulf War troop tracking and environmental exposure monitoring data so that improvements can be made in this key DoD strategy for characterizing exposures during deployment.

Characterizing personnel exposures during deployment depends extensively on a system of troop location tracking and environmental monitoring

that can be coordinated to characterize Service members' exposures. This approach is relatively new and, while promising, faces some key limitations as currently implemented that may significantly affect the degree to which the approach can adequately characterize individual Service member exposures. Experience acquired during the Gulf War, and subsequent uses of tracking systems in Afghanistan and Iraq, offer important opportunities to evaluate effectiveness so that refinements can be implemented.

Recommendation 14. Establish registries of Service members and veterans based on exposure, deployment, and disease histories.

Creating registries of Service members based on common groupings that may be important for future health surveillance or research is most easily performed at the time the Service members are together in those groupings. Making lists years after the common experience can lead to inaccuracies from lost records and recall bias. Groupings for registries can be based on many characteristics, including common exposures, common jobs, common deployment experiences, or common illnesses.

Recommendation 15. Develop a plan for an overall integrated surveillance strategy for the health of Service members and veterans.

DoD and VA need to work together to define a common strategy for integrated health surveillance of Service members and veterans. The need for surveillance can be identified at many points along a veteran's service to post-service experience. Surveillance studies that are initiated during a Service member's service career may need to extend beyond the period of military service. Data requirements for the specific surveillance activity may have been generated during military service, after military service, or both.

Recommendation 16. Improve the data linkage between the electronic health record data systems used by DoD and VA—including capabilities for handling individual Service member exposure information that is included as part of the individual's health record.

There is immediate benefit to be gained by a robust electronic sharing of military health records, including exposure information, by DoD with VA. DoD has mandated inclusion of service exposure records into its health records. Military health records are a routine part of VA's approach to assessing veteran health and disability. The final link in the chain is the complete transfer of those exposure and health records from DoD to VA.

Recommendation 17. Ensure implementation of the DoD strategy for improved exposure assessment and exposure data collection.

DoD has an ambitious and robust plan for improving the breadth and depth of its exposure evaluations and in consolidating records and approaches. These data would be especially useful for the longitudinal characterization of Service member exposures. Given the importance of the success of this initiative to the future understanding of service-related exposures, it is critical that the plan be fully implemented. The Committee recommends that the Veterans' Disability Benefits Commission work through Congress to establish a specific DoD budget line for the Defense Occupational and Environmental Health Readiness System (DOEHRS) implementation, including the appropriate training of personnel in exposure assessment and in use of the system, and that Congress receive annual reports from DoD on the status of DOEHRS development and implementation.

Recommendation 18. Develop a data interface that allows VA to access the electronic exposure data systems used by DoD.

DoD continues to invest heavily in electronic systems for documenting exposures experienced by Service members during their military service. These data are critical to VA's ability to manage veteran health and disabilities and to the presumptive disability decision-making process, yet VA has direct access to little of DoD's data. DoD and VA should begin to work together immediately to assess the available systems and to define and construct appropriate interfaces for these systems. The Committee recommends that the Veterans' Disability Benefits Commission work through Congress to establish specific DoD and VA budget lines to enable the development and implementation of a data interface that allows electronic access between DoD and VA records, and that Congress receive annual reports from DoD and VA on the development and implementation efforts.

Recommendation 19. DoD and VA should establish and implement mechanisms to identify, monitor, track, and medically treat individuals involved in research and other activities that have been classified and are secret.

The major requirements for interaction between DoD and VA regarding classified activities would be the following:

- Prospectively identify classified studies and activities involving humans.

- Develop a registry of Service members involved in the studies and activities.
- Develop a tracking mechanism to maintain contact with the Service members involved.
- Provide periodic medical evaluations and surveillance of Service members involved.
- Determine appropriate medical treatment if an adverse health effect is detected.
- Develop a mechanism to make information public as necessary.
- Keep the veterans, and families as applicable, fully informed regarding potential health effects of the materials that were used in the studies and activities.

The Advisory Committee, mentioned previously, could be assigned to oversee these functions.

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Appendix A

Statement of the Veterans' Disability Benefits Commission to the Institute of Medicine's Committee on the Presumptive Disability Decision-Making Process, May 31, 2006

The Veterans' Disability Benefits Commission created by Public Law 108-136 is charged with studying the benefits provided to compensate and assist veterans for disabilities attributable to military service. The Commission was mandated to consult with the Institute of Medicine (IOM) of the National Academy of Sciences with respect to the medical aspects of contemporary disability compensation policies. The Commission will evaluate and assess:

- The appropriateness of benefits
- The appropriateness of the level of those benefits
- The appropriate standard(s) for determining whether the disability should be compensated

In order to meet the three goals above, the Commission produced a list of 31 research questions to be answered during its investigation. IOM has established four committees that will address some of these questions in whole or in part. Your Committee will research and report on presumptions. Another committee, the Committee on Medical Evaluation of Veterans for Disability Compensation, was created to research and report on several aspects of compensation policies. IOM also established two committees to deal with various aspects of PTSD including diagnosis, treatment, and compensation. The Commission encourages your Committee to collaborate with the other three committees since there are many areas of overlapping and complementary interests.

The Commission consists of 13 members who were appointed by the President and the leaders of Congress. Twelve of the Commissions have served in the military. Nine members have combat experience. Combined, the members have over 260 years of military experience. The establishing statute requires that seven members have received combat decorations such as the Silver Star or higher. The Commission is charged to submit its report by October 1, 2007, to the President and Congress.

The Commission is looking forward to receiving expert advice from your Committee regarding the process by which presumptions of service connections are established. The Commission asks that you evaluate the current model used to determine diseases that qualify for service connection on a presumptive basis, and if appropriate, propose improvements in the model.

The Commission requests that your Committee assess the overall process used to establish a presumption. Currently, in determining if a herbicide disease should have a presumption established, the Secretary must determine that the results upon which the presumption is based are statistically significant, are capable of replication, and withstand peer review.

The Commission previously provided IOM an analysis of the history of presumptions completed by the VA Office of General Counsel in 1993. The Commission also provided an analysis completed this year by Mr. Donald Zeglin, legal consultant to the Commission, which summarized the General Counsel analysis and analyzed decisions on presumptions that occurred since the completion of the General Counsel analysis.

A presumptive condition is an injury or illness in which VA presumes a relationship exists between service and the conditions being claimed. A recurring theme within the compensation program has been the expansion of the definition of service connection, mainly under the presumption basis.

In general terms, presumptions shift the burden of proof from the veteran to the Government. Among the earliest presumptions, not dealing with service connection, are the presumption of sound condition upon entry on active military duty, the presumption relating to aggravation of pre-existing conditions during service, and the presumption of death after an absence of seven years.

In many instances, presumptions of service connection have been created when the manifestation of disability is remote from the veteran's service. This could be because medical science could not determine the origin or cause of some disabilities such as multiple sclerosis or how long the time period should be between exposure to the origin and initial diagnosis. In some cases, delayed onset is recognized as a feature of a disability such as posttraumatic stress disorder. In other cases, evidence supporting the need for a presumption can only be obtained through epidemiological studies

of the frequency of disease among groups of people and research into the effects of various exposures on health.

Some presumptions were mandated by statute and some of those were based more on a political decision than a scientific decision. Often, the basis for presumption consisted of a combination of expert opinion, advocacy from organizations and individuals, and Congress' sense of justice, rather than scientific evidence.

The Commission would like you to thoroughly assess the processes used in the past and at the current time to make decisions on presumptions. In some cases, you may find that the processes are ad hoc in nature, varying from time to time and depending on the political and management philosophies of those involved. An understanding of past processes will be very instructive in deciding what the most appropriate process should be in the future.

The Commission is aware, as is the Institute of Medicine, that several presumptions were approved because it was not possible to document exposure to biological, chemical, radiological, or other environmental agents by accurate information on the exact locations to which military service members were assigned during precise periods of time. This lack of information prevented definitive studies. Your Committee may be able to provide substantive advice concerning how to ensure that this situation is not repeated in the future. Currently everyone who served in Vietnam is presumed to have been exposed to dioxin from Agent Orange. Do we have a better way of making these determinations?

A review of the history of the process for some presumption determinations indicates that many years can elapse between the onset of the disease and the establishment of the presumption. Examples of this include diseases associated with herbicide exposure during Vietnam service and experimental exposure to mustard gas during WWII service. Such long periods of time without compensation have no doubt resulted in significant hardship for many veterans and their families. What are the factors that contribute to these long periods of elapsed time? What can be done about these factors to improve the result?

Agent Orange, Radiation, and Gulf War Syndrome have resulted in a rapidly growing area of environmental presumptions that have prompted some to raise questions about the disability compensation program. War often affects men and women in profound ways that are not easily explainable or treatable. Many veterans experience problems/diseases that they attribute to chemical or radiation exposure. Leaving aside questions of the possible effect of psychic injuries inflicted by war on these questions, it seems that science cannot easily or quickly resolve these issues particularly where (1) chemical/radiation exposure levels are often unknowable or difficult to ascertain and (2) the effect of exposure on diseases experienced is scientifically unsettled.

Notwithstanding this uncertainty, the intense emotions surrounding those genuinely suffering and the perceived unfairness of forcing veterans to "prove" the environments or places where they served related to their possible exposure has led Congress and the Executive Branch to create presumptions. Certain studies (not even necessarily involving veterans), for example, showing that those exposed to dioxin have slightly higher rates of diabetes or prostate cancer, have resulted in an inexorable push to compensate all veterans with diabetes/prostate cancer even if it is likely that dioxin exposure is a determinative factor in only a small percentage of cases. Since it is impossible to know what role dioxin played in any particular case, all Vietnam veterans with diabetes and prostate cancer have been and are being granted presumptive service connection. Is this presumption fully supported by medical evidence? What amount of increase in occurrence rate is enough to warrant compensation? What approaches could be considered to alleviate this costly result?

Your Committee should consider if a different methodology should be used in determining causal relationships other than the environmental aspect used for the current method. Should the Committee on Presumptions review the Gulf War Illness presumptions? Should there be a defined process in place at VA to review and establish presumptions? Should the same or a different process be used periodically to review existing presumptions?

The Commission also requests that your Committee provide advice, from an epidemiological and statistical standpoint, on what strength of evidence would be the appropriate requirement when the Secretary of Veterans Affairs considers whether to establish a presumption. Currently, in determining if a herbicide disease should have a presumption established, the Secretary must determine that the results upon which the presumption is based are statistically significant, are capable of replication, and withstand peer review. And, an association is considered positive if the credible evidence for the association is equal to or outweighs the credible evidence against the association. Should the standards for inferential statistical evidence in finding an association between causative factors and disabilities change? From whom should VA accept sound medical and scientific information to analyze and to consider whether a condition be added as a presumption?

Are medical advancements occurring so rapidly and new medical findings becoming available so quickly that a formal regulatory process for presumption impedes decision making? How could a regulatory process react in a timely manner to the accelerating changes in medical science? Is a significant change in the methodology used to establish a presumption something to be considered?

During your Committee's review, the Commission would ask you to analyze all key documents and literature regarding presumptions to include

all legislative and committee reports. We also encourage you to review published research on and medical studies of disease exposure and the subsequent development of those diseases.

Requesting your Committee to study these issues underlining the research question should not be taken as directing any disposition or finding with respect to the research question. Rather the Commission is asking that particular attention be focused on the issue.

SUMMARY

The Commission recognizes the challenges that the Committee on Presumptive Disability Decision Making Process faces in dealing with this issue. Your Committee has been asked to help ensure that future veterans are granted service connection under a presumption basis based on the best scientific evidence available. Your advice is crucial. The Commission anticipates that you will provide suggestions that will improve the processes that establish future presumptions. Presumptions are intended to protect a service member from being denied service connection for a disease or injury because he/she is unable to confirm the incurrence of the injury during combat or exposure to the disease through no fault of his or her own. To the extent possible, suggestions that will avoid the necessity for many future presumptions by ensuring that exposure of service members is documented and scientific evidence is made available would be important.

Having a method of granting service connection quickly and fairly based on a presumption is of critical importance to our disabled veterans and their surviving spouses. A through review of the present processes is needed. The presumptions must also be understandable to raters to allow for uniform and equitable application to veterans' claims regardless of where the rating is prepared. Ensuring that future presumption processes reflect the then current medical knowledge about the causal relationship would benefit entire veteran community.

Your suggestions will be considered by the Commission in determining the appropriateness of benefits, the appropriateness of the level of such benefits, and the appropriate standard or standards for determining whether a disability or death of a veteran should be compensated.

The Commission will consider the Committee's findings and suggestions in framing its response to the charge from Congress and the President.

We look forward to hearing the results of your Committee's deliberations in the coming months.

Appendix B

Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans Open Session Meeting Agendas

Committee Meeting #1
May 31, 2006
Keck Center of the National Academies
Washington, D.C.

AGENDA

Wednesday, May 31 Room 201

8:30 a.m.	Closed Session (Committee Members and IOM Staff Only)
10:30 a.m.	Open Session Begins
10:30 a.m.	Welcome and Introductory Remarks, Introduction of Committee Member and Attendees *Jonathan Samet, M.D., M.S., Committee Chair*
10:40 a.m.	Expectations of the Study Sponsor *Commissioner John Grady (Member, Veterans' Disability Benefits Commission)*
11:00 a.m.	An Overview of the Disability Benefits Program and Presumptions Affecting Veterans' Benefits *Thomas Pamperin, M.B.A. (Assistant Director for Policy, Compensation and Pension Service, Department of Veterans Affairs)*
11:45 a.m.	Legislative and Regulatory History of Presumptions *David Barrans, J.D. (Deputy Assistant General Counsel, Office of General Counsel, Department of Veterans Affairs)*

12:15 p.m. Lunch
1:15 p.m. The Role of Science in Establishing VA Disability Compensation Policies
Mark Brown, Ph.D. (Director, VA's Environmental Agents Service, Office of Public Health and Environmental Hazards, Department of Veterans Affairs)
1:45 p.m. Presumptions in VA's Disability Program—The Effect
Thomas Pamperin, M.B.A. (Assistant Director for Policy, Compensation and Pension Service, Department of Veterans Affairs)
2:05 p.m. PANEL Q&A—VA Presenters and Committee Members
2:45 p.m. Break
3:00 p.m. An Examiner's Use of the Clinician's Guide and How Examiners Are Selected and Trained by VHA
Patrick Joyce, M.D., J.D., M.P.H. (Chief Physician, Compensation and Pension Program, VA Medical Center, Washington, D.C.)
3:45 p.m. Making Decisions Based on Medical Evidence
Bradley Flohr (Chief of Advisory Review Staff, Compensation and Pension Service)
4:15 p.m. Public Comments (Attendees will be given the opportunity to make brief remarks to the Committee Members)
5:15 p.m. Open Session Ends
5:15 p.m. Closed Session (Committee Members and IOM Staff Only)
6:15 p.m. Adjourn

Committee Meeting #2
July 27, 2006
Keck Center of the National Academies
Washington, D.C.

AGENDA

Thursday, July 27 Room 101

8:30 a.m. Closed Session (Committee Members and IOM Staff Only)
9:00 a.m. Open Session Begins
9:00 a.m. Welcome and Introductory Remarks, Introduction of Committee Members and Attendees
Jonathan Samet, M.D., M.S., Committee Chair

9:10 a.m.	Summary of Recent IOM Studies Conducted for VA *Rose Marie Martinez, Sc.D. (Director, Board on Population Health and Public Health Practice, Institute of Medicine)*
9:45 a.m.	VA Health Care Utilization Among Operation Iraqi Freedom/ Operation Enduring Freedom Veterans *Han K. Kang, Dr.P.H. (Director, Environmental Epidemiology Service, Department of Veterans Affairs)*
10:15 a.m.	Overview of VA Registries *Han K. Kang, Dr.P.H. (Director, Environmental Epidemiology Service, Department of Veterans Affairs)*
10:45 a.m.	Break
11:00 a.m.	Assessing Environmental and Occupational Exposures—VA Disability and Compensation Policies *Lawrence R. Deyton, M.S.P.H., M.D. (Chief Officer, Public Health and Environmental Hazards, Department of Veterans Affairs)*
12:00 p.m.	Lunch
1:00 p.m.	Overview of DoD Deployment and Installation-Based Occupational and Environmental Health Programs *R. Craig Postlewaite, D.V.M., M.P.H. (Senior Analyst, Environmental Health Surveillance, DoD Deployment Health Support Directorate)*
1:20 p.m.	Deployment Health Surveillance: Past, Current, and Future Operations *Jack M. Heller, Ph.D. (Director, Health Risk Management, U.S. Army Center for Health Promotion and Preventive Medicine)*
2:05 p.m.	DoD Occupational Health Exposure Assessment Processes *John Seibert, C.I.H., C.S.P. (Assistant for Safety, Health and Fire Protection, Office of the Deputy Under Secretary of Defense for Installations and Environment)*
2:50 p.m.	Break
3:00 p.m.	Panel Discussion with DoD Representatives
4:00 p.m.	Public Comments from Veterans Service Organizations The American Legion *Cathy Wiblemo, M.H.A. (Deputy Director, Veterans Affairs and Rehabilitation Division)* AMVETS *Jim Doran (National Service Director)* United Spinal Association *Leonard Selfon, Esq. (National Service Director)*

Veterans of Foreign Wars of the United States
Quentin Kinderman (Deputy Director, National Legislative Service)
Vietnam Veterans of America
Rick Weidman (Executive Director for Policy and Government Affairs)

4:30 p.m. Public Comments from Attendees
(Attendees will also be given the opportunity to make brief remarks to the Committee Members)
5:00 p.m. Open Session Ends
5:15 p.m. Closed Session (Committee Members and IOM Staff Only)
6:00 p.m. Adjourn

Committee Meeting #3
October 4, 2006
Emily Morgan Hotel
705 East Houston Street
San Antonio, Texas

AGENDA

Wednesday, October 4 Emily Morgan Hotel (Room 2)

7:30 a.m. Closed Session (Committee Members and IOM Staff Only)
8:00 a.m. Open Session Begins
8:00 a.m. Welcome and Introductory Remarks, Introduction of Committee Members and Attendees
Jonathan M. Samet, M.D., M.S., (Chair, Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans)
8:10 a.m. Presentations from Past Congressional Staffers
Laura Petrou
Patrick Ryan, J.D.
Edward Scott, J.D.
Chris Yoder
9:10 a.m. Panel Q&A—Panel Presenters and Committee Members
9:50 a.m. Break
10:00 a.m. DoD and Veterans Affairs: Health Information Sharing
Nhan Do, M.D., M.S., F.A.C.P. (Information Manager, Medical Informatics, TricareManagement Activity)
Cliff Freeman, M.A., M.S. (Director, VA/DoD Health IT Sharing Program)

10:30 a.m.	Panel Q&A—Health IT Presenters and Committee Members
11:00 a.m.	Public Comments from Veterans Service Organizations Public Comments from Attendees (Attendees will also be given the opportunity to make brief remarks to the Committee Members) *Comments from LTG James Terry Scott, U.S. Army (Ret.) (Chairman, Veterans Disability Benefits Commission)* *Closing Comments from Jonathan M. Samet, M.D., M.S. (Chair, Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans)*
12:00 p.m.	Open Session Ends
1:00 p.m.	Closed Session (Committee Members and IOM Staff Only)
6:00 p.m.	Adjourn

Appendix C

Glossary

a priori—Proceeding from a known or assumed cause to a necessarily related effect; based on a hypothesis or theory rather than on experiment or experience; made before or without examination and not supported by factual study.

Accession—Entry into the service.

Acidosis—A pathologic state characterized by an increase in the concentration of hydrogen ions in the arterial blood above the normal level, 40 nmol/L, or pH 7.4; may be caused by an accumulation of carbon dioxide or acidic products of metabolism, or by a decrease in the concentration of alkaline compounds. (Stedman's medical dictionary 28th ed., 2005)

Acneiform (or acneform) lesions—Lesions resembling acne. (Stedman's medical dictionary 28th ed., 2005)

Active duty—(A) Full-time duty in the Armed Forces, other than active duty for training; (B) Full-time duty (other than for training purposes) as a commissioned officer of the Regular or Reserve Corps of the Public Health Service (i) on or after July 29, 1945, or (ii) before that date under circumstances affording entitlement to "full military benefits" or (iii) at any time, for the purposes of chapter 13 of this title (38 U.S.C.S. § 1301 et seq.); (C) Full-time duty as a commissioned officer of the National Oceanic and Atmospheric Administration or its predecessor organization the Coast and Geodetic Survey (i) on or after July 29, 1945, or (ii) before that date (I) while on transfer to one of the Armed Forces, or (II) while, in time of war or national emergency declared by the President, assigned to duty on a project for one of the Armed Forces

in an area determined by the Secretary of Defense to be of immediate military hazard, or (III) in the Philippine Islands on December 7, 1941, and continuously in such islands thereafter, or (iii) at any time, for the purposes of chapter 13 of this title (38 U.S.C.S. § 1301 et seq.); (D) Service as a cadet at the United States Military, Air Force, or Coast Guard Academy, or as a midshipman at the United States Naval Academy; and (E) Authorized travel to or from such duty or service. (Definitions. 2006. 38 U.S.C. § 101.)

Active duty for training—(A) Full-time duty in the Armed Forces performed by Reserves for training purposes; (B) Full-time duty for training purposes performed as a commissioned officer of the Reserve Corps of the Public Health Service (i) on or after July 29, 1945, or (ii) before that date under circumstances affording entitlement to "full military benefits," or (iii) at any time, for the purposes of chapter 13 of this title (38 U.S.C.S. § 1301 et seq.); (C) In the case of members of the National Guard or Air National Guard of any State, full-time duty under section 316, 502, 503, 504, or 505 of title 32 (32 U.S.C.S. § 316, 502, 503, 504, or 505), or the prior corresponding provisions of law; and (D) Duty performed by a member of a Senior Reserve Officers' Training Corps program when ordered to such duty for the purpose of training or a practice cruise under chapter 103 of title 10 (10 U.S.C.S. § 2101 et seq.) for a period of not less than four weeks and which must be completed by the member before the member is commissioned; and (E) Authorized travel to or from such duty. The term does not include duty performed as a temporary member of the Coast Guard Reserve. (Definitions. 2006. 38 U.S.C. § 101.)

Active military, naval, or air service—(A) Active duty; (B) any period of active duty for training during which the individual concerned was disabled or died from a disease or injury incurred or aggravated in line of duty; and (C) Any period of inactive duty training during which the individual concerned was disabled or died—(i) from an injury incurred or aggravated in line of duty; or (ii) from an acute myocardial infarction, a cardiac arrest, or a cerebrovascular accident occurring during such training. (Definitions. 2006. 38 U.S.C. § 101.)

Acute myelogenous leukemia (AML)—A form of leukemia characterized by an uncontrolled proliferation of myelopoietic cells in the bone marrow and in extramedullary sites, and the presence of large numbers of immature and mature granulocytic forms in various tissues (and organs) and in the circulating blood.

Acute nonlymphocytic leukemia (ANLL)—Any of several forms of myelogenous leukemia marked by an abnormal increase in the number of immature white blood cells; risk of disease is increased among people who have been exposed to massive doses of radiation.

Addison's anemia (also known as primary anemia, pernicious anemia)—A chronic progressive anemia of older adults (occurring more frequently during the fifth and later decades, rarely before 30 years of age), due to the failure of absorption of vitamin B_{12}, usually resulting from a defect of the stomach accompanied by mucosal atrophy and associated with lack of secretion of "intrinsic" factor; characterized by numbness and tingling, weakness, and a sore smooth tongue, as well as dyspnea after slight exertion, faintness, pallor of the skin and mucous membranes, anorexia, diarrhea, loss of weight, and fever; laboratory studies usually reveal greatly decreased red blood cell counts, low levels of hemoglobin, numerous characteristically oval shaped macrocytic erythrocytes (color index greater than normal, but not truly hyperchromic), and hypo- or achlorhydria, in association with a predominant number of megaloblasts and relatively few normoblasts in the bone marrow; the leukocyte count in peripheral blood may be less than normal, with relative lymphocytosis and hypersegmented neutrophils; a low level of vitamin B_{12} is found in peripheral red blood cells; administration of vitamin B_{12} results in a characteristic reticulocyte response, relief from symptoms, and an increase in erythrocytes, provided that pernicious anemia is not complicated by another disease; the condition is not actually "pernicious," as it was prior to the availability of therapy with vitamin B_{12}. At least two autosomal recessive forms are known. In one there is a defect of intrinsic factor and in the other a defective absorption of vitamin B_{12} from the intestine. (Stedman's medical dictionary 28th ed., 2005)

Additive model—A model in which the combined effect of several factors is the sum of the effects that would be produced by each of the factors in the absence of the others. For example, if factor X adds x percent to risk in the absence of Y, and if factor Y adds y percent to risk in the absence of X, an additive model states that the two factors together will add $(x + y)$ percent to risk. (Last, 2001)

Adult fibrosarcoma—A sarcoma of relatively low malignancy consisting chiefly of spindle-shaped cells that tend to form collagenous fibrils.

Agent Orange—An herbicide and defoliant consisting of 2,4,5-trichlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, and dioxin, that was widely used during the Vietnam War; it has been shown to produce residual postexposure carcinogenic and teratogenic effects in humans. (Stedman's medical dictionary 28th ed., 2005)

Alveolar (alveolus)—A small cell, cavity, or socket. (1) Syn: *pulmonary alveolus*. (2) One of the terminal secretory portions of an alveolar or racemose gland. (3) One of the honeycomb pits in the wall of the stomach. (4) Syn: *tooth socket*. (Stedman's medical dictionary 28th ed., 2005)

Ambient air—The surrounding or encompassing air; pertaining to the environment in which an organism or apparatus functions.

Amebiasis—Infection with the protozoon *Entamoeba histolytica*. (Stedman's medical dictionary 28th ed., 2005)

Amebic dysentery—An inflammation of the intestine caused by infestation with *Entamoeba histolytica*. Marked by dysentery, abdominal pain, and erosion of the intestinal wall.

Amputation—The cutting off of a limb or part of a limb, the breast, or other projecting part.

Amyloidosis—A disease characterized by extracellular accumulation of amyloid in various organs and tissues of the body; may be primary or secondary.

Amyotrophic lateral sclerosis (ALS)—A rare fatal progressive degenerative disease that affects pyramidal motor neurons, usually begins in middle age, and is characterized especially by increasing and spreading muscular weakness. Also known as Lou Gehrig's disease. (Stedman's medical dictionary 28th ed., 2005)

Anemia—Any condition in which the number of red blood cells/mm^3, the amount of hemoglobin in 100 ml of blood, and/or the volume of packed red blood cells/100 ml of blood is less than normal; clinically, generally pertaining to the concentration of oxygen-transporting material in a designated volume of blood, in contrast to total quantities as in oligocythemia, oligochromemia, and oligemia. Anemia is frequently manifested by pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and tendency to fatigue. (Stedman's medical dictionary 28th ed., 2005)

Angioendotheliomatosis—Proliferation of endothelial cells within blood vessels. (Stedman's medical dictionary 28th ed., 2005)

Angiosarcoma—A rare malignant neoplasm occurring most often in soft tissues; believed to originate from the endothelial cells of blood vessels; microscopically composed of spindle-shaped cells, some of which line small spaces resembling vascular clefts. (Stedman's medical dictionary 28th ed., 2005)

Anthrax—Infection by the bacterium *Bacillus anthracis*, which in humans is caused by infected animals or animal products, and ingestion or inhalation of spores of the bacterium. The most common naturally occurring form of human anthrax is the cutaneous, and both the inhalational and the gastrointestinal forms are quite rare. Anthrax in animals occurs throughout the world, primarily in herbovores, especially cattle, horses, goats, and sheep. (Stedman's medical dictionary 28th ed., 2005)

Anxiety neurosis—Apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.

Aplastic anemia—Anemia characterized by a greatly decreased formation of erythrocytes and hemoglobin, usually associated with pronounced granulocytopenia and thrombocytopenia, as a result of hypoplasticity or aplasticity of bone marrow. (Stedman's medical dictionary 28th ed., 2005)

Appendectomy—Surgical removal of the appendix. (Stedman's medical dictionary 28th ed., 2005)

Armed Forces—The United States Army, Navy, Marine Corps, Air Force, and Coast Guard, including the reserve components thereof. (Definitions. 2006. 38 U.S.C. § 101.)

Arrhythmia—Loss or abnormality of rhythm; denoting especially an irregularity of the heartbeat. (Stedman's medical dictionary 28th ed., 2005)

Arteriosclerosis—Hardening of the arteries; types generally recognized are: atherosclerosis, Mönckeberg arteriosclerosis, and arteriolosclerosis. (Stedman's medical dictionary 28th ed., 2005)

Arthritis—Inflammation of a joint or a state characterized by inflammation of joints. (Stedman's medical dictionary 28th ed., 2005)

Asbestosis—Pneumoconiosis due to inhalation of asbestos fibers suspended in the ambient air; sometimes complicated by pleural mesothelioma or bronchogenic carcinoma; ferruginous bodies are the histologic hallmark of exposure to asbestos. (Stedman's medical dictionary 28th ed., 2005)

Assay—(1) The quantitative or qualitative evaluation of a substance for impurities, toxicity, etc.; the results of such an evaluation. (2) To examine; to subject to analysis. (3) Test of purity; trial. (Stedman's medical dictionary 28th ed., 2005)

Assigned share—For two groups of people that are alike, except that one group is exposed and the other is not exposed, the excess number of cases in the exposed group expressed as a fraction of the total number of cases in the exposed group.

Association—Statistical dependence between two or more events, characteristics, or other variables. An association is present if the probability of occurrence of an event or characteristic, or the quantity of a variable, is related to the occurrence of one or more other events, the presence of one or more other characteristics, or the quantity of one or more other variables. The association between two variables is described as positive when higher values of a variable are associated with higher values of another variable. In a negative association, the occurrence of higher values of one variable is associated with lower values of the other variable. An association may be fortuitous or may be produced by various other circumstances; the presence of an association does not necessarily imply a causal relationship. If the use of the term *association* is confined to situations in which the relationship between two variables is statistically significant, the terms *statistical association* and *statistically*

significant association become tautological. However, ordinary usage is seldom so precise at this. The terms *association* and *relationship* are often used interchangeably. Associations can be broadly grouped under two headings, noncausal and causal. (Adapted from Last, 2001)

Asthma—An inflammatory disease of the lungs characterized by reversible (in most cases) airway obstruction. Originally, a term used to mean "difficult breathing"; now used to denote bronchial asthma. (Stedman's medical dictionary 28th ed., 2005)

Atherosclerosis—Arteriosclerosis characterized by irregularly distributed lipid deposits in the intima of large and medium sized arteries, causing narrowing of arterial lumens and proceeding eventually to fibrosis and calcification. Lesions are usually focal and progress slowly and intermittently. Limitation of blood flow accounts for most clinical manifestations, which vary with the distribution and severity of lesions. (Stedman's medical dictionary 28th ed., 2005)

Atrophy—A wasting of tissues, organs, or the entire body, as from death and reabsorption of cells, diminished cellular proliferation, decreased cellular volume, pressure, ischemia, malnutrition, lessened function, or hormonal changes. (Stedman's medical dictionary 28th ed., 2005)

Attributable fraction (AF)—Fraction of disease in the population that would not have occurred had the exposure not occurred. A term sometimes used to refer to the attributable fraction in the population, and sometimes to the attributable fraction among the exposed (Last, 2001). The AF may be best understood by seeing how it is calculated: $AF = (R_1 - R_0) / R_1$, where R_1 is the rate of a disease (typically incidence rate) in an exposed population and R_0 is the rate in that same population if unexposed. AF, then, is the fraction of the rate of disease in the exposed that is due to exposure. Dividing numerator and denominator by R_0, since R_1/R_0 is the relative risk (RR), produces the more familiar expression, $AF = (RR - 1) / RR$. See Population attributable fraction.

Avitaminosis—Properly, hypovitaminosis. (Stedman's medical dictionary 28th ed., 2005)

Bacillary dysentery (also known as shigellosis)—Infection with *Shigella dysenteriae*, *Shingella flexneri*, or other organisms. (Stedman's medical dictionary 28th ed., 2005)

Bancroft[ian] filariasis—Filariasis caused by *Wuchereria bancrofti*. (Stedman's medical dictionary 28th ed., 2005)

Bari Harbor Disaster—On December 2, 1943, German Junkers Ju 88 bombers attacked the port of Bari, a key supply center for Allied forces fighting their way up the Italian peninsula. Several Allied ships were sunk in the overcrowded harbor, including *John Harvey*, which was carrying mustard gas, intended for use if German forces initiated chemical warfare. The presence of the gas was highly classified, and

authorities ashore had no knowledge of it. This increased the number of fatalities, since physicians—who had no idea that they were dealing with the effects of mustard gas—prescribed treatment proper for those suffering from exposure and immersion, which proved fatal in many cases.

Basophil—(1) A cell with granules that stain specifically with basic dyes. (2) Syn: *basophilic*. (3) A phagocytic leukocyte of the blood characterized by numerous basophilic granules containing heparin and histamine and leukotrines; except for its segmented nucleus, it is morphologically and physiologically similar to the mast cell though they originate from different stem cells in the bone marrow. (Stedman's medical dictionary 28th ed., 2005)

Bayes' Theorem—A theorem for probability first derived and described by Thomas Bayes (1702-1761), an English clergyman and mathematician, in his Essay Towards Solving a Problem in the Doctrine of Chances (1763, published posthumously). In epidemiology, the theorem is often used to obtain the probability of disease in a group of people with some characteristic on the basis of the overall rate of that disease (the *prior probability* of disease) and the likelihoods of that characteristic in healthy and diseased individuals. The most familiar application is in clinical decision analysis, where it is used for estimating the probability of a particular diagnosis given the appearance of some symptoms or test results. A simplified version of the theorem is

$$P(D|S) = \frac{P(S|D)P(D)}{P(S|D)P(D) + P(S|\bar{D})P(\bar{D})}$$

where D = disease, S = symptom, and $\bar{D}$ = no disease. The probability of disease given the symptom is the *posterior probability.* The probability of disease before knowing of the presence or absence of the symptom is the *prior probability*. The formula emphasizes what clinical intuition often overlooks, namely, that the probability of disease *given* the symptom depends not only on how characteristic that symptom is of the disease but also on how frequent the disease is among the population being served.

The theorem can also be used for estimating exposure-specific rates from case-control studies if there is added information about the overall rate of disease in that population.

The theorem is sometimes presented in terms of the odds of disease before knowing the symptom (*prior odds*) and after knowing the symptom (*posterior odds*). (Adapted from Last, 2001)

Bayesian approach—A method of statistical inference that begins with the state of knowledge, i.e., the facts, prior to an exposure or an intervention, and augments this with the study data to yield the state of knowledge posterior to the study.

Benzene—The basic six-carbon ring structure in most aromatic compounds; a highly toxic hydrocarbon from light coal tar oil; used as a solvent. (Stedman's medical dictionary 28th ed., 2005)

Beriberi—A specific nutritional deficiency syndrome occurring in endemic form in eastern and southern Asia, sporadically in other parts of the world without reference to climate, and sometimes in alcoholic patients, resulting mainly from a dietary deficiency of thiamin; the "dry" form is characterized by painful polyneuropathy that involves both large and small somatic nerve fibers, as well as autonomic nerve fibers, the initial symptom is burning feet, and later symptoms consist of painful parathesias in the distal upper limbs as well, weakness and atrophy of the feet and hands, and distal atrophic skin and hair loss; the "wet" form is characterized by edema resulting from a high-output form of heart failure, but usually there is evidence of a coexisting polyneuropathy as well. (Stedman's medical dictionary 28th ed., 2005)

Beryllium disease—Various conditions resulting from exposure to beryllium and its compounds or alloys.

Bias—Deviation of results or inference from the truth, or process leading to such deviation; any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth. Among the ways in which deviation from the truth can occur, are the following:

1. Systematic (one-sided) variation of measurements from the true values (syn: *systematc error*)
2. Variation of statistical summary measures (means, rates, measurements of association, etc.) from their true values as result of systematic variation of measurements, other flaws in data collection, or flaws in study design or analysis
3. Deviation of inferences from the truth as a result of flaws in study design, data collection, or the analysis or interpretation of results
4. A tendency of procedures (in study design, data collection, analysis, interpretation, review, or publication) to yield results or conclusions that depart from the truth
5. Prejudice leading to the conscious or unconscious selection of study procedures that departs from the truth in a particular direction or to one-sidedness in the interpretation of results

The term *bias* does not necessarily carry an imputation of prejudice or other subjective factor, such as the experimenter's desire for a particular outcome.This differs from conventional usage, in which bias refers to a partisan point of view. (Adapted from Last, 2001)

Biological plausibility—The criterion that an observed, presumably or putatively causal association is coherent with previously existing biological or medical knowledge. This judgment should be used cautiously since it could impede development of new knowledge that does not fit existing ideas. (Last, 2001)

Bipolar disorder—An affective disorder characterized by the occurrence of alternating manic, hypomanic, or mixed episodes and with major depressive episodes. The DSM specifies the commonly observed patterns of bipolar I and bipolar II disease and cyclothymia. (Stedman's medical dictionary 28th ed., 2005)

Black lung—A form of pneumoconiosis, common in coal miners, characterized by deposits of carbon particles in the lung. (Stedman's medical dictionary 28th ed., 2005)

Black water fever—Hemoglobinuria resulting from severe hemolysis occurring in falciparum malaria. (Stedman's medical dictionary 28th ed., 2005)

Bonus Expeditionary Forces—About 20,000 WWI veterans, their families, and other affiliated groups who demonstrated in Washington, D.C., during the spring and summer of 1932 seeking immediate payment of a "bonus" granted by the Adjusted Service Certificate Law of 1924 for payment in 1945.

Bradford Hill criteria—Heuristic criteria for interpreting when evidence supports moving beyond observed association to causation. The criteria include strength of association, consistency, specificity, temporality, dose-response, plausibility, coherence, experimental evidence, and analogy. Named after Sir Austin Bradford Hill.

Bradley Commission—Formed in 1987 in response to concerns regarding the quality and quantity of the history taught in American classrooms.

Brain hemorrhage (cerebral hemorrhage)—Hemorrhage into the substance of the cerebrum, usually in the region of the internal capsule by the rupture of the lenticulostriate. (Stedman's medical dictionary 28th ed., 2005)

Brain thrombosis (cerebral thrombosis)—Clotting of the blood in a cerebral vessel. (Stedman's medical dictionary 28th ed., 2005)

Bronchiectasis—Chronic dilation of bronchi or bronchioles as a sequel of inflammatory disease or obstruction often associated with heavy sputum production.

Bronchiolo-alveolar carcinoma—A relatively uncommon lung cancer which is a type of non-small cell lung cancer.

Bronchitis—Inflammation of the mucous membranes of the bronchi. (Stedman's medical dictionary 28th ed., 2005)

Buccal cavity—That part of the mouth bounded anteriorally and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflection of the mucosa from the lips and cheeks to the gums. (Stedman's medical dictionary 28th ed., 2005)

Buerger's disease—Thromboangiitis (thromboangiitis—an inflammation of the blood vessels associated with thrombosis) of the small arteries and veins of the extremities and especially the feet resulting in occlusion, ischemia, and gangrene.

Bulbar—(1) Relating to a bulb. (2) Relating to the rhombencephalon (hindbrain). (3) Bulb-shaped; resembling a bulb. (Stedman's medical dictionary 28th ed., 2005)

Burden of persuasion—The duty upon a party in a legal proceeding to persuade the fact-finder to decide for that party on an assertion of fact.

Burden of proof—The duty of proving a disputed assertion or charge.

Butadiene—A flammable gaseous open-chain hydrocarbon used in making synthetic rubbers.

Cacodylic acid—Arsenical contact herbicide that defoliates or desiccates a wide variety of plant species. (Stedman's medical dictionary 28th ed., 2005)

Calculi (Calculus)—A concretion formed in any part of the body, most commonly in the passages of the biliary and urinary tracts; usually composed of salts of inorganic or organic acids, or of other material such as cholesterol. (Stedman's medical dictionary 28th ed., 2005)

Cancer—General term frequently used to indicate any of various types of malignant neoplasms, most of which invade surrounding tissues, may metastasize to several sites, and are likely to recur after attempted removal and to cause death of the patient unless adequately treated; especially, any such carcinoma or sarcoma, but, in ordinary usage, especially the former. (Stedman's medical dictionary 28th ed., 2005)

Cannikin—A nuclear device detonated beneath Amchitka Island, Alaska, in 1971.

Carcinogen—Any cancer-producing substance or organism, such as polycyclic aromatic hydrocarbons, or agents such as in certain types of irradiation. (Stedman's medical dictionary 28th ed., 2005)

Carcinoma—Any of various types of malignant neoplasm derived from epithelial cells, chiefly glandular (adenocarcinoma) or squamous (squamous cell carcinoma); the most commonly occurring kind of cancer. (Stedman's medical dictionary 28th ed., 2005)

Cardiovascular disease—Any abnormal condition characterized by dysfunction of the heart and blood vessels.

Case-control study—An epidemiologic study design in which a population sample is defined on the basis of whether (cases) or not (controls) a disease (or other endpoint) is present; cases and controls are then compared with respect to disease risk factors, typically exposure.

Cataracts (posterior subcapsulary)—Complete or partial opacity of the ocular lens. (Stedman's medical dictionary 28th ed., 2005)

Causal association—An association between two events or characteristics that arises because one causes the other.

Causal inference—Examining the structure and results of many investigations in an attempt to assess and, if possible, eliminate all possible noncausal reasons for observed associations.

Causal pathway—A sequence mechanism, possibly involving several intermediate factors, by which one factor causes another.

Causation—The relating of causes to the effects they produce. A relationship between events (specific, or individual causation) or between variables (general, or population level causation) in which an outside intervention to change the cause would result in a change in the effect.

Child—Except for purposes of chapter 19 of this title (38 U.S.C.S. § 1901 et seq.) (other than with respect to a child who is an insurable dependent under section 1965[10][B] of such chapter [38 U.S.C.S. § 1965(10)(B)] and section 8502[b] of this title [38 U.S.C.S. § 8502(b)]) a person who is unmarried and—(i) who is under the age of eighteen years; (ii) who, before attaining the age of eighteen years, became permanently incapable of self-support; or (iii) who, after attaining the age of eighteen years and until completion of education or training (but not after attaining the age of twenty-three years), is pursuing a course of instruction at an approved educational institution; and who is a legitimate child, a legally adopted child, a stepchild who is a member of a veteran's household or was a member at the time of the veteran's death, or an illegitimate child but, as to the alleged father, only if acknowledged in writing signed by him, or if he has been judicially ordered to contribute to the child's support or has been, before his death, judicially decreed to be the father of such child, or if he is otherwise shown by evidence satisfactory to the Secretary to be the father of such child. A person shall be deemed, as of the date of death of a veteran, to be the legally adopted child of such veteran if such person was at the time of the veteran's death living in the veteran's household and was legally adopted by the veteran's surviving spouse before August 26, 1961, or within two years after the veteran's death; however, this sentence shall not apply if at the time of the veteran's death, such person was receiving regular contributions toward the person's support from some individual other than the veteran or the veteran's spouse, or from any public or private welfare organization which furnishes services or assistance for

children. A person with respect to whom an interlocutory decree of adoption has been issued by an appropriate adoption authority shall be recognized thereafter as a legally adopted child, unless and until that decree is rescinded, if the child remains in the custody of the adopting parent or parents during the interlocutory period. A person who has been placed for adoption under an agreement entered into by the adopting parent or parents with any agency authorized under law to so act shall be recognized thereafter as a legally adopted child, unless and until such agreement is terminated, if the child remains in the custody of the adopting parent or parents during the period of placement for adoption under such agreement. A person described in clause (ii) of the first sentence of this subparagraph who was a member of a veteran's household at the time the person became 18 years of age and who is adopted by the veteran shall be recognized as a legally adopted child of the veteran regardless of the age of such person at the time of adoption. (B) For the purposes of subparagraph (A) of this paragraph, in the case of an adoption under the laws of any jurisdiction other than a State (as defined in section 101[20] of this title [para. (20) of this section] and including the Commonwealth of the Northern Mariana Islands)—(i) a person residing outside any of the States shall not be considered to be a legally adopted child of a veteran during the lifetime of such veteran (including the purposes of this subparagraph a Commonwealth Army veteran or new Philippine Scout, as defined in section 3566 of this title (38 U.S.C.S. § 3566) unless such person—(I) was less than eighteen years of age at the time of adoption; (II) is receiving one-half or more of such person's annual support from such veteran; (III) is not in the custody of such person's natural parent, unless such natural parent is such veteran's spouse; and (IV) is residing with such veteran (or in the case of divorce following adoption, with the divorced spouse who is also an adoptive or natural parent) except for periods during which such person is residing apart from such veteran (or such divorced spouse) for purposes of full-time attendance at an educational institution or during which such person or such veteran (or such divorced spouse) is confined in a hospital, nursing home, other health-care facility, or other institution; and (ii) a person shall not be considered to have been a legally adopted child of a veteran as of the date of such veteran's death and thereafter unless—(I) at any time within the one-year period immediately preceding such veteran's death, such veteran was entitled to and was receiving a dependent's allowance or similar monetary benefit under this title for such person; or (II) for a period of at least one year prior to such veteran's death, such person met the requirements of clause (i) of this subparagraph. (Definitions. 2006. 38 U.S.C. § 101.)

Chloracne—An acnelike eruption due to occupational contact, by inhalation or ingestion or through the skin, with certain chlorinated compounds (naphthalenes and diphenyls) used as insulators, insecticides, fungicides, and herbicides, including Agent Orange; keratinous plugs (comedones) form in the pilosebaceous orifices, and various sized small papules (2 to 4 mm) develop. (Stedman's medical dictionary 28th ed., 2005)

Chlorophenols—Several substitution products obtained by the action of chlorine on phenol; used as antiseptics. (Stedman's medical dictionary 28th ed., 2005)

Cholecystitis—Inflammation of the gallbladder. (Stedman's medical dictionary 28th ed., 2005)

Cholera—An acute epidemic infectious disease caused by the bacterium *Vibrio cholerae*. A soluble toxin elaborated in the intestinal tract by the bacterium activates the adenylate cylase of the mucosa, causing active secretion of an isotonic fluid resulting in profuse watery diarrhea, extreme loss of fluid and electrolytes, and dehydration and collapse, but no gross morphologic change in the intestinal mucosa. (Stedman's medical dictionary 28th ed., 2005)

Chondrosarcoma—A malignant neoplasm derived from cartilage cells, occurring most frequently in pelvic bones or near the ends of long bones, in middle-aged and older people; most chondrosarcomas arise de novo, but some may develop in a preexisting benign cartilaginous lesion. (Stedman's medical dictionary 28th ed., 2005)

Chronic fatigue syndrome—A disorder of uncertain cause that is characterized by persistent profound fatigue usually accompanied by impairment in short-term memory or concentration, sore throat, tender lymph nodes, muscle or joint pain, and headache unrelated to any preexisting medical condition.

Chronic multisymptom illness—Chronic illness characterized by a complex of multiple symptoms. More common in deployed Gulf War I (1991) veterans than in non-deployed veterans.

Chronic obstructive pulmonary disease—Comprised of two related diseases (chronic bronchitis and emphysema); chronic obstruction of the flow of air through the airways and out of the lungs, and the obstruction generally is permanent and progressive over time.

Cirrhosis of the liver—A chronic degenerative disease of the liver in which the lobes are covered with fibrous tissue, the parenchyma degenerates, and the lobules are infiltrated with fat. Caused by any of various chronic progressive conditions affecting the liver.

Class Action—A legal action undertaken by one or more plaintiffs on behalf of themselves and all other persons having an identical interest in the alleged wrong.

Classification—Assignment to predesignated classes on the basis of perceived common characteristics (e.g., exposure). A means of giving order to a group of disconnected facts.

Clofibrate—An antilipemic agent that reduces plasma levels of cholesterol, triglycerides, and uric acid; used in the treatment of hypercholesterolemia and atherosclerosis.

Coccidioidomycosis—A variable, benign, severe, or sometimes fatal systemic mycosis due to inhalation of arthroconidia of *Coccidioides immitis*. In benign forms of the infection, the lesions are limited to the upper respiratory tract, lungs, and near lymph nodes; in a low percentage of cases, the disease disseminates to other visceral organs, meninges, bones, joints, and skin and subcutaneous tissues. (Stedman's medical dictionary 28th ed., 2005)

Cohort study—An epidemiologic study design in which a population sample of persons is defined on the basis of some characteristic, typically exposure, and then observed for occurrence of disease events, e.g., death. Comparisons are made between those with varying degrees of exposure or other characteristics.

Compensation—A monthly payment made by the Secretary to a veteran because of service-connected disability, or to a surviving spouse, child, or parent of a veteran because of the service-connected death of the veteran occurring before January 1, 1957. (Definitions. 2006. 38 U.S.C. § 101.)

Confidence interval (CI)—The computed interval with given probability—e.g., 95%—that the true value of a variable such as a mean, proportion, or rate is contained within the interval. (Last, 2001)

Confounder—A variable that can cause or prevent the outcome of interest, is not in the causal pathway between the exposure and the disease on a causal pathway from the cause to the effect, and is associated with the factor under investigation (e.g., exposure). Confounders can create associations between two variables that are not themselves causally related; these associations are often referred to as spurious associations.

Conjunctivitis—Inflammation of the conjunctiva. (Stedman's medical dictionary 28th ed., 2005)

Corneal opacities—Dense, thick white areas in the cornea, through which one cannot see.

Corpuscular—Relating to a corpuscle. (1) A small mass or body. (2) A blood cell. (Stedman's medical dictionary 28th ed., 2005)

Cortisol—The principal glucocorticoid produced by the zona fasciculata of the adrena cortex. It promotes gluconeogenisis and lipolysis, suppresses protein synthesis, inhibits inflammatory and immune responses, and has mild mineralocorticoid (e.g., hypernatremic, kaliuretic, antidiuretic) effects. Most plasma cortisol is bound to transcortin and albumin. Syn-

thetic cortisol administered as a drug is usually known by the alternative name hydrocortisone. (Stedman's medical dictionary 28th ed., 2005)

Counterfactual—A measure in which at least one of the two circumstances in the definition of variables must be contrary to fact. An example is a hypothetical control group that represents what the distribution of exposure would have been if past events had been different from what they actually were. In a *case-specular* study design, the counterfactual control group comprises (imaginary) dwellings on the opposite side of the street from the dwellings occupied by the cases. The purpose is to asses what the exposure would have been in these hypothetical dwellings. The counterfactual difference in past exposure must be defined precisely to facilitate unambiguous calculating of variables in the hypothetical control group. (Adapted from Last, 2001)

Covariate—A possible confounder that is to be adjusted in a statistical analysis—a variable that is considered to be possibly associated with the outcome under study and may or may not be of direct interest to the study. A covariate may be a confounding variable, an effect modifier, or unrelated to the outcome or the exposure.

Crossover study—A method of comparing two or more treatments or interventions in which the subjects or patients, upon completion of the course of one treatment, are switched to another. In the case of two randomly allocated treatments, A and B, half the subjects are randomly allocated to receive these in the order of A, B, and half to receive them in the order of B, A.

CROSSROADS (Operation)—An atmospheric nuclear weapons test series conducted in the summer of 1946 in the Marshall Islands.

Cross-sectional study—An epidemiologic study design in which the relationship between diseases (or other health endpoints) and health-related characteristics is examined as they exist in a defined population at one particular time. The interpretation of associations in cross-sectional studies is limited by the fact that the time order cannot be determined. Thus, an association between A and B may be because A caused B, or B caused A.

Defoliate—To cause the leaves of a plant, tree, or forest to fall off, especially by the use of chemicals.

Dehydroepiandrosterone (DHEA)—A steroid secreted chiefly by the adrenal cortex, but also by the testis; it is the principal precursor of urinary 17-ketosteroids. Weakly androgenic itself, it is metabolized to delta-5 androstenediol, a hormone with both androgenic and estrogenic effects, and is one of the precursors of testosterone. Serum levels are elevated in adrenal virilism. It may function as a neurotransmitter. DHEA secretion begins during fetal life, reaches a peak in the 3rd decade, and declines steadily thereafter; the level at age 80 is only 10-20 percent of the peak

level. This decline has been speculatively associated with the changes of aging. Commercial formulations of DHEA are marketed as dietary supplements, although this substance is neither a nutrient nor a component of the human food chain. Available from health food stores in 10-, 25-, and 50-mg capsules, DHEA has been promoted for the prevention of degenerative diseases including atherosclerosis, Alzheimer's dementia, and parkinsonism, and other effects of aging. None of the alleged benefits have been demonstrated in large, randomized clinical trials. Long-term administration to postmenopausal women has been associated with insulin resistance, hypertension, and reduction of LDL cholesterol. An analysis of 16 preparations of DHEA by high-performance liquid chromatography showed a variation in content from 0 to 150 percent of the labeled strength; only 7 products fell between the expected 90-110 percent of labeled strength. (Stedman's medical dictionary 28th ed., 2005)

Department—Department of Veterans Affairs. (Definitions. 2006. 38 U.S.C. § 101.)

Dependency and indemnity compensation—A monthly payment made by the Secretary to a surviving spouse, child, or parent (A) because of a service-connected death occurring after December 31, 1956, or (B) pursuant to the election of a surviving spouse, child, or parent, in the case of such a death occurring before January 1, 1957. (Definitions. 2006. 38 U.S.C. § 101.)

Depleted uranium—A modestly radioactive heavy metal used in projectiles and armament.

Depressive neurosis—A mental state or chronic mental disorder characterized by feelings of sadness, loneliness, despair, low self-esteem, and self-reproach; accompanying signs include psychomotor retardation or less frequently agitation, withdrawal from social contact, and vegetative states such as loss of appetite and insomnia. (Stedman's medical dictionary 28th ed., 2005)

Dermatitis—Inflammation of the skin. (Stedman's medical dictionary 28th ed., 2005)

Dermatofibrosarcoma protuberans—A relatively slowly growing dermal neoplasm consisting of one or several firm nodules that are usually covered by dark red-blue skin, which tends to be fixed to the palpable masses; histologically, the neoplasm resembles a cellular dermatofibroma with a pronounced storiform pattern; metastases are unusual, but the incidence of recurrence is fairly high. (Stedman's medical dictionary 28th ed., 2005)

Diabetes insipidus—Chronic excretion of very large amounts of pale urine of low specific gravity, causing dehydration and extreme thirst; ordinarily results from inadequate output of pituitary antidiuretic hormone;

the urine abnormalities may be mimicked as a result of excessive fluid intake, as in psychogenic polydipsia. Several types exist: central, neurohypophyseal, and nephrogenic. Autosomal dominant, X-linked, and even autosomal recessive forms have been described. (Stedman's medical dictionary 28th ed., 2005)

Diabetes mellitus—A chronic metabolic disorder in which utilization of carbohydrate is impaired and that of lipid and protein enhanced; it is caused by an absolute or relative deficiency of insulin and is characterized, in more severe cases, by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma; long-term complications include neuropathy, retinopathy, nephropathy, generalized degenerative changes in large and small blood vessels, and increased susceptibility to infection. (Stedman's medical dictionary 28th ed., 2005)

Diabetes Type 1—A condition characterized by high blood glucose levels caused by a total lack of insulin. Occurs when the body's immune system attacks the insulin-producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin. Type 1 diabetes develops most often in young people but can appear in adults. (Stedman's medical dictionary 28th ed., 2005)

Diabetes Type 2—A condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can appear in young people. (Stedman's medical dictionary 28th ed., 2005)

2,4-Dichlorophenoxyacetic acid—An herbicide, more toxic to broad-level dicotyledonous plants (weeds) than to monocotyledonous ones (grains and grass), used with 2,4,5-trichlorophenoxyacetic acid as a constituent of Agent Orange.

Dioxin—A contaminant in the herbicide 2,4,5-T; it is potentially toxic, teratogenic, and carcinogenic.

Direct causation—There are no intervening causes between an act and the resulting harm.

Disability Compensation—A benefit paid to a veteran because of injuries or diseases that happened while on active duty, or were made worse by active military service; also paid to certain veterans disabled from VA health care.

Discharge or release—(A) Retirement from the active military, naval, or air service, and (B) The satisfactory completion of the period of active military, naval, or air service for which a person was obligated at the time of entry into such service in the case of a person who, due to enlistment or reenlistment, was not awarded a discharge or release from such period of service at the time of such completion thereof and who, at such time, would otherwise have been eligible for the award

of a discharge or release under conditions other than dishonorable. (Definitions. 2006. 38 U.S.C. § 101.)

Disfigure—To impair (as in physicality) by deep and persistent injuries.

Distal amputation—An amputation situated away from the center of the body, or from the point of origin.

Dizygotic twins—Relating to twins derived from two separate zygotes, i.e., bearing the same genetic relationship as full sibs but sharing a common intrauterine environment. (Stedman's medical dictionary 28th ed., 2005)

Dose-response—The relationship of risk for observed outcomes (responses) in a population with varying levels of an agent or characteristic, often an exposure.

Dosimeter—A device for measuring doses of radiations (as X-rays).

Double blind design—A procedure of assignment to study (or treatment) and control (or placebo) groups in which neither the investigator nor the study subject has knowledge of the group to which the subject was assigned.

Doubling dose—The dose of a causal factor required to increase the risk of disease twofold.

Dracontiasis (also known as Dracunculosis)—Infection with *Dracunculus medinensis*. (Stedman's medical dictionary 28th ed., 2005)

Dysentery—A disease marked by frequent watery stools, often with blood and mucus, and characterized clinically by pain, tenesmus, fever, and dehydration. (Stedman's medical dictionary 28th ed., 2005)

Dysthymic disorder—(1) A chronic disturbance of mood characterized by mild depression or loss of interest in usual activities. (2) A DSM diagnosis is established when the specified criteria are met. (Stedman's medical dictionary 28th ed., 2005)

Ectomesenchymoma—A rare tumor that may arise in the brain or soft tissue.

Edema—(1) An accumulation of an excessive amount of watery fluid in cells or intercellular tissues. (2) At the gross level, used to describe the physical sign commonly likened to swelling or increased girth that often accompanies the accumulation of fluid in a body part, most often a limb. (Stedman's medical dictionary 28th ed., 2005)

Effect modifier—A factor that modifies the effect on a health outcome of a putative causal factor under study. For example, age is an effect modifier for many conditions, and immunization status is an effect modifier for the consequences of exposure to pathogenic organisms. (Adapted from Last, 2001)

Electrocardiogram—Graphic record of the heart's integrated action currents obtained with the electrocardiograph displayed as voltage changes over time. (Stedman's medical dictionary 28th ed., 2005)

Emphysema—(1) Presence of air in the interstices of the connective tissue of a part. (2) A condition of the lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole (those parts containing alveoli), with destructive changes in their walls and reduction in their number. Clinical manifestation is breathlessness on exertion, due to the combined effect (in varying degrees) of reduction of alveolar surface for gas exchange and collapse of smaller airways with trapping of alveolar gas in expiration; this causes the chest to be held in the position of inspiration ("barrel chest"), with prolonged expiration and increased residual volume. Symptoms of chronic bronchitis often, but not necessarily, coexist. Two structural varieties are panlobular (panacina) emphysema and centrilobular (centriacinar) emphysema; paracicatricial, paraseptal, and bullous emphysema are also common. (Stedman's medical dictionary 28th ed., 2005)

Encephalitis—Inflammation of the brain. (Stedman's medical dictionary 28th ed., 2005)

Encephalitis lethargica residuals—Any diffuse inflammation of the brain occurring in epidemic form.

Endocarditis—Inflammation of the endocardium. (Stedman's medical dictionary 28th ed., 2005)

Endocrinopathy—A disorder in the function of an endocrine gland and the consequences thereof. (Stedman's medical dictionary 28th ed., 2005)

Entitlement—A right to benefits specified especially by law or contract; a government program providing benefits to members of a specified group and funds supporting or distributed by such a program; belief that one is deserving of certain privileges.

Eosinophil—A polymorphonuclear leukocyte characterized by many large or prominent, refractile, cytoplasmic granules that are fairly uniform in size and bright yellow-red or orange when treated with Wright or similar stains; the nuclei are usually larger than those of neutrophils, do not stain as deeply, and characteristically have two lobes (a third lobe is sometimes interposed on the connecting strand of chromatin); these leukocytes are motile phagocytes with distinctive antiparasitic functions; they also phagocytose antigen-antibody complexes. (Stedman's medical dictionary 28th ed., 2005)

Epidemiology—The study of the distribution and determinants of illnesses or diseases in specified populations, and the application of this study to control of health problems. "Study" includes surveillance, observation, hypothesis testing, analytic research, and population experiments. "Distribution" refers to analysis by time, place, and classes of persons affected. (Adapted from Last, 2001)

Epilepsies—Any of various disorders marked by abnormal electrical discharges in the brain and typically manifested by sudden brief episodes

of altered or diminished consciousness, involuntary movements, or convulsions.

Epithelioid leiomyosarcoma—An uncommon neoplasm of smooth muscle in which the cells are polygonal in shape. It usually develops in the stomach.

Epithelioid sarcoma—Malignant mesenchymal tumor showing nodular granulomalike growth of eosinophilic epithelioid and spindle cells palisading around the centrally located necrotic areas. Two subtypes are recognized: a classic distal and fibromalike form. Tumors typically occur in the subcutaneous tissue along the tendons and the fascia. (Stedman's medical dictionary 28th ed., 2005)

Equipoise—A state of uncertainty about the benefit or harm that may result from a suspected causal factor, in which evidence for and against the causal association is equally balanced.

Erythrocyte—A mature red blood cell. (Stedman's medical dictionary 28th ed., 2005)

Escherichia coli—A species that occurs normally in the intestines of man and other vertebrates, is widely distributed in nature, and is a frequent cause of infections of the urogenital tract and of diarrhea in infants. Enteropathogenic strains (serovars) of *Escherichia coli* cause diarrhea due to enterotoxin, the production of which seems to be associated with a transferable episome; the type species of the genus. (Stedman's medical dictionary 28th ed., 2005)

Etiology—Literally, the science of causes, causality; in common usage, cause. See also Causality; Pathogenesis. (Last, 2001)

Ewing's tumor—A malignant neoplasm that occurs usually before the age of 20 years, about twice as frequently in males, and in about 75 percent of patients involves bones of the extremities, including the shoulder girdle, with a predilection for the metaphysis; histologically, there are conspicuous foci of necrosis in association with irregular masses of small, regular, rounded, or ovoid cells (2–3 times the diameter of erythrocytes), with very scanty cytoplasm. (Stedman's medical dictionary 28th ed., 2005)

Exanthema—A skin eruption occurring as a symptom of an acute viral or coccal disease, as in scarlet fever or measles. (Stedman's medical dictionary 28th ed., 2005)

False negative error—The mistake made in accepting a null hypothesis in the presence of a causal association (type I error, alpha error). In the context of diagnostic tests or criteria (or compensation), the number (or percentage) diagnosed not to have the condition who in fact had it.

False positive error—The mistake made in rejecting a null hypothesis in the absence of a causal association (type II error, beta error). In the context of diagnostic tests or criteria (or compensation), the number (or percentage) diagnosed with the condition who in fact did not have it.

Fasting blood glucose—Measures the amount of glucose in your blood after you have not eaten for at least eight hours. It is often done to check for diabetes.

Fibromyalgia—A common syndrome of chronic widespread soft-tissue pain accompanied by weakness, fatigue, and sleep disturbances; the cause is unknown. (Stedman's medical dictionary 28th ed., 2005)

Fibrosarcoma—A malignant neoplasm derived from deep fibrous tissue, characterized by bundles of immature proliferating fibroblasts arranged in a distinctive herringbone pattern with variable collagen formation, which tends to invade locally and metastasize by the bloodstream. (Stedman's medical dictionary 28th ed., 2005)

Fibrous histocytoma—A cutaneous nodule that is painless, round, firm, gray or red, elevated, and commonly found on the extremities.

Filariasis—Presence of filariae in the tissues of the body or in blood (microfilaremia) or tissue fluids (microfilariasis), occurring in tropical and subtropical regions; living worms cause minimal tissue reaction, which may be asymptomatic, but death of the adult worms leads to granulomatous inflammation and permanent fibrosis causing obstruction of the lymphatic channels from dense hyalinized scars in the subcutaneous tissues; the most serious consequence is elephantiasis or pachyderma. (Stedman's medical dictionary 28th ed., 2005)

Five Series Study—Included Operations GREENHOUSE, UPSHOT-KNOTHOLE, CASTLE, REDWING, and PLUMBBOB; these were chosen for a study of atomic veterans to represent tests at both the Nevada Test Site and the Pacific Proving Grounds.

Flat-rate pension—A uniform pension or one based on years of service.

Follicle-stimulating hormone—An acidic glycoprotein hormone of the anterior pituitary that stimulates the graafian follicles of the ovary and assists subsequently in follicular maturation and the secretion of estradiol; in the male, it stimulates the epithelium of the seminiferous tubules and is partially responsible for inducing spermatogenesis. (Stedman's medical dictionary 28th ed., 2005)

Formaldehyde—A pungent gas, HCHO; used as an antiseptic, disinfectant, and histologic fixative, usually in an aqueous solution. (Stedman's medical dictionary 28th ed., 2005)

Former prisoner of war—A person who, while serving in the active military, naval or air service, was forcibly detained or interned in line of duty—(A) By an enemy government or its agents, or a hostile force, during a period of war; or (B) By a foreign government or its agents, or a hostile force, under circumstances which the Secretary finds to have been comparable to the circumstances under which persons have generally been forcibly detained or interned by enemy governments during periods of war. (Definitions. 2006. 38 U.S.C. § 101.)

Frostbite—Local tissue destruction resulting from exposure to extreme cold; in mild cases, it results in superficial, reversible freezing followed by erythema and slight pain (frostnip); in severe cases, it can be painless or paresthetic and result in blistering, persistent edema, and gangrene. Frostbite is currently treated by rapid rewarming. (Stedman's medical dictionary 28th ed., 2005)

Gallstone—A concretion in the gallbladder or a bile duct, composed chiefly of a mixture of cholesterol, calcium bilirubinate, and calcium carbonate, occasionally as a pure stone composed of just one of these substances. (Stedman's medical dictionary 28th ed., 2005)

Ganglionar neuroma—A tumor composed of a solid mass of ganglia and nerve fibers. Usually found in abdominal tissues.

Gardner's syndrome—Multiple polyposis predisposing to carcinoma of the colon; also multiple tumors, osteomas of the skull, epidermoid cysts, and fibromas; autosomal dominant inheritance, caused by mutation in the adenomatous polyposis coli gene (APC) on chromosome 5q. This disorder is allelic to familial adenomatous polyposis (FAP). (Stedman's medical dictionary 28th ed., 2005)

Garrison—A military post; a permanent military installation.

Gastroenteritis—Inflammation of the mucous membrane of both stomach and intestine. (Stedman's medical dictionary 28th ed., 2005)

Gastrointestinal disorder—A disorder relating to the stomach and intestines.

Generalizability—The degree to which the inference drawn from a study can be extended to a different population. Such generalization is warranted when appropriate account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn. (Adapted from Last, 2001)

Geneva Convention—One of a series of agreements concerning the treatment of prisoners of war and of the sick, wounded, and dead in battle first made at Geneva, Switzerland, in 1864 and subsequently accepted in later revisions by most nations.

Genitourinary—Relating to the organs of reproduction and urination collectively. (Stedman's medical dictionary 28th ed., 2005)

Genotoxicity—Denoting a substance that by damaging DNA may cause mutation or cancer. (Stedman's medical dictionary 28th ed., 2005)

Glomus tumor—A vascular neoplasm composed of specialized pericytes (sometimes termed glomus cells), usually in single encapsulated nodular masses that may be several millimeters in diameter and occur almost exclusively in the skin, often subungually in the upper extremity; it is exquisitely tender and may be so painful that patients voluntarily immobilize an extremity, sometimes leading to atrophy of muscles; multiple glomus tumors occur, sometimes with autosomal dominant

inheritance. Tumors with cavernous spaces lined by glomus cells are called *glomangiomas*. (Stedman's medical dictionary 28th ed., 2005)

Goldenhar syndrome—A syndrome characterized by epibulbar dermoids, preauricular appendages, micrognathia, and vertebral and other anomalies. (Stedman's medical dictionary 28th ed., 2005)

Gout—A disorder of purine metabolism, occurring especially in men, characterized by a raised but variable blood uric acid level and severe recurrent acute arthritis of sudden onset resulting from deposition of crystals of sodium urate in connective tissues and articular cartilage; most cases are inherited, resulting from a variety of abnormalities of purine metabolism. The familial aggregation is for the most part galtonian with a threshold of expression determined by the solubility of uric acid. However, gout is also a feature of the Lesch-Nyhan syndrome, an X-linked disorder. (Stedman's medical dictionary 28th ed., 2005)

Gulf War—A conflict (August 2, 1990–February 28, 1991) between Iraq and a coalition force of approximately 30 nations led by the United States and mandated by the United Nations in order to liberate Kuwait.

Gulf War Syndrome—A syndrome of various health problems experienced by U.S. military personnel after serving in the Persian Gulf conflict of 1991; includes fatigue, musculoskeletal pain, headaches, dyspnea, memory loss, and diarrhea; thought to be related to exposure to low levels of neurotoxins, including sarin, pesticides, and pyridostigmine bromide (the latter supplied to troops as a protective anti-toxin). (Stedman's medical dictionary 28th ed., 2005)

Hansen's disease (also known as Leprosy)—A chronic granulomatous infection caused by *Mycobacterium leprae* affecting the cooler body parts, especially the skin, peripheral nerves, and testes. Leprosy is classified into two main types, lepromatous and tuberculoid, representing extremes of immunologic response. (Stedman's medical dictionary 28th ed., 2005)

HARDTACK (Operation)—A series of 72 nuclear tests conducted by the United States in 1958; HARDTACK I was carried out in the Pacific Ocean at Bikini Atoll, Enewetak Atoll, and Johnston Island; HARDTACK II was carried out at the Nevada Test Site.

Heart disease—An abnormal organic condition of the heart or of the heart and circulation.

Helminthiasis—The condition of having intestinal vermiform parasites. Syn: *helminthism*, *invermination*. (Stedman's medical dictionary 28th ed., 2005)

Hemangiopericytoma—An uncommon vascular, usually benign, neoplasm composed of round and spindle cells that are derived from the pericytes and surround endothelium-lined vessels; malignant hemangiopericytomas are difficult to distinguish microscopically from the benign. (Stedman's medical dictionary 28th ed., 2005)

Hematocrit—(1) Percentage of the volume of a blood sample occupied by cells. (2) Obsolete term for a centrifuge or device for separating the cells and other particulate elements of the blood from the plasma. (Stedman's medical dictionary 28th ed., 2005)

Hemochromatosis—A disorder of iron metabolism characterized by excessive absorption of ingested iron, saturation of iron-binding protein, and deposition of hemosiderin in tissue, particularly in the liver, pancreas, and skin; cirrhosis of the liver, diabetes (bronze diabetes), bronze pigmentation of the skin, and, eventually heart failure may occur; also can result from administration of large amounts of iron orally, by injection, or in forms of blood transfusion therapy. (Stedman's medical dictionary 28th ed., 2005)

Hemoglobin (Hb)—The red respiratory protein of erythrocytes, consisting of approximately 3.8 percent heme and 96.2 percent globin, with a molecular weight of 64,450, which as oxyhemoglobin (HbO_2) transports oxygen from the lungs to the tissues where the oxygen is readily released and HbO_2 becomes Hb. When Hb is exposed to certain chemicals, its normal respiratory function is blocked; e.g., the oxygen in HbO_2 is easily displaced by carbon monoxide, thereby resulting in the formation of fairly stable carboxyhemoglobin (HbCO), as in asphyxiation resulting from inhalation of exhaust fumes from gasoline engines. When the iron in Hb is oxidized from the ferrous to the ferric state, as in poisoning with nitrates and certain other chemicals, a nonrespiratory compound, methemoglobin (MetHb), is formed.

In humans there are at least five kinds of normal Hb: two embryonic Hb's (Hb Gower-1, Hb Gower-2), fetal (Hb F), and two adult types (Hb A, Hb A_2). There are two α globin chains containing 141 amino acid residues, and two of another kind (β, γ, δ, ε, or ζ), each containing 146 amino acid residues in four of the Hb's. Hb Gower-1 has two ζ chains and two ε chains. The production of each kind of globin chain is controlled by a structural gene of similar Greek letter designation; normal individuals are homozygous for the normal allele at each locus. Substitutions of one amino acid for another in the polypeptide chain can occur at any codon in any of the five loci and have resulted in the production of many hundreds of abnormal Hb types, most of no known clinical significance. In addition, deletions of one or more amino acid residues are known, as well as gene rearrangements due to unequal crossing over between homologous chromosomes. Newly discovered abnormal Hb types are first assigned a name, usually the location where discovered, and a molecular formula is added when determined. (Stedman's medical dictionary 28th ed., 2005)

Hemoglobinuria (paroxysmal)—The presence of hemoglobin in the urine, including certain closely related pigments that are formed from slight

alteration of the hemoglobin molecule; when present in sufficient quantities, they result in the urine being colored in shades varying from light reddish-yellow to fairly dark red. (Stedman's medical dictionary 28th ed., 2005)

Hemophilia—An inherited disorder of blood coagulation characterized by a permanent tendency to hemorrhages, spontaneous or traumatic, because of a defect in the blood coagulating mechanism. (Stedman's medical dictionary 28th ed., 2005)

Hemorrhagic—Relating to or marked by hemorrhage. (Stedman's medical dictionary 28th ed., 2005)

Hepatitis B—A virus disease with a long incubation period (usually 50-160 days), caused by a hepatitis B virus, a DNA virus and member of the family *Hepadnaviridae*, usually transmitted by injection of infected blood or blood derivatives or by use of contaminated needles, lancets, or other instruments; clinically and pathologically similar to viral hepatitis type A, but there is no cross-protective immunity; HB_sAg is found in the serum and the hepatitis delta virus occurs in some patients. May lead to acute or chronic liver disease. Syn: *viral hepatitis type b*. (Stedman's medical dictionary 28th ed., 2005)

Herbicide—An agent used to destroy or inhibit plant growth.

Heterozygous—Having different alleles at one locus on the pair of chromosomes present at the diploid state; for example, having a normal beta globin gene (coding for normal hemoglobin, HbA) at locus p15.5 on one chromosome 11 and an abnormal gene (coding for sickle-cell hemoglobin, Hb S) at the same locus on the other chromosome 11. (Stedman's medical dictionary 28th ed., 2005)

Hirsutism—Presence of excessive bodily and facial hair, usually in a male pattern, especially in women; may be present in normal adults as an expression of an ethnic characteristic or may develop in children or adults as the result of androgen excess due to tumors or drugs, or of nonandrogenetic or other drugs. (Stedman's medical dictionary 28th ed., 2005)

Hodgkin's disease—A disease marked by chronic enlargement of the lymph nodes, often local at the onset and later generalized, together with enlargement of the spleen and often of the liver, no pronounced leukocytosis, and commonly anemia and continuous or remittent (Pel-Ebstein) fever; considered to be a malignant neoplasm of lymphoid cells of uncertain origin (Reed-Sternberg cells), associated with inflammatory infiltration of lymphocytes and eosinophilic leukocytes and fibrosis; can be classified into lymphocytic predominant, nodular sclerosing, mixed cellularity, and lymphocytic depletion type. (Stedman's medical dictionary 28th ed., 2005)

Homozygous—Having identical alleles at one or more loci. (Stedman's medical dictionary 28th ed., 2005)

Hydrocephalus—A condition marked by an excessive accumulation of fluid resulting in dilation of the cerebral ventricles and raised intracranial pressure; may also result in enlargement of the cranium and atrophy of the brain. (Stedman's medical dictionary 28th ed., 2005)

Hypercoagulability—Abnormally increased coagulability. (Stedman's medical dictionary 28th ed., 2005)

Hyperglycemia—An abnormally high concentration of glucose in the circulating blood, seen especially in patients with diabetes mellitus. (Stedman's medical dictionary 28th ed., 2005)

Hyperinsulinemia—Increased levels of insulin in the plasma due to increased secretion of insulin by the beta cells of the pancreatic islets. Decreased hepatic removal of insulin is a cause in some patients, although hyperinsulinism usually is associated with insulin resistance and is commonly found in obesity in association with varying degrees of hyperglycemia. Syn: *hyperinsulinism*. (Stedman's medical dictionary 28th ed., 2005)

Hyperlipidemia—Elevated levels of lipids in the blood plasma. There are several types of hyperlipidemia; one is associated with a deficiency of α-aminoadipic semialdehyde synthase. (Stedman's medical dictionary 28th ed., 2005)

Hyperpigmentation—An excess of pigment in a tissue or part. (Stedman's medical dictionary 28th ed., 2005)

Hypertension—High blood pressure; transitory or sustained elevation of systemic arterial blood pressure to a level likely to induce cardiovascular damage or other adverse consequences. Hypertension has been arbitrarily defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg. Consequences of uncontrolled hypertension include retinal vascular damage (Keith-Wagener-Barker changes), cerebrovascular disease and stroke, left ventricular hypertrophy and failure, myocardial infarction, dissecting aneurysm, and renovascular disease. An underlying disorder (e.g., renal disease, Cushing's syndrome, pheochromocytoma) is identified in fewer than 10 percent of all cases of hypertension. The remainder, traditionally labeled "essential" hypertension, probably arise from a variety of disturbances in normal pressure-regulating mechanisms (which involve baroreceptors, autonomic influences on the rate and force of cardiac contraction and vascular tone, renal retention of salt and water, formation of angiotensin II under the influence of renin and angiotensin-converting enzyme, and other factors known and unknown), and most are probably genetically conditioned. (Stedman's medical dictionary 28th ed., 2005)

Hypertrophy—General increase in bulk of a part of organ, not due to

tumor formation. Use of the term may be restricted to denote greater bulk through increase in size, but not in number, of cells or other individual tissue elements. (Stedman's medical dictionary 28th ed., 2005)

Hypochondriasis—A morbid concern about one's own health and exaggerated attention to any unusual bodily or mental sensations; a delusion that one is suffering from some disease for which no physical basis is evident. (Stedman's medical dictionary 28th ed., 2005)

Hypomania—A mild degree of mania. (Stedman's medical dictionary 28th ed., 2005)

Hypothyroidism—Diminished production of thyroid hormone, leading to clinical manifestations of thyroid insufficiency, including low metabolic rate, tendency to weight gain, somnolence, and sometimes myxedema. (Stedman's medical dictionary 28th ed., 2005)

Hysteria—Denoting maladies involving physical symptoms that seem better explained by psychological factors. The concept of hysteria is historically differentiated into somatization disorder and conversion disorder, both of which are considered types of somatoform disorders in the DSM. The current ICD-10, however, places conversion disorder with dissociative disorders, not with somatoform disorders. (Adapted from Stedman's medical dictionary 28th ed., 2005)

Inactive duty training—(A) Duty (other than full-time duty) prescribed for Reserves (including commissioned officers of the Reserve Corps of the Public Health Service) by the Secretary concerned under section 206 of title 37 (37 U.S.C.S. § 206) or any other provision of law; (B) Special additional duties authorized for Reserves (including commissioned officers of the Reserve Corps of the Public Health Service) by an authority designated by the Secretary concerned and performed by them on a voluntary basis in connection with the prescribed training or maintenance activities of the units to which they are assigned; and (C) Training (other than active duty for training) by a member of, or applicant for membership (as defined in section 8140[g] of title 5 [5 U.S.C.S. § 8140(g)]) in, the Senior Reserve Officers' Training Corps prescribed under chapter 103 of title 10 (10 U.S.C.S. § 2101 et seq.). In the case of a member of the National Guard or Air National Guard of any State, such term means duty (other than full-time duty) under sections 316, 502, 503, 504, or 505 of title 32 (32 U.S.C.S. § 316, 502, 503, 504, or 505), or the prior corresponding provisions of law. Such term does not include (i) work or study performed in connection with correspondence courses, (ii) attendance at an educational institution in an inactive status, or (iii) duty performed as a temporary member of the Coast Guard Reserve. (Definitions. 2006. 38 U.S.C. § 101.)

Incidence—The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. More

generally, the number of new events, e.g., new cases of disease in a defined population, within a specified period of time. The term incidence is sometimes wrongly used to denote incidence rate. Syn: *incident number*. (Last, 2001)

Indemnity—A security against hurt, loss, or damage; exemption from incurred penalties or liabilities.

Influenza—An acute infectious respiratory disease, caused by influenza viruses, which are found in the family Orthomyxoviridae, in which the inhaled virus attacks the respiratory epothelial cells of susceptible persons and produces a cararrhal inflammation; characterized by sudden onset, chills, fever of short duration (3-4 days), severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections that can last up to 10 days. The disease commonly occurs in epidemics, sometimes in pandemics, which develop quickly and spread rapidly; mortality rate is usually low, but may be high in cases with secondary bacterial pneumonia, particularly in the elderly and those with underlying debilitating diseases; strain-specific immunity develops, but mutations in the virus are frequent, and the immunity usually does not affect antigenically different strains. (Stedman's medical dictionary 28th ed., 2005)

Information bias (observational bias)—A flaw in measuring exposure or outcome data that results in different quality (accuracy) or information between comparison groups. (Last, 2001)

Instrumental variable—A factor related directly to the putative cause, but independent of all potential confounders, used to estimate the strength of causal influence even in the presence of confounding.

Instrumental variable (IV) estimation—In linear regression, used when the error distribution cannot be considered independent of the regressor's distribution.

Interaction—(1) The interdependent operation of two or more causes to produce or prevent an effect. *Biological interaction* means the interdependent operation of two or more causes to produce, prevent, or control disease. (2) Differences in the effects of one or more factors according to the level of the remaining factor(s). (Last, 2001) In epidemiology, synonymous with effect modification (see Effect modification).

Ionizing radiation—Either particle radiation or electromagnetic radiation in which an individual particle/photon carries enough energy to ionize an atom or molecule by completely removing an electron from its orbit; if enough occur, can be very destructive to living tissue and can cause DNA damage and mutations. (Last, 2001)

Irritable bowel syndrome (IBS)—A condition characterized by gastrointestinal signs and symptoms including constipation, diarrhea, gas, and bloating, all in the absence of organic pathology. Associated with unco-

ordinated and inefficient contractions of the large intestine. (Stedman's medical dictionary 28th ed., 2005)

Ischemic heart disease—Deficient supply of blood to the heart that is due to obstruction of the inflow of arterial blood (as by the narrowing of arteries by spasm or disease).

Jaundice—A yellowish staining of the integument, sclerae, deeper tissues, and excretions with bile pigments, resulting from increased levels in the plasma. (Stedman's medical dictionary 28th ed., 2005)

Kala-azar—(1) A chronic disease, occurring in India, China, Pakistan, the Mediterranean littoral, the Middle East, South and Central America, Asia, and Africa caused by *Leishmania donovani* and transmitted by the bite of an appropriate species of sandfly of the genus *Phlebotomus* or *Lutzomyia;* the organisms grow and multiply in macrophages, eventually causing them to burst and liberate amastigote parasites that then invade other macrophages; proliferation of macrophages in the bone marrow causes crowding out of erythroid and myeloid elements, resulting in leukopenia, and anemia, splenomegaly, and hepatomegaly, which are characteristic, along with enlargement of lymph nodes; fever, fatigue, malaise, and secondary infections also occur; different strains of *L. donovani* occur; *L. infantum* in Eurasia, *L. chagasi* in Latin America. (2) Visceral leishmaniasis caused by *Leishmania tropica*, cultured from bone marrow aspirates of some military patients following the Gulf War. Syn: *visceral leishmaniasis*. (Stedman's medical dictionary 28th ed., 2005)

Kaposi's sarcoma—A multifocal malignant neoplasm of primitive vasoformative tissue, occurring in the skin and sometimes in lymph nodes or viscera, consisting of spindle cells and irregular small vascular spaces frequently infiltrated by hemosiderin-pigmented macrophages and extravasated red cells; clinically manifested by cutaneous lesions consisting of reddish-purple to dark-blue macules, plaques, or nodules; seen most commonly in men over 60 years of age and, in AIDS patients, as an opportunistic disease associated with human herpes virus 8 infection. (Stedman's medical dictionary 28th ed., 2005)

Keratitis—Inflammation of the cornea. (Stedman's medical dictionary 28th ed., 2005)

Korean conflict—The period beginning on June 27, 1950, and ending on January 31, 1955. (Definitions. 2006. 38 U.S.C. § 101.)

K-Z syndrome (POW syndrome)—Marked by severe, permanent psychological scars and nonspecific physical problems and is attributed to organic brain disease.

Laryngeal cancer—Cancer of the organ of voice production, the part of the respiratory tract between the pharynx and the trachea.

Laryngitis—Inflammation of the mucous membrane of the larynx. (Stedman's medical dictionary 28th ed., 2005)

Leiomyosarcoma—A malignant neoplasm derived from smooth (nonstriated) muscle. (Stedman's medical dictionary 28th ed., 2005)

Leishmaniasis—Infection with a species of *Leishmania* resulting in a clinically ill-defined group of diseases traditionally divided into four major types: (1) visceral leishmaniasis (kala-azar); (2) Old World cutaneous leishmaniasis; (3) New World cutaneous leishmaniasis; (4) mucocutaneous leishmaniasis. Each is clinically and geographically distinct and each has in recent years been subdivided further into clinical and epidemiological categories. Transmission is by various sandfly species of the genus *Phlebotomus* or *Lutzomyia*. (Stedman's medical dictionary 28th ed., 2005)

Leprosy (Hansen's disease)—(1) A chronic granulomatous infection caused by *Mycobacterium leprae* affecting the cooler body parts, especially the skin, peripheral nerves, and testes. Leprosy is classified into two main types, lepromatous and tuberculoid, representing extremes of immunologic response. (Stedman's medical dictionary 28th ed., 2005)

Leukemia—Progressive proliferation of abnormal leukocytes found in hemopoietic tissues, other organs, and usually in the blood in increased numbers. Leukemia is classified by the dominant cell type, and by duration from onset to death. This occurs in *acute leukemia* within a few months in most cases, and is associated with acute symptoms including severe anemia, hemorrhages, and slight enlargement of the lymph nodes or the spleen. The duration of *chronic leukemia* exceeds one year, with a gradual onset of symptoms of anemia or marked enlargement of the spleen, liver, or lymph nodes. (Stedman's medical dictionary 28th ed., 2005)

Lewisite—A war gas; a vesicant, a lung irritant like mustard gas; a systemic poison entering the circulation through the lungs or skin, and a mitotic poison arresting mitosis in the metaphase. Dimercaprol is the antidote. (Stedman's medical dictionary 28th ed., 2005)

Likelihood ratio—The ratio of the likelihood of the observed data in a sample for two competing hypotheses about the true unknown characteristic ("parameter value") of the population sampled; or comparison of various model conditions to assess which model provides the best fit. Likelihood ratios are used to evaluate screening and diagnostic tests in clinical epidemiology. (Last, 2001)

Limited/suggestive evidence—From the IOM series Veterans and Agent Orange; "evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent."

Line of duty—All that is authorized, required, or normally associated with some field of responsibility.

Linear relationship—The condition in which a given variable changes by an absolute constant amount with each unit change in another variable.

Liposarcoma—A malignant neoplasm of adults that occurs especially in the retroperitoneal tissues and the thigh, usually deep in the intermuscular or periarticular planes; histologically, liposarcoma is a large tumor that may be composed of well-differentiated fat cells or may be dedifferentiated, either myxoid, round-celled, or pleomorphic, usually in association with a rich network of capillaries; recurrences are common, and dedifferentiated liposarcoma metastasizes to the lungs or serosal surfaces. (Stedman's medical dictionary 28th ed., 2005)

Loiasis—A chronic disease caused by the filarial nematode *Loa loa*, with symptoms and signs first occurring approximately 3-4 years after a bite by an infected tabanid fly. When the infective larvae mature, the adult worms move about in an irregular course through the connective tissue of the body (as rapidly as 1 cm per minute), frequently becoming visible beneath the skin and mucous membranes; e.g., in the back, scalp, chest, inner surface of the lip, and especially on the conjunctiva. The worms provoke hyperemia and exudation of fluid, often a host response to the worm products, a Calabar or fugitive swelling that causes no serious damage and subsides as the parasites move on; the patient is annoyed by the "creeping" in the tissues and intense itching, as well as occasional pain, especially when the swelling is in the region of tendons and joints. Most patients have marked eosinophilia of 10-40 percent. (Stedman's medical dictionary 28th ed., 2005)

Long Shot—A nuclear device detonated beneath Amchitka Island, Alaska, in 1965.

Longitudinal study—See Cohort study.

Lung epithelium—The purely cellular avascular layer covering the lung's internal surfaces.

Lung fibrosis—Formation of fibrous tissue as a reparative or reactive process, as opposed to formation of fibrous tissue as a normal constituent of the lung.

Lung pleura (visceral pleura)—The serous membrane investing the lungs and dipping into the fissures between the lobes of the lungs. (Stedman's medical dictionary 28th ed., 2005)

Lupus erythematosus (systemic)—An inflammatory connective tissue disease with variable features, frequently including fever, weakness and fatigability, joint pains or arthritis resembling rheumatoid arthritis, diffuse erythematous skin lesions on the face, neck, or upper extremities, with liquefaction degeneration of the basal layer and epidermal atrophy, lymphadenopathy, pleurisy or pericarditis, glomerular

lesions, anemia, hyperglobulinemia, and a positive LE cell test result, with serum antibodies to nuclear protein and sometimes to double-stranded DNA and other substances. (Stedman's medical dictionary 28th ed., 2005)

Luteinizing hormone (lutropin)—One of two glycoprotein hormones that stimulate the final ripening of the follicles and the secretion of progesterone by them, their rupture to release the egg, and the conversion of the ruptured follicle into the corpus luteum. Syn: *lutropin.* (Stedman's medical dictionary 28th ed., 2005)

Lymphocyte—A white blood cell formed in bone marrow and distributed throughout the body in lymphatic tissue (e.g., lymph nodes, spleen, thymus, tonsils, Peyer patches), where it undergoes proliferation. In normal adults, lymphocytes make up 22-28 percent of the total number of leukocytes in the circulating blood. Lymphocytes are generally small (7-8 μm), although larger forms (10-20 μm) occur frequently. With Wright or similar stain, the nucleus is colored a deep purple-blue and is composed of dense aggregates of chromatin within a sharply defined nuclear membrane; the nucleus usually is round, but may be slightly indented, and is eccentrically situated within a relatively small amount of light blue cytoplasm that ordinarily contains no granules; especially in larger forms, the cytoplasm may be fairly abundant and include several fine granules of bright red-violet; unlike granules of the myeloid series of cells, those in lymphocytes do not yield a positive oxidase or peroxidase reaction. Lymphocytes are divided into two principal groups, T and B cells, based on their function and on characteristics of their surface molecules. Null cells, which include natural killer cells, represent a small percentage of the lymphocyte population. (Stedman's medical dictionary 28th ed., 2005)

Lymphohaematopoietic cancer—Cancer of the lymph (a clear, transparent, sometimes faintly yellow and slightly opalescent fluid that is collected from the tissues throughout the body, flows in the lymphatic vessels, and is eventually added to the venous blood circulation) and the blood cells.

Lymphoma—Any neoplasm of lymphoid or reticuloendothelial tissues, in general use, synonymous with malignant lymphoma; present as apparently solid tumors composed of cells that appear primitive or resemble lymphocytes, plasma cells, or histiocytes. Lymphomas appear most frequently in the lymph nodes, spleen, or other normal sites of lymphoreticular cells; may invade other organs or manifest as leukemia. Lymphomas are now classified by histology, immunophenotype, and cytogenic analysis, according to cell or origin (B or T cells) and degree of maturation. The current World Health Organization (WHO) classification of lymphoid neoplasms is based on the Revised European-

American Lymphoma (REAL) classification and effectively replaces older schemes such as the Working Formulation and Rappaport classification, which were based solely on morphology. (Stedman's medical dictionary 28th ed., 2005)

Malaria—A disease caused by the presence of the sporozoan *Plasmodium* in human or other vertebrate red blood cells, usually transmitted to humans by the bite of an infected female mosquito of the genus *Anopheles* that previously sucked the blood from a person with malaria. Human infection begins with the exoerythrocytic cycle in liver parenchyma cells, followed by a series of erythrocytic schizogenous cycles repeated at regular intervals; production of gametocytes in other red cells provides future gametes for another mosquito infection; characterized by episodic severe chills and high fever, prostration, occasionally fatal termination. (Stedman's medical dictionary 28th ed., 2005)

Malnutrition (including optic atrophy)—Faulty nutrition resulting from malabsorption, poor diet, or overeating. (Stedman's medical dictionary 28th ed., 2005)

Manhattan Project—The project to develop the first nuclear weapons during World War II by the United States, the United Kingdom, and Canada. Refers specifically to the period of the project from 1942 to 1946.

Measurement error/bias—Systematic error arising from inaccurate measurements (or classification) of subjects of study variable(s).

Melioidosis—An infectious disease of rodents in India and Southeast Asia that is caused by *Pseudomonas pseudomallei* and is communicable to humans. The characteristic lesion is a small caseous nodule, found generally throughout the body, which breaks down into an abscess; symptoms vary according to the tracts or organs involved. (Stedman's medical dictionary 28th ed., 2005)

Mesenchymoma—Rarely used term for a neoplasm in which there is a mixture of mesenchymal derivatives, other than fibrous tissue. A benign mesenchymoma may contain foci of vascular, muscular, adipose, osteoid, osseous, and cartilaginous tissue; such neoplasms are sometimes classed under a compounded name, e.g., angioleiomyolipoma, and the like, but the broader term may be preferred. A malignant mesenchymoma may also occur as a similar mixture of two or more types of mesenchymal cells that are malignant (other than fibrous tissue cells). (Stedman's medical dictionary 28th ed., 2005)

Mesothelioma—A rare neoplasm derived from the lining cells of the pleura and peritoneum, which grows as a thick sheet covering the viscera, and is composed of spindle cells or fibrous tissue that may enclose gland-like spaces lined by cuboidal cells. (Stedman's medical dictionary 28th ed., 2005)

Meta-analysis—A statistical synthesis of the data from separate but similar, i.e., comparable, studies, leading to a quantitative summary of the pooled results. In the biomedical sciences, the systematic, organized, and structured evaluation of a problem of interest, using information (commonly in the form of statistical tables or other data) from a number of independent studies of the problem. A frequent application has been the pooling of results from a set of randomized controlled trials, none in itself necessarily powerful enough to demonstrate statistically significant differences, but in aggregate capable of doing so. Meta-analysis has a qualitative component, i.e., application of predetermined criteria of quality (e.g., completeness of data, absence of biases) and a quantitative component, i.e., integration of the numerical information. The aim is to integrate the findings, pool the data, and identify the overall trend of results. An essential prerequisite is that the studies must stand up to critical appraisal, and various biases, e.g., *publication bias*, must be allowed for. (Last, 2001)

Mexican border period—The period beginning on May 9, 1916, and ending on April 5, 1917, in the case of a veteran who during such period served in Mexico, on the borders thereof, or in the waters adjacent thereto. (Definitions. 2006. 38 U.S.C. § 101.)

Milrow—A nuclear device detonated beneath Amchitka Island, Alaska, in 1969.

Misclassification—The erroneous classification of an individual, value, or an attribute into a category other than that to which it should be assigned. The probability of misclassification may be the same in all study groups (nondifferential misclassification) or may vary between groups (differential misclassifications). (Last, 2001)

Model averaging—Computing the average of a parameter from a model.

Monocyte—A relatively large mononuclear leukocyte (16-22 μm in diameter), that normally constitutes 3-7 percent of the leukocytes of the circulating blood, and is normally found in lymph nodes, spleen, bone marrow, and loose connective tissue. When treated with the usual dyes, monocytes manifest an abundant pale blue or blue-gray cytoplasm that contains numerous, fine, dustlike, red-blue granules; vacuoles are frequently present; the nucleus is usually indented, or slightly folded, and has a stringy chromatin structure that seems more condensed where the delicate strands are in contact. Monocytes that leave the blood stream and enter the connective tissue spaces are called macrophages. (Stedman's medical dictionary 28th ed., 2005)

Mononucleosis—Presence of abnormally large number of mononuclear leukocytes in the circulating blood, especially with reference to forms that are not normal. (Stedman's medical dictionary 28th ed., 2005)

Monozygotic twins—Twins resulting from one zygote that at an early stage

of development becomes separated into independently growing cell aggregations giving rise to two individuals of the same sex and identical genetic constitution. (Stedman's medical dictionary 28th ed., 2005)

Multiple myeloma—An uncommon disease that occurs more frequently in men than in women and is associated with anemia, hemorrhage, recurrent infections, and weakness. Ordinarily, it is regarded as a malignant neoplasm that originates in bone marrow and involves chiefly the skeleton, with clinical features attributable to the sites of involvement and to abnormalities in formation of plasma protein; characterized by numerous diffuse foci or nodular accumulations of abnormal or malignant plasma cells in the marrow of various bones (especially the skull), causing palpable swellings of the bones, and occasionally in extraskeletal sites; radiologically, the bone lesions have a characteristic punched-out appearance. The myeloma cells produce abnormal proteins in the serum and urine; those formed in any one example of multiple myeloma are different from other myeloma proteins, as well as from normal serum proteins, the most frequent abnormalities in the metabolism of protein being (1) the occurrence of Bence Jones proteinuria, (2) a great increase in monoclonal γ-globulin in the plasma, (3) the occasional formation of cryoglobulin, and (4) a form of primary amyloidosis. The Bence Jones protein is not a derivative of abnormal serum protein, but seems to be formed de novo from amino acid precursors. (Stedman's medical dictionary 28th ed., 2005)

Multiple regression model—Given data on an outcome variable y and more than one possible predictive variables x_1, x_2, etc., regression analysis involves finding the "best" mathematical model (within some restricted class of models) to describe y as a function of the x's, or to predict y from the x's. Not to be confused with multivariate analysis.

Multiple sclerosis (MS)—Common demyelinating disorder of the central nervous system, causing patches of sclerosis (plaques) in the brain and spinal cord; occurs primarily in young adults, and has protean clinical manifestations, depending upon the location and size of the plaque; typical symptoms include visual loss, diplopia, nystagmus, dysarthria, weakness, paresthesias, bladder abnormalities, and mood alterations; characteristically, the plaques are "separated in time and space" and clinically the symptoms show exacerbations and remissions. (Stedman's medical dictionary 28th ed., 2005)

Multiplicative model—A model in which the joint effect of two or more causes is the product of their individual effects. For instance, if factor a multiplies risk by the amount a in the absence of factor b, and factor b multiplies risk by the amount b in the absence of factor a, the combined effect of factors a and b on risk is $a \times b$. (Last, 2001)

Multivariate model—A model where the variation in several variables is

studied simultaneously; in statistics, any analytic method that allows the simultaneous study of two or more dependent variables.

Mustard gas—An irritant, vesicant, oily liquid used especially as a chemical weapon.

Mutagenic—Promoting mutation.

Myasthenia gravis—A disorder of neuromuscular transmission marked by fluctuating weakness and fatigue of certain voluntary muscles, including those innervated by brainstem motor nuclei; caused by a marked reduction in the number of acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction, resulting from an autoimmune mechanism. (Stedman's medical dictionary 28th ed., 2005)

Mycosis (mycoses)—Any disease caused by a fungus. (Stedman's medical dictionary 28th ed., 2005)

Myelitis—(1) Inflammation of the spinal cord. (2) Inflammation of the bone marrow. (Stedman's medical dictionary 28th ed., 2005)

Myelodysplastic syndrome (MDS)—A heterogeneous group of clonal hematopoietic stem cell disorders characterized by the presence of dysplastic changes in one or more of hematopoietic lineages. The common clinical picture may include anemia, infections, and bleeding problems. Occurs generally in elderly patients, or those with prior exposure to leukemogenic agents. Transformation rates to acute leukemia range from 10 to 80 percent. Cytogenetic abnormalities are associated with a poor prognosis. (Stedman's medical dictionary 28th ed., 2005)

Myocarditis—Inflammation of the muscular walls of the heart. (Stedman's medical dictionary 28th ed., 2005)

Nasopharyngeal cancer—Cancer of the nose or naval cavity and the pharynx.

National Childhood Vaccine Injury Act—Enacted in 1986 to reduce the potential financial liability of vaccine makers due to vaccine injury claims; created the National Vaccine Injury Compensation Program to provide a federal no-fault system for compensating vaccine-related injuries or death.

Necessary cause—A causal factor whose presence is required for the occurrence of a given effect.

Negative predictive value (NPV)—The probability that a person with a negative test does not have the disease or condition (Last, 2001); specifically, the ratio of those who are identified by a test not to have the condition who in fact do not have it, divided by all those identified by a test not to have the condition (i.e., true negatives, divided by the sum of true negatives and false negatives). See Positive predictive value.

Nephritis—Inflammation of the kidneys. (Stedman's medical dictionary 28th ed., 2005)

Nephrolithiasis—Presence of renal calculi. (Stedman's medical dictionary 28th ed., 2005)

Neuropsychiatric disease—A disease of both neurology (nervous system) and psychiatry (mental disorders).

Neutrophil—(1) A mature white blood cell in the granulocytic series, formed by myelopoietic tissue of the bone marrow (sometimes also in extramedullary sites), and released into the circulating blood, where they normally represent 54-65 percent of the total number of leukocytes. When stained with the usual Romanovsky type of dyes, neutrophils are characterized by (a) a dark purple-blue nucleus, lobated (three to five distinct lobes joined by thin strands of chromatin), and with a rather coarse network of fairly dense chromatin; and (b) a cytoplasm that is faintly pink (sharply contrasted with the nucleus) and contains numerous fine pink or violet-pink granules, i.e., not acidophilic or basophilic (as in eosinophils or basophils). The precursors of neutrophils, in order of increasing maturity, are: myeloblasts, promyelocytes, myelocytes, metamyelocytes, and band forms. Although the terms neutrophilic leukocytes and neutrophilic granulocytes include younger cells in which neutrophilic granules are recognized, the two expressions are frequently used as synonyms for neutrophils, which are mature forms unless otherwise indicated by a modifying term, such as immature neutrophil. (2) Any cell or tissue that manifests no special affinity for acid or basic dyes, i.e., the cytoplasm stains approximately equally with either type of dye. (Stedman's medical dictionary 28th ed., 2005)

Nodule—A small node; in skin, a node up to 1.0 cm in diameter, solid, with palpable depth; a pulmonary or pleural lesion seen on a radiographic image as a well-defined, discrete, roughly circular opacity 2-30 mm in diameter. (Stedman's medical dictionary 28th ed., 2005)

Non-Hodgkin's lymphoma (NHL)—A lymphoma other than Hodgkin's disease, classified by Rappaport into a nodular or diffuse tumor pattern and by cell type; a working or international formulation separates such lymphomas into low-, intermediate-, and high-grade malignancy and into cytologic subtypes reflecting follicular center cell or other origin. (Stedman's medical dictionary 28th ed., 2005)

Nonlymphocytic leukemia—A malignant neoplasm of blood-forming tissues characterized by the uncontrolled proliferation of immature granular leukocytes. The risk of the disease is increased among people who have been exposed to massive doses of radiation.

Non-service-connected—With respect to disability or death, that such disability was not incurred or aggravated, or that the death did not result from a disability incurred or aggravated, in line of duty in the active military, naval, or air service. (Definitions. 2006. 38 U.S.C. § 101.)

Normalized data—Data that are continuous and have a symmetrical distribution, both tails extend to infinity; the arithmetic mean, mode, and median are identical; the distribution shape is completely determined by the mean and standard deviation.

Null hypothesis—The statistical hypothesis that one variable has no association with another variable or set of variables, or that two or more population distributions do not differ from one another; states that the results observed in a study, experiment, or test are no different from what might have have occurred as a result of the operation of chance alone. (Last, 2001)

Nursing home care—The accommodation of convalescents or other persons who are not acutely ill and not in need of hospital care but who require nursing care and related medical services. (Definitions. 2006. 38 U.S.C. § 101.)

Obesity—An excess of subcutaneous fat in proportion to lean body mass. Excess fat accumulation is associated with increase in the size (hypertrophy) as well as the number (hyperplasia) of adipose tissue cells. Obesity is variously defined in terms of absolute weight, weight-height ratio, distribution of subcutaneous fat, and societal and esthetic norms. Measures of weight in proportion to height include relative weight (RW, body weight divided by median desirable weight for a person of the same height and medium frame according to actuarial tables), body mass index (BMI, kg/m^2), and ponderal index (kg/m^3). These do not differentiate between excess adiposity and increased lean body mass. In contrast, subscapular and triceps skinfold measurements and determination of the waist-to-hip ratio help define the regional deposition of fat and differentiate the more medically significant central obesity from peripheral obesity in adults. No single cause can explain all cases of obesity. Ultimately it results from an imbalance between energy intake and energy expenditure. While faulty eating habits related to failure of normal satiety feedback mechanisms may be responsible for some cases, many obese persons neither consume more calories nor eat different proportions of foodstuffs than nonobese persons. Contrary to popular belief, obesity is not caused by disorders of pituitary, thyroid, or adrenal gland metabolism. However, it is often associated with hyperinsulinism and relative insulin resistance. Studies of obese twins strongly suggest the presence of genetic influences on resting metabolic rate, feeding behavior, changes in energy expenditures in response to overfeeding, lipoprotein lipase activity, and basal rate of lipolysis. Environmental factors associated with obesity include socioeconomic status, race, region of residence, season, urban living, and being part of a smaller family. The prevalence of obesity is greater when weight is measured during winter rather than summer. Obesity is much more

common in the southeastern United States, although the northeastern and midwestern states also have high rates, a phenomenon independent of race, population density, and season. (Stedman's medical dictionary 28th ed., 2005)

Observational study—An epidemiologic study that does not involve any experimental intervention, such as randomizing exposure or treatment.

Obstructive pulmonary disease—A progressive and irreversible condition characterized by diminished inspiratory and expiratory capacity of the lungs.

Occult blood—Blood in the feces in amount too small to be seen but detectable by chemical tests. (Stedman's medical dictionary 28th ed., 2005)

Ochronosis—A rare, autosomal recessive disease characterized by alkaptonuria with pigmentation of the cartilages and sometimes tissues such as muscle, epithelial cells, and dense connective tissue; may affect also the sclera, mucous membrane of the lips, and skin of the ears, face, and hands, and cause standing urine to be dark-colored and contain pigmented casts; pigmentation is thought to result from oxidized homogentisic acid, and cartilage degeneration results in osteoarthritis, particularly of the spine. (Stedman's medical dictionary 28th ed., 2005)

Odds ratio (OR)—The ratio of two odds, often used in case-control studies as an estimate of relative risk. Consider the following notation for the distribution of a binary exposure and a disease in a population or a sample.

	Exposed	Unexposed
Disease	*a*	*b*
No disease	*c*	*d*

The odds ratio (cross-product ratio) is *ad/bc*. Syn: *cross-product ratio, relative odds*. (Adapted from Last, 2001)

Onchocerciasis—Infection with *Onchocerca* (especially *O. volvulus*, a filarial nematode transmitted from person to person by black flies of the genus *Simulium*), marked by nodular swellings forming a fibrous cyst enveloping the coiled parasites (onchocercoma); microfilariae move freely out of the nodule and escape into the intercellular lymph in the dermis. Dermatologic changes often develop, especially in Africa, resulting in intense pruritus, scaly or lichenoid skin, depigmentation, and destruction of elastic fibers. Most important are the ocular complications that may develop after a long chronic course, with blindness frequently occurring in advanced cases, caused by the presence of living or dead microfilariae seen by slitlamp biomicroscopy. (Stedman's medical dictionary 28th ed., 2005)

Operation Ranch Hand—The military code name for the spraying of herbicides from U.S. Air Force aircraft in Southeast Asia from 1962 through 1971.

Operation TOP HAT—Conducted in Fort McClellan, Alabama, in 1953; used Chemical Corps personnel in tests of decontamination methods for biological welfare agents, sulfur mustard, and nerve gases.

Ophthalmological changes—Changes concerned with the eye, its disease, and refractive errors.

Organic disease of the nervous system (organic disease)—A disease in which there are anatomic or pathophysiologic changes in some bodily tissue or organ, in contrast to a functional disorder; particularly one of psychogenic origin. (Stedman's medical dictionary 28th ed., 2005)

Organic residuals of frostbite—Any detectable or observable changes due to frostbite.

Oroya fever (also known as bartonellosis and carrion)—A generalized, acute, febrile, endemic, and systemic form of bartonellosis; marked by high fever, rheumatic pains, progressive, severe anemia, and albuminuria. (Stedman's medical dictionary 28th ed., 2005)

Osteitis (Paget's disease)—Inflammation of bone. (Stedman's medical dictionary 28th ed., 2005)

Osteoarthritis—Arthritis characterized by erosion of articular cartilage, either primary or secondary to trauma or other conditions, which becomes soft, frayed, and thinned with eburnation of subchondral bone and outgrowths of marginal osteophytes; pain and loss of function result; mainly affects weight-bearing joints, is more common in old people and animals. (Stedman's medical dictionary 28th ed., 2005)

Osteomalacia—A disease in adults characterized by a gradual softening and bending of the bones with varying severity of pain; softening occurs because the bones contain osteoid tissue that has failed to calcify because of lack of vitamin D or renal tubular dysfunction; more common in women than in men, osteomalacia often begins during pregnancy. (Stedman's medical dictionary 28th ed., 2005)

Osteopathy—(1) Any disease of bone. (2) A school of medicine based upon a concept of the normal body as a vital machine capable, when in correct adjustment, of making its own remedies against infections and other toxic conditions; practitioners use the diagnostic and therapeutic measures of conventional medicine in addition to manipulative measures. (Stedman's medical dictionary 28th ed., 2005)

Osteoporosis—Reduction in the quantity of bone or atrophy of skeletal tissue; an age-related disorder characterized by decreased bone mass and loss of normal skeletal microarchitecture, leading to increased susceptibility to fractures. (Stedman's medical dictionary 28th ed., 2005)

Osteosarcoma—The most common and malignant of bone sarcomas, which arises from bone-forming cells and affects chiefly the ends of long bones. Its greatest incidence is in the age group between 10 and 25 years. (Stedman's medical dictionary 28th ed., 2005)

Paget's disease—(1) A generalized skeletal disease, frequently familial, of older persons in which bone resorption and formation are both increased, leading to thickening and softening of bones (e.g., the skull), and bending of weight-bearing bones; Syn: *osteitis deformans*. (2) A disease of elderly women, characterized by an infiltrated, somewhat eczematous lesion surrounding and involving the nipple and areola, and associated with subjacent intraductal cancer of the breast and infiltration of the lower epidermis by malignant cells. (3) Syn: *extramammary Paget's disease*. (Stedman's medical dictionary 28th ed., 2005)

Palsy—Paralysis or paresis. (Stedman's medical dictionary 28th ed., 2005)

Paralysis agitans—Obsolete term for parkinsonism. (Stedman's medical dictionary 28th ed., 2005)

Paranoia—A severe but relatively rare mental disorder characterized by the presence of systematized delusions often of a persecutory character involving being followed, poisoned, or harmed by other means, in an otherwise intact personality. (Stedman's medical dictionary 28th ed., 2005)

Parathyroid adenoma—Tumors of the parathyroid glands, which are located in the neck and help regulate calcium metabolism.

Parent—A father, a mother, a father through adoption, a mother through adoption, or an individual who for a period of not less than one year stood in the relationship of a parent to a veteran at any time before the veteran's entry into active military, naval, or air service or if two persons stood in the relationship of a father or a mother for one year or more, the person who last stood in the relationship of father or mother before the veteran's last entry into active military, naval, or air service (except for purposes of chapter 19 of this title [38 U.S.C.S. § 1901 et seq.]). (Definitions. 2006. 38 U.S.C. § 101.)

Parkinson's disease (also called paralysis agitans, parkinsonism)—(1) A neurologic syndrome usually resulting from deficiency of the neurotransmitter dopamine as the consequence of degenerative, vascular, or inflammatory changes in the basal ganglia; characterized by rhythmic muscular tremors, rigidity of movement, festination, droopy posture, and masklike facies. (2) A syndrome similar to parkinsonism. Some features seen with Parkinson disease that occur with other disorders (e.g., progressive supranuclear palsy) or as a side effect of certain medications. (Stedman's medical dictionary 28th ed., 2005)

Parsimonious model—A model with as few parameters as possible.

Pathogenesis—The postulated mechanisms by which the etiologic agent

produces disease. The difference between *etiology* and pathogenesis should be noted: The etiology of a disease or disability consists of the postulated causes that initiate the pathogenetic mechanisms; control of these causes might lead to prevention of the disease. (Last, 2001)

Pellagra—An affection characterized by gastrointestinal disturbances, erythema (particularly of exposed areas) followed by desquamation, and nervous and mental disorders; may occur because of a poor diet, alcoholism, or some other disease causing impairment of nutrition; commonly seen when corn (maize) is a main nutrient in the diet, resulting in a deficiency of niacin. (Stedman's medical dictionary 28th ed., 2005)

Pension—A monthly or other periodic payment made by the Secretary to a veteran because of service, age, or non-service-connected disability, or to a surviving spouse or child of a veteran because of the non-service-connected death of the veteran. (Definitions. 2006. 38 U.S.C. § 101.)

Peptic ulcer (gastric or duodenal)—An ulcer of the alimentary mucosa, usually in the stomach or duodenum, exposed to gastric secretion. (Stedman's medical dictionary 28th ed., 2005)

Period of war—The Spanish-American War, the Mexican border period, World War I, World War II, the Korean conflict, the Vietnam era, the Persian Gulf War, and the period beginning on the date of any future declaration of war by the Congress and ending on the date prescribed by Presidential proclamation or concurrent resolution of the Congress. (Definitions. 2006. 38 U.S.C. § 101.)

Peripheral arterial hemodynamics—Blood circulation outside the arteries.

Peripheral nerve disease—See Peripheral neuropathy.

Peripheral neuropathy (acute and subacute)—A disease or degenerative state of the peripheral nerves in which motor, sensory, or vasomotor nerve fibers may be affected and which is marked by muscle weakness and atrophy, pain, and numbness.

Peripheral vasculature—Affecting extremities and abdominal blood vessels.

Persian Gulf War—The period beginning on August 2, 1990, and ending on the date thereafter prescribed by Presidential proclamation or by law. (Definitions. 2006. 38 U.S.C. § 101.)

Pharynx—The superior expanded portion of the alimentary tract, between the mouth and nasal cavities (superiorly and anteriorly) and the esophagus (inferiorly); consisting of the nasopharynx, oropharynx, and laryngopharynx, the first two being shared with the respiratory tract; the pharynx is distinct from the rest of the alimentary tract in that it is composed exclusively of voluntary skeletal muscle arranged in outer circular and inner longitudinal layers. (Stedman's medical dictionary 28th ed., 2005)

Phenoxyherbicides—Related to the growth hormone indoleacetic acid;

when sprayed on broad-leaf plants they induce rapid and uncontrolled growth, eventually killing them.

Phenytoin—An anticonvulsant used in the treatment of generalized tonic clonic and complex partial epilepsy. (Stedman's medical dictionary 28th ed., 2005)

Picloram—A systemic herbicide used for control of woody plants and a wide range of broad-leaved weeds.

Pinta—A disease caused by a spirochete *Treponema carateum*, endemic in Mexico and Central America, and characterized by a small primary papule followed by an enlarging plaque and disseminated secondary macules of varying color called pintids that finally become white. (Stedman's medical dictionary 28th ed., 2005)

Plague—(1) Any disease of wide prevalence or of excessive mortality. (2) An acute infectious disease caused by the bacterium *Yersinia pestis* and marked clinically by high fever, toxemia, prostration, a petechial eruption, lymph node enlargement, pneumonia, or hemorrhage from the mucous membranes; primarily a disease of rodents, transmitted to humans by fleas that have bitten infected animals. In humans the disease takes one of four clinical forms: bubonic plague, septicemic plague, pneumonic plague, or ambulant plague. (Stedman's medical dictionary 28th ed., 2005)

Platelet—An irregularly shaped disklike cytoplasmic fragment of a megakaryocyte that is shed in the marrow sinus and subsequently found in the peripheral blood, where it functions in clotting. A platelet contains granules in the central part (granulomere) and, peripherally, clear protoplasm (hyalomere), but no definite nucleus; is about one-third to one-half the size of an erythrocyte; and contains no hemoglobin. (Stedman's medical dictionary 28th ed., 2005)

Plutonium (Pu)—A transuranium artificial radioactive element, atomic no. 94, atomic wt. 244.064. The best-known α-emitting isotope is ^{239}Pu (half-life 24,110 years) which, like ^{235}U, is fissionable and can be used in atomic bombs and nuclear power plants; ^{238}Pu (half-life 87.74 years) is used as an energy source in pacemakers. Pu ions are bone-seekers; ingestion is a radiation hazard, as with radium and radiostrontium. (Stedman's medical dictionary 28th ed., 2005)

Pneumonia—Inflammation of the lung parenchyma characterized by consolidation of the affected part, the alveolar air spaces being filled with exudated, inflammatory cells, and fibrin. Most cases are due to infection by bacteria or viruses, a few to inhalation of chemicals or trauma to the chest wall, and a small minority to rickettsias, fungi, and yeasts. Distribution may be lobar, segmental, or lobular; when lobular and in associated with bronchitis, it is termed bronchopneumonia. (Stedman's medical dictionary 28th ed., 2005)

Polycythemia (erythremia)—A condition marked by an abnormal increase in the number of circulating red blood cells.

Polydipsia—Excessive thirst that is relatively prolonged. (Stedman's medical dictionary 28th ed., 2005)

Polyuria—Excessive excretion of urine resulting in profuse and frequent micturition. (Stedman's medical dictionary 28th ed., 2005)

Population attributable fraction (PAF)—PAF is the attributable fraction (AF) in the entire population rather than in just the exposed population. To calculate PAF, AF in the exposed is multiplied by the fraction of the entire population that is exposed (i.e., by the prevalence of exposure). See Attributable fraction.

Porphyria cutanea tarda (PCT)—Familial or sporadic porphyria characterized by liver dysfunction and photosensitive cutaneous lesions, with bullae, hyperpigmentation, and scleroderma-like changes in the skin and increased excretion of uroporphyrin; caused by a deficiency of uroporphyrinogen decarboxylase induced in sporadic cases by chronic alcoholism; autosomal dominant inheritance in familial cases. (Stedman's medical dictionary 28th ed., 2005)

Portability—The degree to which the relative risk estimated from one population can be properly applied to another population.

Positive predictive value (PPV)—The probability that a person with a positive test is a true positive (i.e., does have the disease or condition); specifically, the ratio of those who are identified by a test to have the condition who in fact have it, divided by all those identified by a test to have the condition (i.e, true positives, divided by the sum of true positives and false positives). See Negative predictive value.

Posterior subcapsular cataracts—A cataract involving the cortex at the posterior pole of the lens. (Stedman's medical dictionary 28th ed., 2005)

Postirradiation osteosarcoma—Osteosarcoma after radiation therapy; see Osteosarcoma.

Post-traumatic stress disorder (PTSD)—(1) Development of characteristic long-term symptoms following a psychologically traumatic event that is generally outside the range of usual human experience; symptoms include persistently reexperiencing the event and attempting to avoid stimuli reminiscent of the trauma, numbed responsiveness to environmental stimuli, a variety of autonomic and cognitive dysfunctions, and dysphoria. (2) A DSM diagnosis that is established when the specified criteria are met. (Stedman's medical dictionary 28th ed., 2005)

Presumption—A procedural device that dictates that once basic fact A is established, the existence of fact B must be assumed unless the presumed fact is rebutted.

Prevalence—The ratio of the number of those with a given condition in a

population (or sample) divided by the number of the entire population (or sample).

Prima facie—At first view; on the first appearance; legally sufficient to establish a fact or a case unless disproved.

Prisoner of War—A combatant who is imprisoned by an enemy power during or immediately after an armed conflict.

Probability distribution—For a discrete (non-continuous) random variable, the function that given the probabilities that the variable equals each of a sequence of possible values; examples include the binomial and Poisson distributions. For a continuous random variable, often used synonymously with the probability density function; an example is the normal distribution. (Adapted from Last, 2001)

Probability of causation (PC)—The fraction of disease risk *in an exposed individual* that is due to the exposure. This is expressed as $(r_{1i} - r_{0i}) / r_{1i}$, where r_{1i} is the disease risk in individual i if exposed and r_{0i} is the disease risk in that same individual if unexposed (i.e., the counterfactual). PC is also often defined as the probability that the exposure caused the disease in an exposed individual. PC has also been used to refer to the AF when AF is applied to individuals, but this usage is incorrect. Since we can know neither r_{1i} nor r_{0i}, and there is substantial variation in these across individuals in even relatively homogeneous populations, for any individual AF cannot be known to be a good estimate of PC.

Proportionate recovery—A defendant compensates a claimant for a fraction of his/her injury that represents the defendant's statistical share in that injury.

Prosthetics—The art and science of making and adjusting artificial parts of the human body. (Stedman's medical dictionary 28th ed., 2005)

Prothrombin—A glycoprotein, molecular weight approximately 72,500, formed and stored in the parenchymal cells of the liver and present in blood in a concentration of approximately 20 mg/100 ml. In the presence of thromboplastin and calcium ion, prothrombin is converted to thrombin, which in turn converts fibrinogen to fibrin, this process resulting in coagulation of blood; a deficiency of prothrombin leads to impaired blood coagulation. (Stedman's medical dictionary 28th ed., 2005)

Proximal limb amputations—An amputation of a limb situated nearest the trunk or the point of origin.

Psychoneurosis—A mental or behavioral disorder of mild or moderate severity; formerly a classification of neurosis that included hysteria, psychasthenia, neurasthenia, and the anxiety and phobic disorders. (Stedman's medical dictionary 28th ed., 2005)

Psychosis (psychoses)—(1) A mental and behavioral disorder causing gross distortion or disorganization of a person's mental capacity, affective

response, and capacity to recognize reality, communicate and relate to others to the degree of interfering with a person's capacity to cope with the ordinary demands of everyday life. The psychoses are divided into two major classifications according to their origins: those associated with organic brain syndromes (e.g., Korsakoff's syndrome); and those less clearly organic and having some functional component(s) (e.g., the schizophrenias, bipolar disorder). (2) Generic term for any of the so-called insanities, the most common forms of which are the schizophrenias. (3) A severe emotional and behavioral disorder. (Stedman's medical dictionary 28th ed., 2005)

Purpura—A condition characterized by hemorrhage into the skin. Appearance of the lesions varies with the type of purpura, the duration of the lesions, and the acuteness of the onset. The color is first red, gradually darkens to purple, fades to a brownish yellow, and usually disappears in 2-3 weeks; color of residual permanent pigmentation depends largely on the type of unabsorbed pigment of the extravasated blood; extravasations may occur also into the mucous membranes and internal organs. (Stedman's medical dictionary 28th ed., 2005)

Putative cause—A commonly accepted or assumed cause.

***P*-value**—The probability that a test statistic (such as relative risk) would be as extreme as or more extreme than observed if the null hypothesis were true. The letter *P*, followed by the abbreviation n.s. (not significant) or by the symbol < (less than) or > (greater than) and a decimal notation, such as 0.01, 0.05, is a statement of the probability that the difference observed could have occurred by chance if the groups were really alike, i.e., under the null hypothesis.

Investigators may arbitrarily set their own significance levels, but in most biomedical and epidemiologic work, a study result whose probability value is less than 5 percent ($P < 0.05$) or 1 percent ($P < 0.01$) is considered sufficiently unlikely to have occurred by chance to justify the designation "statistically significant." (Adapted from Last, 2001)

Pyridostigmine bromide—A cholinesterase inhibitor useful in the treatment of the disorder of neuromuscular transmission.

Radioepidemiological Tables—Developed by the National Institutes of Health working group in 1985; serve as a reference tool providing probability of causation estimates for individuals with cancer who were exposed to ionizing radiation.

Radiogenic disease—A disease that may be induced by ionizing radiation.

Radionuclide—An isotope of artificial or natural origin that exhibits radioactivity. (Stedman's medical dictionary 28th ed., 2005)

Radium—A metallic element, atomic no. 88, extracted in very minute quantities from pitchblende; ^{226}Ra, its longest-lived isotope, is produced as an intermediate in the uranium series by the emission of an α particle

from thorium-230 (ionium); ^{226}Ra emits α particles and gamma rays with a half-life of 1,599 years breaking down to ^{222}Rn; chemically, it is an alkaline earth metal with properties similar to those of barium. Its therapeutic action is similar to that of x-rays, since the α emission is filtered out. (Stedman's medical dictionary 28th ed., 2005)

Randomized clinical (or controlled) trial (RCT)—An experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not to receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. Randomized controlled trials are generally regarded as the most scientifically rigorous method of hypothesis testing available. (Last, 2001)

Rating schedule—Certain criteria and/or levels of disability are required for entitlement to ancillary and special purpose benefits.

Raynaud's syndrome—Idiopathic paroxysmal bilateral cyanosis of the digits due to arterial and arteriolar contraction; caused by cold or emotion. Syn: *Raynaud Syndrome*. (Stedman's medical dictionary 28th ed., 2005)

Readjustment Counseling Program—Services provided to combat veterans in the effort to make a satisfying transition from military to civilian life.

Receiver operator characteristics (ROC) curve—(1) A plot of percentage of true positive results versus percentage of false positive results, typically used in assessing the value of a diagnostic test. (2) A graphic means for assessing the ability of a screening or diagnostic test to discriminate between healthy and diseased persons. (Adapted from Stedman's medical dictionary 28th ed., 2005)

Registry—An organized system for the collection, storage, retrieval, analysis and dissemination of information on individual persons who have either a particular disease, a condition that predisposes to the occurrence of a health-related event, or prior exposure to substances known or suspected to cause adverse health effects (definition from www.ncvhs.hhs.gov/9701138b.htm).

Relative risk (RR)—(1) The ratio of the risk of disease or death among the exposed compared to the risk among the unexposed. (2) Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed, i.e., the rate ratio. (3) The term *relative risk* has also been used synonymously with *odds ratio* and, in some biostatistical articles, has been used for the ratio of *force of morbidity*. The use of the term *relative risk* for several different quantities arises from the fact that for "rare" diseases (e.g., neonatal mortality in

infants under 1,500-g birth weight), the approximations do not hold. (Last, 2001)

Reserve—A member of a reserve component of one of the Armed Forces. Reserve component: With respect to the Armed Forces—(A) The Army Reserve; (B) The Navy Reserve; (C) The Marine Corps Reserve; (D) The Air Force Reserve; (E) The Coast Guard Reserve; (F) The Army National Guard of the United States; and (G) The Air National Guard of the United States. (Definitions. 2006. 38 U.S.C. § 101.)

Residual confounding—Confounding that persists after incomplete or unsuccessful attempts to account or adjust for it.

Retirement—Leaving the military after at least 20 years of active service.

Reverse causality—An association that arises when the purported cause is actually the effect (A is thought to cause B, when in fact B causes A). See Cross-sectional study.

Rhabdomyosarcoma—A malignant neoplasm derived from skeletal (striated) muscle, occurring in children or, less commonly, in adults; classified as embryonal alveolar (composed of loose aggregates of small round cells) or pleomorphic (containing rhabdomyoblasts). (Stedman's medical dictionary 28th ed., 2005)

Rheumatoid arthritis—A generalized disease, occurring more often in women, that primarily affects connective tissue; arthritis is the dominant clinical manifestation, involving many joints, especially those of the hands and feet, accompanied by thickening of articular soft tissue, with extension of synovial tissue over articular cartilages, which become eroded; the course is variable but often is chronic and progressive, leading to deformities and disability. (Stedman's medical dictionary 28th ed., 2005)

Rickets—A disease due to vitamin D deficiency and characterized by overproduction and deficient calcification of osteoid tissue, with associated skeletal deformities, disturbances in growth, hypocalcemia, and sometimes tetany; usually accompanied by irritability, listlessness, and generalized muscular weakness; fractures are frequent. (Stedman's medical dictionary 28th ed., 2005)

Risk estimate—Combining risk characterization, dose-response relationships, and exposure estimates to quantify the risk level in a specific population. The end result is a qualitative and quantitative statement about the health effects expected and the proportion and number of affected people in a target population. Sometimes used as a general term for effect measure in an epidemiological analysis. (Adapted from Last, 2001)

Roentgenogram (radiograph)—A negative image on photographic film made by exposure to x-rays or gamma rays that have passed through matter or tissue. (Stedman's medical dictionary 28th ed., 2005)

Saccharin—In dilute aqueous solutions it is 300 to 500 times sweeter than sucrose; used as a sweetening agent.

"Safe" dose—A threshold below which there is no increase in risk.

Sandfly fever—An infectious but not contagious disease occurring in the Balkan Peninsula and other parts of southern Europe, caused by several viruses in the family Bunyaviridae apparently introduced by the bite of the sandfly, *Phlebotomus papatasii;* symptoms resemble those of dengue but are less severe and of shorter duration. Syn: *Phlebotomus fever.* (Stedman's medical dictionary 28th ed., 2005)

Sarcoidosis—A systemic granulomatous disease of unknown cause, especially involving the lungs with resulting interstitial fibrosis, but also involving lymph nodes, skin, liver, spleen, eyes, phalangeal bones, and parotid glands; granulomas are composed of epithelioid and multinucleated giant cells with little or no necrosis. (Stedman's medical dictionary 28th ed., 2005)

Sarcoma—A connective tissue neoplasm, usually highly malignant, formed by proliferation of mesodermal cells. (Stedman's medical dictionary 28th ed., 2005)

Sarin—A nerve poison similar to diisopropyl fluorophosphate and tetraethyl pyrophosphate; a very potent irreversible cholinesterase inhibitor and a more toxic nerve gas than tabun or soman. (Stedman's medical dictionary 28th ed., 2005)

Schistosomiasis—Infection with a species of *Schistosoma;* manifestations of this often chronic and debilitating disease vary with the infecting species but depend in large measure upon tissue reaction (granulation and fibrosis) to the eggs deposited in venules and in the hepatic portals, the latter resulting in portal hypertension and esophageal varices, as well as liver damage leading to cirrhosis. (Stedman's medical dictionary 28th ed., 2005)

Schizoaffective disorder—(1) An illness manifested by an enduring major depressive, manic, or mixed episode along with delusions, hallucinations, disorganized speech and behavior, and negative symptoms of schizophrenia. In the absence of major depressive, manic, or mixed episode, there must be delusions or hallucinations for several weeks. (2) A DSM diagnosis that is established when the specific criteria are met. (Stedman's medical dictionary 28th ed., 2005)

Schizophrenia—A term coined by Bleuler, synonymous with and replacing *dementia praecox*, denoting a common type of psychosis, characterized by abnormalities in perception, content of thought, and thought process (hallucinations and delusions) and by extensive withdrawal of interest from other people and the outside world, with excessive focusing on one's own mental life. Now considered a group or spectrum of disorders rather than a single entity, with distinction sometimes made

between process schizophrenia and reactive schizophrenia. The "split" personality of schizophrenia, in which individual psychic components or functions split off and become autonomous, is popularly but erroneously identified with multiple personality, in which two or more relatively complete personalities dominate by turns the psychic life of a patient. (Stedman's medical dictionary 28th ed., 2005)

Schizophreniform disorder—(1) A disorder with essential features that are identical to those of schizophrenia, with the exception that the duration including prodromal, active, and residual phases is shorter than 6 months. (2) A DSM diagnosis that is established when the specific criteria are met. (Stedman's medical dictionary 28th ed., 2005)

Schwannoma—A benign, encapsulated neoplasm in which the fundamental component is structurally identical to a syncytium of Schwann cells; the neoplastic cells proliferate within the endoneurium, and the perineurium forms the capsule. The neoplasm may originate from a peripheral or sympathetic nerve, or from various cranial nerves, particularly the eighth nerve; when the nerve is small, it is usually found (if at all) in the capsule of the neoplasm; if the nerve is large, the neurilemoma may develop within the sheath of the nerve, the fibers of which may then spread over the surface of the capsule as the neoplasm enlarges. Microscopically, neurilemoma is composed of combinations of two patterns, Antoni types A and B, either of which may be predominant in various examples of neurilemomas. (Stedman's medical dictionary 28th ed., 2005)

Scleroderma—Thickening and induration of the skin caused by new collagen formation, with atrophy of pilosebaceous follicles; either a manifestation of progressive systemic sclerosis or localized (morphea). (Stedman's medical dictionary 28th ed., 2005)

Sclerosis—In neuropathy, induration of nervous and other structures by a hyperplasia of the interstitial fibrous or glial connective tissue. (Stedman's medical dictionary 28th ed., 2005)

Scurvy—A disease marked by inanition, debility, anemia, and edema of the dependent parts; a spongy condition sometimes with ulceration of the gums and loss of teeth, hemorrhages into the skin from the mucous membranes and internal organs, and poor wound healing; due to a diet lacking vitamin C. (Stedman's medical dictionary 28th ed., 2005)

Seamless transition—The commitment of DoD and VA to work closely in harmonizing the medical records of Service members for a smooth transition from DoD care to VA care.

Secretary—Secretary of Veterans Affairs; Secretary concerned (A) The Secretary of the Army, with respect to matters concerning the Army; (B) The Secretary of the Navy, with respect to matters concerning the Navy; or the Marine Corps; (C) The Secretary of the Air Force,

with respect to matters concerning the Air Force; (D) The Secretary of Homeland Security, with respect to matters concerning the Coast Guard; (E) The Secretary of Health and Human Services, with respect to matters concerning the Public Health Service; and (F) The Secretary of Commerce, with respect to matters concerning the National Oceanic and Atmospheric Administration or its predecessor organization the Coast and Geodetic Survey. (Definitions. 2006. 38 U.S.C. § 101.)

Selection bias—In a case-control study, occurs when the chance of being selected as a case or a control is influenced by exposure status. In a cohort study, occurs when the chance of participation in a study as exposed or non-exposed is influenced by disease status. Also, error due to systematic differences in characteristics between those who take part in a study and those who do not. Selection bias can invalidate conclusions and generalizations that might otherwise be drawn from such studies.

Sensitivity—The proportion of truly diseased persons in the screened population who are correctly identified as diseased by the screening test; a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test; specifically, the ratio of those who are identified by a test to have the condition who in fact have it, divided by all those who have the condition (i.e., true positives, divided by the sum of true positives and false negatives).

Sensitivity analysis—A method to determine the robustness of a result by examining the extent to which the result is affected by changes in methods, values of variables, or assumptions. (Adapted from Last, 2001)

Separation—Left the military before 20 years; cannot apply for retirement benefits (Source: Personal communication, Col. K. Cox, Department of Defense, January 5, 2007):

1. The act of keeping apart or dividing, or the state of being held apart.
2. In dentistry, the process of gaining slight spaces between the teeth preparatory to treatment. (Stedman's medical dictionary 28th ed., 2005)

Service-attributable disability—Disability caused by a veteran's service.

Service-attributable fraction (SAF)—The attributable fraction (AF) when the specific exposure is military service (see Attributable fraction); in other words, the proportion of a disease attributable to military service.

Service-connected—With respect to disability or death, that such disability was incurred or aggravated, or that the death resulted from a disability incurred or aggravated, in line of duty in the active military, naval, or air service. (Definitions. 2006. 38 U.S.C. § 101.)

Seveso study—The study of a population exposed to dioxin from an indus-

trial accident that occurred in 1976 in a small manufacturing plant in the Lombardy region in Italy.

Shared psychotic disorder—A mental disorder in which a delusion develops in a person in a relationship with another person with an established delusion. (Stedman's medical dictionary 28th ed., 2005)

Shigellosis—Bacillary dysentery caused by bacteria of the genus *Shigella*, often occurring in epidemic patterns; an opportunistic infection of person with AIDS. (Stedman's medical dictionary 28th ed., 2005)

Sliding scale pension—A pension based on income level.

Spanish-American War—(A) The period beginning on April 21, 1898, and ending on July 4, 1902, (B) Includes the Philippine Insurrection and the Boxer Rebellion, and (C) In the case of a veteran who served with the United States military forces engaged in hostilities in the Moro Province, means the period beginning on April 21, 1898, and ending on July 15, 1903. (Definitions. 2006. 38 U.S.C. § 101.)

Specificity—The proportion of truly nondiseased persons who are correctly identified by the screening test; a measure of the probability of correctly identifying a nondiseased person with a screening test; specifically, the ratio of those who are identified by a test to not have the condition who in fact do not have it, divided by all those who do not have the condition (i.e., true negatives, divided by the sum of true negatives and false positives).

Spouse—A person of the opposite sex who is a wife or husband. (Definitions. 2006. 38 U.S.C. § 101.)

Spurious association—A noncausal association due to chance, bias, failure to control for extraneous variables, confounding, etc. (see Confounder).

Squamous cell carcinoma—A malignant neoplasm derived from stratified squamous epithelium, but which may also occur in sites such as bronchial mucosa where glandular or columnar epithelium is normally present; variable amounts of keratin are formed, in relation to the degree of differentiation, and, if the keratin is not on the surface, it may accumulate in the neoplasm as a keratin pearl; in instances in which the cells are well differentiated, intercellular bridges may be observed between adjacent cells. (Stedman's medical dictionary 28th ed., 2005)

Stakeholder—One with an interest or share in an undertaking or enterprise.

State—Each of the several States, Territories, and possessions of the United States, the District of Columbia, and the Commonwealth of Puerto Rico. For the purpose of section 2303 and chapters 34 and 35 of this title (38 U.S.C.S. § 2303, 3451 et seq., and 3500 et seq.), such term also includes the Canal Zone. (Definitions. 2006. 38 U.S.C. § 101.)

State home—A home established by a State (other than a possession) for veterans disabled by age, disease, or otherwise who by reason of such disability are incapable of earning a living. Such term also includes such

a home which furnishes nursing home care for veterans. (Definitions. 2006. 38 U.S.C. § 101.)

Stratum (strata)—Subsamples according to specified criteria, such as age groups, socioeconomic status, etc.

One of the layers of differentiated tissue, the aggregate of which forms any given structure, such as the retina or the skin. (Stedman's medical dictionary 28th ed., 2005)

Stroke—(1) Any acute clinical event, related to impairment of cerebral circulation, that lasts more than 24 hours. (2) A harmful discharge of lightning, particularly one that affects a human being. (3) A pulsation. (4) To pass the hand or any instrument gently over a surface. See also stroking. (5) A gliding movement over a surface. (Stedman's medical dictionary 28th ed., 2005)

Subcapsular cataracts—A cataract in which the opacities are concentrated beneath the capsule. (Stedman's medical dictionary 28th ed., 2005)

Sufficient cause—The minimum set of conditions, factors, or events needed to produce a given outcome. (Adapted from Last, 2001)

Sufficient component causes model—A model that postulates disease resulting from any of several sufficient causal constellations, each of which comprises components that are all necessary to make them a complete cause.

Sulfur mustard—Cytotoxic vesicant chemical warfare agent with the ability to form large blisters on exposed skin (e.g., mustard gas).

Surveillance—Continuous monitoring of disease occurrence within a population.

Surviving spouse—A person of the opposite sex who was the spouse of a veteran at the time of the veteran's death, and who lived with the veteran continuously from the date of marriage to the date of the veteran's death (except where there was a separation which was due to the misconduct of, or procured by, the veteran without the fault of the spouse) and who has not remarried or (in cases not involving remarriage) has not since the death of the veteran, and after September 19, 1962, lived with another person and held himself or herself out openly to the public to be the spouse of such other person (except for purposes of chapter 19 of this title [38 U.S.C.S. § 1901 et seq.]). (Definitions. 2006. 38 U.S.C. § 101.)

Synovial sarcoma—A rare malignant tumor of synovial origin, most commonly involving the knee joint and composed of spindle cells usually enclosing slits or pseudoglandular spaces that may be lined by radially disposed epitheliallike cells. (Stedman's medical dictionary 28th ed., 2005)

Syringomyelia—The presence in the spinal cord of longitudinal cavities lined by dense, gliogenous tissue, that are not caused by vascular insuf-

ficiency. Syringomyelia is marked clinically by pain and paresthesia, followed by muscular atrophy of the hands and analgesia with thermoanesthesia of the hands and arms, but with the tactile sense preserved; later marked by painless whitlows, spastic paralysis in the lower extremities, and scoliosis of the lumbar spine. Some cases are associated with low-grade gliomas or vascular malformations of the spinal cord. (Stedman's medical dictionary 28th ed., 2005)

Systematic error—One-sided variation of measurements from the true values; see also Bias.

Systemic lupus erythematosus—An inflammatory connective tissue disease with variable features, frequently including fever, weakness and fatigability, joint pains or arthritis resembling rheumatoid arthritis, diffuse erythematous skin lesions on the face, neck, or upper extremities, with liquefaction degeneration of the basal layer and epidermal atrophy, lymphadenopathy, pleurisy or pericarditis, glomerular lesions, anemia, hyperglobulinemia, and a positive LE cell test result, with serum antibodies to nuclear protein and sometimes to double-stranded DNA and other substances. (Stedman's medical dictionary 28th ed., 2005)

Testosterone—The most potent naturally occurring androgen, formed in greatest quantities by the interstitial cells of the testes, and possibly secreted also by the ovary and adrenal cortex; may be produced in nonglandular tissues from precursors such as androstenedione; used in the treatment of hypogonadism, cryptorchism, certain carcinomas, and menorrhagia. (Stedman's medical dictionary 28th ed., 2005)

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)—See Dioxin.

Theater—A specific geographic area within which armed conflict occurs.

Thromboangiitis obliterans (Buerger's disease)—Inflammation of the entire wall and connective tissue surrounding medium-sized arteries and veins, especially of the legs of young and middle-aged men; associated with thrombotic occlusion and commonly resulting in gangrene. (Stedman's medical dictionary 28th ed., 2005)

Thyroid nodular disease—Presence of palpable thyroid nodules. These nodules may be solitary or one or more within a multi-nodular thyroid. Most are benign, colloid nodules.

Thyroxine—The *l*-isomer is the active iodine compound existing normally in the thyroid gland and extracted therefrom in crystalline form for therapeutic use; also prepared synthetically; used for the relief of hypothyroidism, cretinism, and myxedema. (Stedman's medical dictionary 28th ed., 2005)

Tolman Committee—Also known as the Committee on Declassification; appointed by General Groves in 1944 to study the declassification of Manhattan Project research.

Tonsillectomy—Removal of the entire tonsil. (Stedman's medical dictionary 28th ed., 2005)

Tort litigation—Legal proceeding for a wrongful act other than a breach of contract for which relief may be obtained in the form of damages or an injunction.

Toxicant—Any poisonous agent, specifically alcohol or other poison, causing symptoms of what is popularly called intoxication. (Stedman's medical dictionary 28th ed., 2005)

Toxicogenomics—A scientific subdiscipline that combines toxicology (the study of the nature and effects of poisons) with genomics (the investigation of the way that our genetic makeup translates into biological functions).

Transparency—Characterized by visibility or accessibility of information, especially concerning business practices.

2,4,5-Trichlorophenoxyacetic acid—An herbicide and defoliant synthesized by condensation of chloracetic acid and 2,4,5-trichlorophenol, used as the principal constituent of Agent Orange.

Triglyceride—Glycerol esterified at each of its three hydroxyl groups by a fatty (aliphatic) acid. Syn: *triacylglycerol.* (Stedman's medical dictionary 28th ed., 2005)

Trypanosomiasis—Any disease caused by a trypanosome. (Stedman's medical dictionary 28th ed., 2005)

Tuberculosis (TB)—A specific disease caused by infection with *Mycobacterium tuberculosis*, the tubercle bacillus, which can affect almost any tissue or organ of the body, the most common seat of the disease being the lungs. Primary tuberculosis is typically a mild or asymptomatic local pulmonary infection. Regional lymph nodes may become involved, but in otherwise healthy people generalized disease does not immediately develop. A cell-mediated immune response arrests the spread of organisms and walls off the zone of infection. Infected tissues and lymph nodes may eventually calcify. The tuberculin skin test becomes positive within a few weeks, and remains positive throughout life. Organisms in a primary lesion remain viable and can become reactivated months or years later to initiate secondary tuberculosis. Progression to the secondary stage eventually occurs in 10-15 percent of people who have had primary tuberculosis. The risk of reactivation is increased by diabetes mellitus, HIV infection, silicosis, and various systemic or malignant conditions, as well as in alcoholics, IV drug abusers, nursing home residents, and those receiving adrenocortical steroid or immunosuppressive therapy. Secondary or reactivation tuberculosis usually results in a chronic, spreading lung infection, most often involving the upper lobes. Minute granulomas (tubercles), just visible to the naked eye, develop in involved lung tissue, each consisting of a zone

of caseation necrosis surrounded by chronic inflammatory cells (epithelioid histiocytes and giant cells). These lesions, which give the disease its name, are also found in other tissues (lymph nodes, bowel, kidney, skin) to which the disease may spread. Rarely, reactivation results in widespread dissemination of tubercles throughout the body (miliary tuberculosis). The symptoms of active pulmonary tuberculosis are fatigue, anorexia, weight loss, low-grade fever, night sweats, chronic cough, and hemoptysis. Local symptoms depend on the parts affected. Active pulmonary tuberculosis is relentlessly chronic and, if untreated, leads to progressive destruction of lung tissue. Cavities form in the lungs, and erosion into pulmonary blood vessels can result in life-threatening hemorrhage. Gradual deterioration of nutritional status and general health culminates in death due to wasting, infection, or multiple organ failure. Variant syndromes (tuberculous lymphadenitis in children, severe systemic disease in persons with AIDS) are caused by organisms of the *Mycobacterium avium-intracellulare* complex (MAIC). The diagnosis of TB is based on tuberculin skin testing (negaitive in 20 percent of people with active TB), imaging studies (computed tomography is more sensitive than standard chest radiography in detecting pleural effusion, miliary disease, and cavitation), and the finding of the causative organism in sputum of tissue specimens by acid-fast or fluorochrome staining, nucleic acid amplification, or culture. (Stedman's medical dictionary 28th ed., 2005)

Tumors—(1) Any swelling or tumefaction. (2) Syn: *neoplasm*. (3) One of the four signs of inflammation (t., calor, dolor, rubor) enunciated by Celsus. (Stedman's medical dictionary 28th ed., 2005)

Malignant tumor—A tumor that invades surrounding tissues, is usually capable of producing metastases, may recur after attempted removal, and is likely to cause death of the host unless adequately treated. (Stedman's medical dictionary 28th ed., 2005)

Type I presumptions—Shifts both the burden of production and the burden of persuasion.

Type II presumptions—Establishment of the basic fact does not shift to the opponent the burden of persuading the adjudicator that the presumed fact does not exist. The opponent of the presumption only has to produce evidence that is contrary to or meets the presumption.

Ulcer—A lesion through the skin or a mucous membrane resulting from loss of tissue, usually with inflammation. (Stedman's medical dictionary 28th ed., 2005)

Ulceration—(1) The formation of an ulcer. (2) An ulcer or aggregation of ulcers. (Stedman's medical dictionary 28th ed., 2005)

Uncertainty—The state of being indeterminate, not certain to occur, not reliable, not having certain knowledge, or not clearly identified or defined.

Undiagnosed illness (or unexplained illness)—A constellation of symptom complaints; was called "Gulf War Syndrome."

Vaccine Injury Table—Lists and explains injuries/conditions that are presumed to be caused by vaccines and covered under the National Vaccine Injury Compensation Program.

Valvulitis—Inflammation of a valve, especially a heart valve. (Stedman's medical dictionary 28th ed., 2005)

Vesicant—An agent that produces a vesicle. (Stedman's medical dictionary 28th ed., 2005)

Veteran—A person who served in the active military, naval, or air service, and who was discharged or released therefrom under conditions other than dishonorable. (Definitions. 2006. 38 U.S.C. § 101.)

Veteran of any war—Any veteran who served in the active military, naval, or air service during a period of war. (Definitions. 2006. 38 U.S.C. § 101.)

Vietnam era—(A) The period beginning on February 28, 1961, and ending on May 7, 1975, in the case of a veteran who served in the Republic of Vietnam during that period. (B) The period beginning on August 5, 1964, and ending on May 7, 1975, in all other cases. (Definitions. 2006. 38 U.S.C. § 101.)

Viral exanthemas—A skin eruption occurring as a symptoms of an actual viral disease.

von Recklinghausen's neurofibromatosis (Type I neurofibromatosis)—Characterized clinically by the combination of patches of hyperpigmentation and cutaneous and subcutaneous tumors. The hyperpigmented skin areas, present from birth and found anywhere on the body surface, can vary markedly in size and color—the dark brown ones are called café-au-lait spots. The multiple cutaneous and subcutaneous tumors, called neurofibromas, can develop anywhere along the peripheral nerve fibers, from the roots distally. Neurofibromas can become quite large, causing a major disfigurement, eroding bone, and compressing various peripheral nerve structures; a small hamartoma (Lisch nodule) can be found in the iris of almost all patients. Has autosomal dominant inheritance, with the gene locus on chromosome 17q11, and is caused by mutation in the NF1 gene that encodes neurofibromin. Syn: *Type I neurofibromatosis*. (Stedman's medical dictionary 28th ed., 2005)

World War I—(A) The period beginning on April 6, 1917, and ending on November 11, 1918, and (B) In the case of a veteran who served with the United States military forces in Russia, means the period beginning on April 6, 1917, and ending on April 1, 1920. (Definitions. 2006. 38 U.S.C. § 101.)

World War II—The period beginning on December 7, 1941, and ending on December 31, 1946 (except for purposes of chapters 31 and 37 of this

title [38 U.S.C.S. § 3100 et seq. and 3701 et seq.]). (Definitions. 2006. 38 U.S.C. § 101.)

Yaws—An infectious tropical disease caused by *Treponema pertenue* and characterized by the development of crusted granulomatous ulcers on the extremities; may involve bone, but, unlike syphilis, does not produce central nervous system or cardiovascular pathology. (Stedman's medical dictionary 28th ed., 2005)

Yellow fever—A tropical mosquito-borne viral hepatitis, due to yellow fever virus, a member of the family Flaviviridae, with an urban form transmitted by *Aedes aegypti*, and a rural, jungle, or sylvatic form from tree-dwelling mammals by various mosquitoes of the *Haemagogus* species complex; characterized clinically by fever, slow pulse, albuminuria, jaundice, congestion of the face, and hemorrhages, especially hematemesis; used to occur in epidemics mainly in port cities, especially in late summer, with 20-40 percent case fatality rates; immunity to reinfection accompanies recovery. (Stedman's medical dictionary 28th ed., 2005)

LEGISLATION

1818 Service Pension Law
1862 General Pension Act
1862 Homestead Act
1890 Dependent Pension Act
1917 War Risk Insurance Act Amendments
1918 Vocational Rehabilitation Act
1924 World War Adjustment Compensation Act
1933 Economy Act
1943 Disabled Veterans' Rehabilitation Act
1944 Servicemen's Readjustment Act (GI Bill of Rights)
1950 Vocational Rehabilitation Act
1952 Veteran's Readjustment Assistance Act (Korean GI Bill)
1954 War Claims Act Amendments
1959 Veterans' Pension Act
1978 Veterans Disability Compensation and Survivor Act
1979 The Veterans Health Care Amendments
1979 Veterans Health Program Extension and Improvement Act
1981 Former Prisoners of War Benefits Act
1981 Veterans' Health Care, Training, and Small Business Loan Act
1984 The Veterans Dioxin and Radiation Exposure Compensation Standards Act (VDRECSA)
1984 Veterans' Compensation and Program Improvements Amendments

1984	Veterans' Dioxin and Radiation Exposure Compensation Standards Act
1986	Veterans Benefits Improvement and Health Care Authorization Act
1988	The Radiation-Exposed Veterans Compensation Act (REVCA)
1988	Veterans Benefits and Services Act
1990	The Radiation Exposure Compensation Act (RECA)
1991	Agent Orange Act
1994	Persian Gulf War Veterans' Benefit Act
2000	Veterans Millennium Health Care and Benefits Act
2003	Veterans Benefits Act

IMPROVING THE PRESUMPTIVE DISABILITY DECISION-MAKING PROCESS FOR VETERANS

Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans

Board on Military and Veterans Health

Jonathan M. Samet and Catherine C. Bodurow, *Editors*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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

Appendix D

Historical Background[1]

FROM THE BEGINNING

Our nation has recognized military veterans' service and sacrifices since its very earliest days. On August 26, 1776, the Continental Congress adopted the first national pension law provided for compensation payments to be made to "every officer, soldier, or sailor losing a limb in any engagement or being so disabled in the service of the United States as to render him incapable of earning a livelihood" (VA, 1971, p. 306; VA, 2006a).

The 1818 Service Pension Law "provided that every person who had served in the War for Independence and was in need of assistance would receive a fixed pension for life. The rate was $20 a month for officers and $8 a month for enlisted men" (VA, 2006a, p. 4). Because pensions had previously been to disabled veterans only, the number of pensioners quickly increased from 2,200 to 17,730, and the cost from $120,000 to $1.4 million (VA, 2006a, p. 4).

CIVIL WAR AND AFTERMATH

> When the Civil War broke out in 1861, the nation had about 80,000 war veterans. By the end of the war in 1865, another 1.9 million veterans had been added to the rolls. This included only veterans of Union forces. . . . The General Pension Act of 1862 provided disability payments based on rank and degree of disability, and liberalized benefits for widows, children, and dependent relatives. The law covered military service in time of peace as well as during the Civil War. The act included, for the first time, compensation for diseases such as tuberculosis incurred while in service. Union veterans also were assigned a special priority in the Homestead Act of 1862, which provided land in the West at $1.25 an acre. The year 1862 also marked the establishment of the National Cemetery System to provide burial for the many Union dead of the Civil War.
>
> (VA, 2006a, p. 4)

> Until 1890, Civil War pensions were granted only to servicemen discharged because of illness or disability attributable to military service. The Dependent Pension Act of 1890 substantially broadened the scope of eligibility, providing pensions to veterans incapable

[1] The Historical Background section is an adapted version of *VA History in Brief* (VA, 2006a) except where otherwise noted.

> of manual labor. Within the next three years the number of veterans on the pension roll increased from 489,000 to 996,000 and expenditures doubled. Legislation passed in the nineteenth century had established a general pension system that could be applied to future pension recipients. As a consequence, new pension laws did not follow the Spanish-American War in 1898 or the Philippine Insurrection, 1899 to 1901.
>
> (VA, 2006a, p. 5)

WORLD WAR I

The United States' entry into World War I directed significant attention toward the existing system of benefits for veterans. "Some 4.7 million Americans fought in World War I. Of these, 116,000 died in service and 204,000 were wounded" (VA, 2006a, p. 7). Many felt the existing system needed revision, and this new, huge mobilization provided the impetus.

> Among the provisions of the War Risk Insurance Act Amendments of 1917 was the authority to establish courses for rehabilitation and vocational training for veterans with dismemberment, sight, hearing, and other permanent disabilities.
>
> (VA, 2006a, p. 7)

> The Vocational Rehabilitation Act of 1918 authorized the establishment of an independent agency, the Federal Board for Vocational Education. Under the new law, any honorably discharged disabled veteran of World War I was eligible for vocational rehabilitation training. Those incapable of carrying on a gainful occupation were also eligible for special maintenance allowances.
>
> (VA, 2006a, p. 7)

In addition to these provisions, the War Risk Insurance Act of 1917 addressed features of the pension system, or what today is known as "disability compensation."

> There was a change in emphasis from payment of a gratuity towards indemnification, and there was elimination of rank as a factor in determining the amount of compensation. . . . [T]he new Bureau of War Risk Insurance was instructed to set up a schedule for rating disabilities. The schedule was to represent average impairments in earning capacity caused by specific injuries or combination of injuries. In this way the individual who overcame his handicap was not penalized but encouraged to reenter the labor force, with the knowledge that his payments would not be reduced or terminated.
>
> (VA, 1971, p. 308)

THE DEPRESSION YEARS

The Great Depression had a staggering economic impact across America. World War I veterans, like others, were seriously affected by this huge economic downturn. After returning from the Great War, many veterans faced destitution. Congress passed the World War Adjustment Compensation Act in 1924 that authorized a bonus to World War I veterans based on the length and location of their service. "The payments were intended to bring about economic balance between the veterans—who generally received low wages in the service—and those who stayed home and benefited from wartime industry" (VA, 2006a, p. 9). However, the certificates for payment, which generally had a face value of $1,500, were in the form of an endowment policy payable 20 years from the date of issue (VA, 2006a, p. 9).

> As the Depression worsened, veterans began calling for immediate payment of their "bonuses," as the certificates came to be known. In March 1932, a small group of veterans from Oregon began marching to Washington, DC, to demand payment. Word of the march spread like wildfire and soon small bands of unemployed veterans from across the country began descending on the nation's capital.
>
> (VA, 2006a, p. 9)

The thousands of veteran marchers became known as the "Bonus Expeditionary Forces." They camped wherever they could, and living conditions quickly deteriorated.

> President Hoover knew he had to curb the escalating violence. He gave the order for Army Chief of Staff Gen. Douglas MacArthur to forcibly remove from the city the approximately 3,500 veterans, many with their wives and children, who refused to leave. No shots were fired, but many were injured.
>
> (VA, 2006a, p. 10)

> Though the marchers failed to get immediate results, in 1936 Congress authorized early payment of the bonuses. By June 30, 1937, the Veterans Administration (VA) had certified as payable nearly 3.5 million applications from World War I veterans for settlement of their certificates.
>
> (VA, 2006a, p. 10)

> President Hoover, in his 1929 State of the Union message, proposed consolidating agencies administering veterans benefits. The following year Congress created the Veterans Administration by uniting three bureaus. . . . The new agency was responsible for medical services for war veterans, disability compensation and allowances for World War I veterans, life insurance, and bonus certificates and other veterans benefits.
>
> (VA, 2006a, p. 12)

> In March 1933, President Roosevelt persuaded Congress to pass the Economy Act. A response to the Great Depression, the measure included a repeal of all previous laws granting benefits for veterans of the Spanish-American War and all subsequent conflicts and periods of peacetime service. It also gave the president authority to authorize new veterans benefits. Roosevelt then promulgated regulations that radically reduced veterans benefits. When the president's authority to establish benefits by executive order expired in 1935, Congress reenacted most of the laws that had been in effect earlier.
>
> (VA, 2006a, p. 12)

> The Board of Veterans' Appeals was established in July 1933. It was given authority to hear appeals on benefit decisions. Members were appointed by the administrator with the approval of the President.
>
> (VA, 2006a, p. 12)

> Demand for hospital care grew dramatically in the Depression years.
>
> (VA, 2006a, p. 12)

> From 1931 to 1941, the number of VA hospitals would increase from 64 to 91, and the number of beds would rise from 33,669 to 61,849.
>
> (VA, 2006a, p. 12)

> At first, tuberculosis predominated among the conditions treated at VA hospitals. But by the middle of the 1930s, tuberculosis patients had dropped to only 13 percent—thanks partly to VA's own research and treatment efforts. Neuropsychiatric conditions then accounted for more than half of the patients.
>
> (VA, 2006a, pp. 12-13)

WORLD WAR II

> With war on the horizon, Congress in 1940 created a new insurance program for servicemen and veterans. National Service Life Insurance was designed to eliminate any inequities in premiums that would have resulted if the young men had been grouped with the older World War I veterans covered by U.S. Government Life Insurance.
>
> (VA, 2006a, p. 13)

> The Disabled Veterans' Rehabilitation Act of 1943 established a vocational rehabilitation program for disabled World War II veterans who served after Dec. 6, 1941. As a result of this law, VA provided 621,000 disabled World War II veterans with job training.
>
> (VA, 2006a, p. 13)

In 1944, the federal government foresaw the return of millions of servicemen and women. The need to accommodate their needs and to facilitate their readjustment to, and reentry into, civilian life resulted in the enactment of the Servicemen's Readjustment Act, popularly known as the "GI Bill of Rights" (VA, 2006a, p. 13). The measure, signed into law by President Roosevelt, contained three key provisions that "dramatically transformed the concept of veterans benefits" (VA, 2006a, p. 13).

> The first benefit provided up to four years of education or training. The education package included the payment of up to $500 a school year for tuition, fees, books, and supplies, plus a monthly subsistence allowance. The second benefit provided veterans with federally guaranteed home, farm, and business loans with no down payment. This feature was designed to generate jobs in the housing industry while providing housing and assistance for veterans and their families. Veterans could apply for loans up to $2,000 with 50 percent guaranteed by the government. The third feature was unemployment compensation.
>
> (VA, 2006a, pp. 13-14)

This benefit was designed to ease the unemployment market, which was making the transition to a peacetime economy.

> The new law provided that veterans who had served a minimum of 90 days were entitled to a weekly payment of $20 for a maximum of 52 weeks. The new benefits were popular with veterans. When the World War II GI Bill program ended in 1956, some 7.8 million had received some kind of training, and VA had guaranteed 5.9 million home loans totaling $50.1 billion.
>
> (VA, 2006a, p. 14)

The large influx of 15 million World War II veterans also placed great stress on the VA medical system. Existing VA hospitals were soon filled to capacity, and there were waiting lists

for admission at most hospitals. "Until more VA hospitals could be opened, the Navy and Army both made beds available" (VA, 2006a, p. 15). "To handle the dramatic increase in veterans claims, VA central office staff was increased" by 30 percent and field staff for medical care and benefits increased by nearly 76 percent (VA, 2006a, p. 15).

KOREAN WAR

> Following the outbreak of the Korean War in June 1950, Congress passed the Vocational Rehabilitation Act of 1950, which reactivated vocational rehabilitation for veterans of the new war and extended the program to peacetime veterans. The Veterans' Readjustment Assistance Act of 1952, called the "Korean GI Bill," provided unemployment insurance, job placement, home loans, and mustering-out benefits similar to those offered World War II veterans.
>
> (VA, 2006a, p. 16)

> The Korean GI Bill made several changes, however, in education benefits, reducing financial benefits generally and imposing new restrictions. In contrast to the 48 months of education allowed by the 1944 law, the Korean GI Bill permitted a maximum of 36 months.
>
> (VA, 2006a, p. 16)

Because of past abuses under the World War II GI Bill program, "[t]he Korean GI Bill also did not provide tuition payments to the colleges. Instead, veterans were paid subsistence checks, which were also to cover their college expenses. The effect of the changes was that the benefit no longer completely covered the cost of the veteran's education" (VA, 2006a, p. 16).

> In the late 1950s, [VA's] Chief Medical Director William Middleton expanded VA's research programs to address the chronic-care problems of most of its patients, including the aged. Congress, agreeing on its importance, began earmarking funds for research within the VA budget.
>
> (VA, 2006a, pp. 16-17)

Following a study of pensions and resulting legislation, VA introduced a sliding scale of pension payments for non-service-connected disabilities in 1959, based on the recipient's income, rather than a flat-rate pension. "The net assets of the veteran's and spouse's income were considered in determining the veteran's level of need. The Veterans' Pension Act of 1959 also specified that anyone already on the pension rolls as of June 30, 1960, could elect to remain under the old law" (VA, 2006a, p. 17).

VIETNAM WAR

> During this [Vietnam War] period, more than 6 million Vietnam-era veterans were separated from military service. A major difference of Vietnam-era veterans from those of earlier wars was the larger percentage of disabled. Advances in airlift and medical treatment meant that many wounded and injured personnel survived who would have died in earlier wars. By 1972 there were 308,000 Vietnam veterans with disabilities connected to military service.
>
> (VA, 2006a, p. 18)

"The return within days of veterans from combat zones to civilian life also was new" and added to their difficulties in readjusting to civilian life (VA, 2006a, p. 18). To complicate matters, returning Vietnam veterans were often reluctant to seek treatment at VA medical facilities, an institutional setting they often regarded with discomfort and distrust. To help address this issue VA instituted a new program aimed specifically at the wary Vietnam veterans: the Readjustment Counseling program, or Vet Centers. These new Vet Centers were established as storefront operations located in downtown areas, away from VA Medical Centers. They were staffed with Vietnam combat veterans and trained counselors who offered a relaxed, informal setting. The program has been successful and has expanded over the last two decades.

Environmental exposures also became an important issue for Vietnam veterans.

> Between 1962 and 1971, U.S. military forces sprayed nearly 19 million gallons of herbicides over approximately 3.6 million acres in Vietnam. The preparation known as Agent Orange accounted for approximately 11.2 million gallons of the total amount sprayed. Herbicides were used to strip the thick jungle canopy that helped conceal opposition forces, to destroy crops that enemy forces might depend upon, and to clear tall grass and bushes from around the perimeters of U.S. base camps and outlying fire support bases. Most large-scale spraying operations were conducted using airplanes and helicopters, but considerable quantities of herbicides were sprayed from boats and ground vehicles, as well as by soldiers wearing back-mounted equipment. Spraying began in 1962 and increased greatly in 1967. After a scientific report in 1969 concluded that one of the primary chemicals used in Agent Orange, namely, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) could cause birth defects in laboratory animals, U.S. forces suspended use of this herbicide in 1970 and halted all herbicide spraying in Vietnam the next year.
>
> (IOM, 1994, p. 1)

As the decade wore on, concern about possible long-term health consequences of Agent Orange and other herbicides heightened. This concern was fueled in particular by reports from growing numbers of Vietnam veterans that they had developed cancer or fathered handicapped children, which they attributed to wartime exposure to the herbicides.

VA's position was that none of the veterans' health problems were caused by Agent Orange with the exception of chloracne. All other disability claims were routinely turned down, though in 1981 VA did begin providing free health care for those who claimed their illnesses were attributable to Agent Orange (Veterans' Health Care, Training and Small Business Loan Act. 1981. Public Law 97-72. 97th Cong., 1st Sess.).

The veterans then turned to the courts. The first lawsuit was filed in July 1978; in it the plaintiff alleged that the herbicide had caused his abdominal cancer (Shuck, 1987, p. 37). Eventually, more than 600 separate actions were filed by more than 15,000 individuals throughout the United States. These actions were ultimately consolidated in the U.S. District Court for the Eastern District of New York into one class action on behalf of 2.4 million Vietnam veterans, their wives and children, and others (Shuck, 1987, pp. 4-5, 45). In addition, there were almost 400 individual cases that were not included in the class action (Shuck, 1987, p. 4). On May 7, 1984, the class action was settled, only hours before jury selection was to begin, for $180 million, then the largest tort settlement in history (Shuck, 1987, pp. 5, 166). The individual suits were dismissed on the ground that plaintiffs could not establish specific causation due to the lack of exposure data and positive epidemiologic findings (Shuck, 1987).

The lawsuits garnered enormous publicity and contributed a focus around which the Vietnam veterans could organize. Although the lawsuits failed to establish that Agent Orange was the

cause of diseases and birth defects from which veterans and their children suffered, Congress in 1984 took a first step in establishing service-connected presumptions for Vietnam veterans (Economic Systems Inc., 2004, p. 68; Shuck, 1987).

To address this difficult issue, Congress enacted the Veterans' Dioxin and Radiation Exposure Compensation Standards Act in 1984 (Public Law 98-542. 98th Cong., 2d Sess.). This act "provided a presumption of service connection for the occurrence of certain diseases related to exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era" (Economic Systems Inc., 2004, p. 68). It "directed the administrator of Veterans Affairs to establish guidelines and criteria for resolving claims for benefits resulting from a service-connected death or disability based on a veteran's exposure during active duty service to . . . herbicides containing dioxin in Vietnam" (as well as to radiation exposure prior to July 1, 1946) (Economic Systems Inc., 2004, p. 68). The measure directed VA to determine whether any of several specified diseases should be considered service connected if they developed after a veteran's departure from Vietnam (Economic Systems Inc., 2004, p. 68).

This legislation did not resolve the issue as veterans continued to present claims for Vietnam service-related diseases, for which they received what they considered to be less than satisfactory responses. As a result of the continuing controversy, Congress passed the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.). This law designated certain diseases to be service connected and resulting from exposure to dioxins and other herbicide agents during service in Vietnam during the Vietnam era. It also established a mechanism for periodic reviews of scientific evidence (by the National Academy of Sciences) concerning the association between exposure to an herbicide agent during service in Vietnam and each disease suspected to be associated with such exposure (Economic Systems Inc., 2004, p. 74).

GULF WAR PERIOD

The Gulf War "brought with it a number of difficult-to-diagnose conditions, syndromes, and diseases" and "[t]he presumption of service connection question became a matter of much scientific, social, and political debate" (Economic Systems Inc., 2004, p. 78). Congress addressed many of the concerns through legislation in 1994 with the Persian Gulf War Veterans' Benefits Act (Public Law 103-446. 103d Cong., 2d Sess.). Among its provisions were requirements to implement a uniform medical evaluation protocol for returning Gulf War veterans; a comprehensive outreach program regarding available benefits; disability compensation payments for chronic disability resulting from an "undiagnosed illness" that manifested during or within a presumptive period after Gulf War service; and the establishment of a scientific review protocol similar to that in the Agent Orange Act of 1991 (Economic Systems Inc., 2004, pp. 78-79).

With a high number of Service members still experiencing combat situations in Iraq and Afghanistan, these issues continue to be a concern.

VA PROGRAMS AND BENEFITS TODAY

The mission of VA was encapsulated in the words of President Lincoln over 140 years ago:

> To care for him who shall have borne the battle and for his widow and his orphan.
>
> (VA, 2006c)

To fulfill this pledge, VA programs are intended to provide timely, high-quality benefits and services to the 24 million living men and women who have served this country with honor in the military. Operating with outlays of over $72 billion during fiscal year (FY) 2006 and a workforce of almost 220,000 employees, VA provided medical care, benefits, social support, and lasting memorials to veterans and their dependents in recognition of veterans' service to this nation (VA, 2006b, p. 15; VA, 2007a, sec. 2, p. 20). These services were provided through three administrations within the department: Veterans Health Administration (VHA), Veterans Benefits Administration (VBA), and the National Cemetery Administration (VA, 2007a).

Through VHA, VA operates the largest direct health-care delivery system in the country, which includes 156 medical centers and more than 1,300 additional sites of care (VA, 2006c, p. 6). In this context, VA meets the health-care needs of America's veterans by providing a broad range of primary care, specialized care, and related medical and social support services. VA focuses on providing health-care services that are uniquely related to veterans' health or special needs.

VA provided care to nearly 5.5 million unique patients enrolled in its system in FY 2006 (VA, 2006b, p. 12). For FY 2006, it handled over 60 million outpatient visits and provided care to approximately 744,000 inpatients (VA, 2007a, sec. 3B, p. 17). In FY 2008 VA expects to treat 5.8 million patients of which 263,000 will be Operation Iraqi Freedom/Operation Enduring Freedom veterans (Nicholson, 2007). To provide this comprehensive medical care VA employed nearly 200,000 people and operated with a budget of approximately $32 billion (VA, 2007a, sec. 3B, pp. 12, 18). About $350 million of this amount was spent on outpatient mental health services for veterans (VA, 2007a, sec. 3B, p. 12). Another $1.25 billion was spent on the purchase and repair of medical equipment and prosthetics (VA, 2007a, sec. 3B, p. 12).

VA has developed an increasing reputation for delivering high-quality care in a cost-efficient manner and has received numerous awards. For the past 6 years VA has outranked private-sector hospitals on patient satisfaction in an annual consumer survey conducted by the National Quality Research Center at the University of Michigan. In December 2004 RAND investigators found that VA outperformed all other sectors of American health care across a spectrum of 294 measures of quality in disease prevention and treatment (VA, 2006b, p. 119).

VA is the nation's largest provider of health-care education and training for medical residents and other health-care trainees. Its education and training programs are designed to help ensure an adequate supply of clinical care providers for veterans and the nation (VA, 2007a).

"VA advances medical research and development in ways that support veterans' needs by pursuing medical research in areas that most directly address the diseases and conditions that affect veterans. Shared VA medical research findings contribute to the public good by improving the nation's overall knowledge of disease and disability" (VA, 2007a, sec. 1, p. 13). Its research budget, composed of VA direct appropriations as well as funds from other federal appropriations and private sources, is proposed to be $1.4 billion for FY 2008 (Nicholson, 2007).

VBA, with 57 regional offices and a staff of over 13,000 employees, delivers a number of programs designed to aid veterans in consequence of their military service (VBA, 2006, p. 14; VA, 2007b, sec. 5, p. 2). The largest of these is the Disability Compensation Program which provides monthly payments and ancillary benefits totaling in excess of $30.8 billion to over 3.5 million veterans, in accordance with rates specified by law, in recognition of the average potential loss of earning capacity caused by a disability, disease, or death incurred or aggravated during active military service (VBA, 2006, p. 19).

About 48 percent of these veterans are rated 10-20 percent disabled with an additional 25 percent rated 30-40 percent disabled (VBA, 2006, p. 21). Seriously disabled—those rated at 50 percent or more—constitute 26 percent of those in receipt of compensation benefits (VBA, 2006, p. 21). The distribution of the most frequently occurring service-connected disabilities by body system for veterans receiving compensation at the end of FY 2005 is as follows: "Muscloskeletal System" (39 percent), "Impairment of Auditory Acuity" (11 percent), "Skin" (10 percent), "Neurological Conditions" (7 percent), "Mental Disorders" (7 percent), "Cardiovascular System" (6 percent), and "Digestive System" (6 percent) (VBA, 2006, p. 28).

In FY 2005, VA received nearly 800,000 claims for processing and determination (VBA, 2006, p. 26). A growing number of these claims involve complex issues resulting from posttraumatic stress disorder, environmental and infectious risks, traumatic brain injuries, complex combat-related issues, and complications arising from diabetes.

This program also provides monthly payments, as specified by law, to nearly 329,000 surviving spouses, dependent children, and dependent parents in recognition of the economic loss caused by the veteran's death during active military service or, subsequent to discharge from military service, as a result of a service-connected disability (VBA, 2006, p. 39).

VA's pension program provides monthly payments, as specified by law, to needy wartime veterans at age 65 or over or who are permanently and totally disabled from non-service-connected causes at an annual cost of over $2.6 billion (VBA, 2006, p. 42). This program also provides monthly payments, as specified by law, to about 207,000 needy surviving spouses and dependent children of deceased wartime veterans who died as a result of a disability unrelated to military service (VBA, 2006, p. 47).

VA's education program assists eligible veterans, Service members, reservists, survivors, and dependents in achieving their educational or vocational goals. VA provided educational assistance benefits totaling over $2.6 billion to approximately 500,000 individuals in FY 2005 (VBA, 2006, p. 55).

The vocational rehabilitation and employment program assists veterans with service-connected disabilities to achieve functional independence in daily activities, become employable, and obtain and maintain suitable employment. Over 60,000 veterans applied for this form of benefits in FY 2005 (VBA, 2006, p. 87).

VA's housing program helps eligible veterans, active duty personnel, surviving spouses, and selected reservists purchase and retain homes. In FY 2006, VA assisted over 135,000 home buyers (VA, 2007a, sec. 6D, p. 3).

VA's insurance program provides 1.8 million veterans, 2.4 million Service members, and 3 million family members with life insurance benefits, some of which are not available from other providers—such as the commercial insurance industry—because of lost or impaired insurability resulting from military service (VA, 2007a, sec. 3A, p. 36). Insurance coverage is made in reasonable amounts and at competitive premium rates comparable to those offered by commercial companies. The program ensures a competitive, secure rate of return on investments held on behalf of the insured.

The National Cemetery Administration, with a budget of about $161 million, honors veterans with final resting places in national shrines and lasting memorials that commemorate the veterans' service to the nation (VA, 2007b, sec. 1A, p. 4). VA maintains more than 2.8 million gravesites at 121 national cemeteries and 33 other cemeterial installations. It will inter about 105,000 veterans in FY 2008 (Nicholson, 2007; VA, 2007a, sec. 3A, p. 36).

BASIC PRINCIPLES OF THE DISABILITY COMPENSATION PROGRAM

VA's disability compensation program provides monthly payments and ancillary benefits to veterans in recognition of the average potential loss for earning capacity caused by disability or disease incurred or aggravated during active military service.

The statutory provision that entitles veterans to disability compensation is found in section 1110 of title 38, United States Code (USC) as follows:

> For disability resulting from personal injury suffered or disease contracted in line of duty, or for aggravation of a preexisting injury suffered or disease contracted in line of duty, in the active military, naval, or air service, during a period of war, the United States will pay to any veteran thus disabled and who was discharged or released under conditions other than dishonorable from the period of service in which said injury or disease was incurred, or preexisting injury or disease was aggravated, compensation as provided in this subchapter . . ., but no compensation shall be paid if the disability is a result of the veteran's own willful misconduct or abuse of alcohol or drugs.
>
> (Basic Entitlement. 2005. 38 USC § 1110)

"In line of duty" is defined in VA regulations as occurring "during a period of active military, naval, or air service unless such injury or disease was a result of the veteran's own willful misconduct or, for claims filed after October 31, 1990, was the result of his or her abuse of alcohol or drugs" (Pension, Compensation, and Dependency and Indemnity Compensation. 2006. 38 CFR § 3.1[m]). For purposes of line-of-duty determinations, a Service member is regarded as being on duty continuously (i.e., around the clock, seven days a week).

It is important to remember also that the disability need not have been directly "caused" by military service but only to have arisen during, or be aggravated coincident with, the period of military service. There is no time limit for filing of disability claims. A veteran may file at date of discharge or may make an initial claim decades later.

Title 38 of the United States Code mandates the existence of a rating schedule for use in evaluating disability claims. This statutory authority is as follows:

> The VA Secretary shall adopt and apply a schedule of ratings of reductions in earning capacity from specific injuries or combination of injuries. The ratings shall be based, as far as practicable, upon the average impairments of earning capacity resulting from such injuries in civil occupations. The schedule shall be constructed so as to provide 10 grades of disability and no more, upon which payments of compensation shall be based, namely, 10 percent, 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, and total, 100 percent. The VA Secretary shall from time to time readjust this schedule of ratings in accordance with experience. However, in no event shall such a readjustment in the rating schedule cause a veteran's disability rating in effect on the effective date of the readjustment to be reduced unless an improvement in the veteran's disability is shown to have occurred.
>
> (Authority for Schedule for Rating Disabilities. 2005. 38 USC § 1155)

This rating schedule has been codified as 38 CFR, Part IV (Schedule for Rating Disabilities. 2005. 38 CFR Part 4), and it provides detailed guidelines for assessing specific disabilities and assigning evaluation levels. The schedule lists hundreds of specific disabilities, with unique di-

agnostic codes for each. It describes each condition and provides descriptors for assigning evaluation levels to the conditions.

Veterans' service-connected disabilities are assigned a percentage rating between 0 and 100 percent in increments of 10, with higher ratings reflecting greater severity. Veterans with disabilities rated 0 percent generally do not receive compensation for their disabilities. However, this rating can provide improved access to health care and other VA benefits.

Disabilities rated 10 percent or more are compensable.

> The 10 percent threshold is not defined explicitly in the law, except that it must be a medical determination. Throughout much of the legislative history of disability compensation for veterans, the percentage determination is based on medical opinion without any specific reference to economic loss or indicating exactly how a given physical impairment translates into a given percentage.
>
> (Economic Systems Inc., 2004, p. 3)

Although the statutory language is couched in terms of "average impairment in earning capacity" it is apparent that other factors are taken into consideration in the payment of disability benefits (Schedule for Rating Disabilities. 2005. 38 CFR Part 4). The Bradley Commission in discussing the "basic purpose" of disability compensation acknowledged that it was a "complex and difficult subject because it deals with a wide range of human factors" including "impairment of earning capacity, loss of physical integrity, shortening of life, social inconvenience, disfigurement, pain, suffering, anguish, and possibly others" (President's Commission on Veterans' Pensions, 1956, p. 164). Although the statute specified that percentage awards were to be based on average impairments of earning capacity, the commission observed that there was evidence that VA ratings "make allowance for shortening of life and social inconvenience resulting from disablement" (President's Commission on Veterans' Pensions, 1956, p. 165). It declared that "[a] balanced compensation program must do more than merely replace lost earning capacity" and concluded that the rating schedule should also make allowance for "'loss of physical integrity,' 'social inadaptability' and 'shortened life expectancy'" (President's Commission on Veterans' Pensions, 1956, pp. 166, 169).

VA acknowledged this in testimony before Congress in 1960 stating that although the schedule was devoted "almost exclusively to so-called economic factors such as loss of earning capacity. There is, for consideration, as we all know, the fact that in many diseases and disabilities there are so-called noneconomic losses or impairments such as shortened life expectancy, loss of physical integrity, or social inadaptability" (U.S. Congress, House of Representatives, 1970, p. 5).

Two recent companion studies of VA's disability compensation program concluded that congressional intent for program goals could include both "compensation for the average impairments of earnings capacity resulting from such injuries in civil occupations" and "compensation for reduction in quality of life due to service-connected disability" (Economic Systems Inc., 2004, p. 2). It observed the following:

> The legislation does not explicitly state that intent of the disability program is to compensate for reduction in quality of life due to service-connected disability. However, this intent is implicit because Congress has set forth certain presumptions of eligibility for disability compensation and higher benefit levels for certain disabling conditions such as loss of a limb that reflect humanitarian concern about quality of life. The quality-of-life

> factor may be a more critical issue than employability for amputees given advances in medical technology and emphasis on occupations not requiring physical labor.
>
> (Economic Systems Inc., 2004, p. 2)

The study also suggests that "recruitment and retention" could be included in the range of possible program goals (Economic Systems Inc., 2004, p. 2): The "[l]egislation does not explicitly state that intent of the VA disability program . . . is to provide incentive value for recruitment and retention" (p. 4). However, "during wartime periods, Congress has provided greater benefits or liberalized rules for eligibility, reflecting the intention of attaining sufficient recruitment and retention. Also, Congress has legislated benefits for veterans using phrases similar to 'in gratitude of service rendered for a grateful Nation,' indicating that benefits are provided for a variety of different reasons" (Veterans' Disability Benefits Commission, 2005, pp. 4-5).

Finally, in looking at disability compensation benefits it should also be kept in mind that "compensation for . . . impairment in earnings capacity . . . is not based on the disabled person's individual capacity loss but only on 'average' capacity" (Economic Systems Inc., 2004, p. 2).

Claims may be established by direct evidence that an injury or disease or its aggravation occurred at a point in time coincident to military service. Medical exams, military service records, expert opinions, and credible statements by those with knowledge of the circumstances of the claim are frequently relied upon. Claims may also be established by unrebutted presumptions that have been adopted by VA either as a result of statutory amendment or by administrative regulation.

EQUIPOISE AND BURDEN OF PROOF

38 USC, Section 5107, sets forth standards for "burden of proof" and "benefit of the doubt" with respect to establishing disability benefits entitlement. Subsection 5107(b) further provides, in pertinent part, with respect to such claims that

> When, after consideration of all evidence . . . there is an approximate balance of positive and negative evidence regarding the merits of an issue material in the determination of the matter, the benefit of the doubt in resolving each such issue shall be given to the claimant.
>
> (see also 38 CFR § 3.102. Reasonable doubt)

Evidence found to be in such "balance" has often been characterized in Board of Veteran Appeals decisions as being in "equipoise."

In *Gilbert v. Derwinski*, 1 Vet. App. 49 (1991), an early decision considering the rule, the court employed the following analogy:

> The "benefit of the doubt" standard is similar to the rule deeply embedded in sandlot baseball folklore that "the tie goes to the runner." If the ball clearly beats the runner, he is out and the rule has no application; if the runner clearly beats the ball, he is safe and again the rule has no application; if however the play is close, then the runner is called safe by operation of the rule that "the tie goes to the runner." . . . Similarly, if a fair preponderance of the evidence is against a veteran's claim, it will be denied and the "benefit of the doubt" rule has no application; if the veteran "establishes a claim by a fair preponderance of the evidence, the claim will be granted and, again, the rule has no application;

> if however, the play is close, *i.e.,* "there is an approximate balance of positive and negative evidence," the veteran prevails by operation of 38 U.S.C. 3007 (b) (now 5107[b]).
>
> (VA, 2006d, p. 16470)

As part of an ongoing project to "reorganize and rewrite in plain language" general provisions applicable to its compensation and pension regulations, the VA, citing *Gilbert v. Derwinski*, defines equipoise as follows:

> Equipoise means that there is an approximate balance between the weight of the evidence in support of and the weight of the evidence against a particular finding of fact, such that it is as likely as not that the fact is true.
>
> (VA, 2006d, p. 16470)

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Appendix E

Arguments Favoring and Opposing Presumptions[1]

[1] VA (Veterans Administration). 2006 (unpublished). *Presumption of service connection. The public policy debate.* Washington, DC: VA.

Arguments Favoring Presumptions	Arguments Opposing Presumptions
Medical uncertainty. "The proposal (by the Bradley Commission) to throw out . . . the presumption for service connection of certain chronic diseases—tropical diseases—was tried and it did not work. The doctors could not agree about whether the disease discovered 1 year of 2 years after separation from the service had its inception while in the service or not. The Congress became so tired of the subject that it decided they would be given a period of time of the subject that it decided they would be given a period of time in which it would be presumed that the disease had its inception while in the service." **O.W. Clark, National Director of Legislation, DAV** **Hearings Before the House Comm. on Veterans' Affairs,** **84th Cong., 2d Sess. (1956)**	*"Question of fact."* "Last year it was determined—and I had hoped permanently—that a service-connected disability is a question of fact rather than a question of law. In other words, each individual case should and must be considered on it merits, and there is no justification for legislative dicta which, contrary to fact, provide that thousands of individual cases of sickness which commenced 4, 5, or 6 years after the termination of the war are caused by war services." **Veto message of President Roosevelt, Independent Offices** **Appropriation Bill (1935)** **H.R. Doc. No. 291, 73d Cong., 2d Sess. (1934)**
"It is the opinion of the American Legion that until American medicine has reached a point where it can determine with more than a reasonable degree of accuracy whether in fact certain types of disease did or did not have their inception during the course of a man's service, the veteran should be entitled, in the areas of doubt . . . to the presumption that his disease or disability, within reasonable periods now or to be specified, was the result of his service." **Statement of Donald R. Wilson, past National Commander,** **American Legion** **Id., 3654-55 (1957)**	*Relationship to service.* "The present list of 'chronic' diseases for which service connection is granted is one deeply rooted in the history of the claims program, but one regarding which it would be futile to contend that inclusion of a disease in the list is substantiated by any likelihood of actual incurrence in service or in any way resulting from the circumstances of service. The diseases when correctly diagnosticated, are indeed of chronic type, and their presence within a year after discharge raises a strong probability that part of the course of the disease (not necessarily an early part, unless the service was much longer than the minimum 90 days required) coincided with the 'period of service, but the likelihood that any of their course was influenced by the facts or circumstances of service is extremely remote." **Internal Memorandum from Assistant Administrator for** **Claims to Assistant Administrator for Legislation** **October 20, 1947**

Arguments Favoring Presumptions	Arguments Opposing Presumptions
For the purpose of providing hospital and nursing home care to veterans exposed during service to dioxin or ionizing radiation for conditions not shown to result from a cause other than exposure under P.L. 97-72. ". . . [U]ntil the scientific community [is] able to make a determination as to the possible cause and effect relationship of the toxic herbicides utilized as defoliants in the Republic of Vietnam during the Vietnam conflict, the Veterans' Administration should do everything possible to provide the care to such veterans. When a doubt exists, the doubt should be resolved in favor of the veteran." **H.R. Rep. No. 79, 97th Cong., 1st Sess. 3**	"Although the exact cause of the disease is unknown, there is nothing in the circumstances of military service in time of war which from a medical and scientific standpoint would warrant a presumption of fact that a manifestation of the disease 3 years after discharge is in any way related to the fact or circumstances of service. In this connection, it does not appear that the disease is any more prevalent among the veteran population than the nonveteran population." **Letter from Carl R. Gray, Jr., Administrator of Veterans Affairs, to Chairman, Senate Committee on Finance** **June 29, 1951**
Inadequacy of service records and examinations. ". . . [P]hysical examinations were hurried and, in many instances, incomplete. As a consequence men were taken into the service with physical and mental defects. The changed life and rigors of service, whether of an active fighting nature or simple employment in and around the military establishment, in many cases, aggravated these defects so that upon discharge these veterans were in need of financial relief and medical treatment." **Federal Laws Relating to Veterans of Wars of the United States, S. Doc. No. 131, 72nd Congress, 1st Sess., 117** **1932**	*Administrative function.* *Developing presumptions of service connection: statutory or regulatory activity?* "It is believed that extreme care should be exercised in augmenting the list of diseases to be afforded the presumption. It is the view of the Veterans' Administration that this can best be accomplished by continuing the existing Veterans Regulation No. 1(a), part I, paragraph I(c), and administrative authority to make the medical and adjudicatory determinations. "Determination governing the selection of diseases to be included under the regulation is essentially one of an involved medical and adjudicatory nature. If a list of diseases is provided by statute it is suggested that the consideration of additions . . . would require detailed technical considerations by the Congress which in the opinion of the Veterans' Administration can best be handled administratively. . . . This statement is made in the light of experience under the War Risk Insurance Act, as amended, and the World War Veterans Act of 1924, as amended. . . ." **Letter from General Omar Bradley, Administrator of Veterans Affairs** **1947**

Arguments Favoring Presumptions	Arguments Opposing Presumptions
"Some feel that Congress should abide by its longstanding tradition that benefits should be paid only where substantive evidence is clearly available to establish that the disabling conditions existed while on active duty or are clearly related to such period of service. It has become apparent that such evidence will never be available in the cases of veterans covered under the provisions of the reported bill because the level of exposure cannot be verified." **H.R. Rep. No. 235, 100th Cong., 1st Sess. 4 1987**	*Regarding Senate bill* S. 1651, *98th Cong. 1st Sess. (1983)* "VA opposed the bill, which directed VA to follow a rulemaking process that involved public participation and consultation with an advisory committee. VA held that legislative action to create presumptions could not be supported on the basis of available evidence, so it would be inappropriate to refer the matter for rulemaking. VA also stated that the procedural process defined in the bill would impede resolution of the issues involved and that the bill would create false expectations among affected veterans and their families." **Letter from Harry N. Walters, Administrator, to Alan K. Simpson, Chairman, Senate Committee on Veterans' Affairs April 10, 1984**
Excessive burden of proof on veteran. "In my opinion, that provision of the law which places the burden upon the disabled veteran of connecting his disease with his service has been responsible for more complaints, dissatisfaction and disappointment . . . than any other single provision. . . . "Consequently, I propose to offer an amendment to section 18 which will shift the burden of proof in the case of two classes of disease only—tubercular and neuropsychiatric. I propose that when it is proved by an incapacitated soldier that he has either of these two types of disease he shall immediately be entitled to compensation unless the Government proves—the burden thus being shifted to the Government—that he has contracted the disease since the time of his discharge and it is not traceable to service in line of duty." **Senator Walsh, 61 Cong. Rec. 4105 1921**	*Improved military procedures/records.* "[T]he facilities and procedures of the service departments in the examination of recruits prior to their induction into service and their facilities for rendering medical care and treatment, the maintenance of records in individual cases and the furnishing of these records to the Veterans' Administration all represent a great advancement and improvement over comparable situations as they existed during World War I." **Letter from Carl R. Gray, Jr., Administrator of Veterans Affairs February 1950**

Arguments Favoring Presumptions
". . . [T]he question is not entirely a medical one. It is also in part a legal one. The purpose of a presumption is to free the veteran from carrying an unconscionable burden of proof in the establishment of the service-connected origin of a disease or a disability. . . . [T]he principle behind the granting of a presumption says to the American veteran that it would be unfair in some cases to require him to prove medically that a given disease or disability did in fact have its inception during the course of his service, or resulted directly from that service. It states in substance that, in those instances in which it would be unfair to impose such a burden upon him, he is entitled to a presumption that the disease or disability did emanate from his service. This is a rebuttable presumption. . . . It enables the Government, if medical knowledge is what the Bradley Commission says that it is, to rebut the presumption. . . ." **Statement of Donald R. Wilson, past National Commander, American Legion Id., 3654-55 1957**
Incidence of disease. "It is very apparent to me that this wave of tuberculosis and of nervous and mental disease that has taken such a deadly hold and grip of late upon our ex-service men must have been contracted in the service. I feel, therefore, that we ought not continue this requirement of endless affidavits, necessarily involving long delay, in demonstrating the fact that their illness is of service origin. The delays resulting from this affidavit requirement have often resulted in men dying before they ever got their compensation. . . ." **Senator Walsh, 61 Cong. Rec. 4105 1921**

Arguments Opposing Presumptions
Advances in medical science. ". . . [T]he advances in medical science since World War I have facilitated the detection and diagnosis of diseases to such an extent that further extension of statutory presumptions of service connection is not believed to be indicated." **Letter from Carl R. Gray, Jr., Administrator of Veterans Affairs February 1950**
Philosophy of program. "A statutory provision which requires a finding of service connection for a disability which cannot be shown to be due to service is inconsistent with the theory of providing compensation for disability or death resulting from injury or disease incurred in line of duty in active military or naval service, and results in providing compensation for disability or death due to causes which are not in any way connected with military or naval service." **Letter from Carl R. Gray, Jr., Administrator of Veterans Affairs Feb. 23, 1950**
Elevates cases without merit. *In opposition to a proposal to extend the presumptive period/or service connection of multiple sclerosis.* "VA commented that singling out multiple sclerosis for a longer presumptive period would be discriminatory and could serve as a precedent for extending the presumptive period for other chronic diseases. The amendment would place 'cases without merit, from the standpoint of service connection' on a par with cases involving conditions medically proven to be service connected." **Letter from Carl R. Gray, Jr., Administrator of Veterans Affairs June 29, 1951**

Arguments Favoring Presumptions
Difficult/delayed Diagnoses. "[I]t is frequently true that tuberculosis is an active process, and yet the person afflicted with it does not have knowledge of the fact that he has tuberculosis. As a matter of fact, most tubercular patients think: that they have something else or think: they are not afflicted with tuberculosis." **Senator Robinson, 61 Cong. Rec. 4105** **1921**
"It is also recommended that this 5-year presumption should not only extend to neuropsychiatric and tubercular disease, but also to other internal [dis]orders which might be placed in like category, such as heart trouble, cancer, diabetes, sleeping sickness, etc. Some of these are even very difficult to ascertain or even see by means of X rays. It is hard to determine just when they did commence. Take the instance of a cancer, it is the general presumption that it must be existent in a small state at least a year before it is found, therefore, it is urged that these diseases be included in the 5-year presumption." **Edwin S. Bettelheim, VFW, in letter to Special Committee of Senate Investigations** **November 5, 1923**
According to a Senate report, only medical specialists, primarily neurologists, were likely to diagnose the disease (MS) in its early stages. The average person "would not be inclined to consult a neurologist for the original symptoms." VA opposed extension of the presumptive period on the grounds that it lacked a sound medical basis. **S. Rep. No. 660, 86 Cong., 1st Sess.** **1959**

Arguments Opposing Presumptions
Provisions are adequate without presumptions. "There is otherwise in the law sufficient protection for the veteran to establish service connection of any and all diseases. Accepted medical principles can reasonably and accurately establish the onset of a disease and the disability process. Where there is reasonable doubt, the law provides for the doubt to be resolved in favor of the veteran. . . . "With respect to chronic and tropical diseases, psychoses, and multiple sclerosis, the physicians surveyed were in general agreement that service-connection should be determined in accordance with sound medical principles, and not by fiat. As to tuberculosis in particular, modern methods of diagnosis have made rapid strides since enactment of the original presumption for this disease 35 years ago. The presumptive period of 4 years is not in accord with present-day accepted medical principles." **President's Commission on Veterans' Pensions (the Bradley Commission), *Veterans' Benefits in the United States*** **1957**
With regard to additional presumptions specific to former POWs. "The VA position was that the conditions under consideration (peripheral neuropathy; irritable bowel syndrome; and duodenal and peptic ulcers) would ordinarily manifest themselves and require treatment upon repatriation or shortly thereafter. Under these circumstances the veteran would be entitled to direct rather than presumptive service connection. Moreover, VA pointed out that the conditions at issue did not lend themselves to presumption. Irritable bowel syndrome, for example, was described as a functional disorder of unknown etiology and pathogenesis." **From Statement of R. J. Vogel, Chief Benefits Director** **VA Compensation and Other Service-Connected Benefits: Hearing Before the Senate Committee on Veterans' Affairs** **100th Congress, 1st Sess.** **1987**

Arguments Favoring Presumptions	**Arguments Opposing Presumptions**
"[P]resumptions are based on the need to ensure that diseases and disabilities incurred in or aggravated during service are, in fact, determined to be service connected. This need arises most clearly in the cases of diseases that have a latency period of varying length causing early manifestations to be easily overlooked or misdiagnosed or diseases that are otherwise difficult to diagnose. "SLE is such a disease. . . . Although the disease may start acutely, the course is usually chronic and irregular with periods of activity alternating with periods of remission, thereby making diagnosis very difficult and the manifestations quite diverse . . . SLE is instigated by a combination of genetic predisposition and environmental factors. Current data stress the importance of various environmental factors as accelerating or causal elements to a greater degree than previously had been assumed. Accordingly, factors present during the veteran's service may trigger onset of the disease and yet not appear on the veteran's service record. . . ." **S. Rep. No. 215, 100th Cong., 1st Sess. 73 1987**	*Qualifying criteria excessively liberal.* "The bill makes no distinction as to the length, or type of service or as to the various diseases. Certain diseases, particularly cardiovascular-renal disease, endocrinopathies, organic diseases of the central nervous system, and the psychoses, reflect a multitude of etiologies, some of which, when analyzed are not even remotely affected by any stress or strain of service. Under the terms of this bill, if enacted into law, a veteran with only 1 day active service in World War II and whose disease was first detected 5 years less 1 day from termination of his active service . . . might very well obtain presumptive, service connection. . . ." **Letter from Frank T. Hines, Administrator to John E. Rankin, Chairman, House Committee on Veterans' Legislation Aug. 9, 1945**
Social benefits. *Regarding extension of the presumptive period for active pulmonary tuberculosis from one year to three years after separation provided in Act of June* 23, *1950.* Extension of the presumption was "fully justified, in view of the nature of this particular chronic disease. . . . The entitlement to compensation and preference in hospitalization generally resulting will lessen the need of veterans to engage in labor injurious to their health, encourage them to take proper measures for recovery, and thus result in improving the health of the Nation generally." The report also noted that the World War Veterans' Act of 1924 provided a longer presumptive period for active tuberculosis in World I veterans. **S. Rep. No. 1745, 81st Congress, 2d Sess. 1950**	

Arguments Favoring Presumptions
The Act of October 30, 1951, provided a presumption of service connection for active psychosis developing within two years of separation. This presumption was enacted for treatment purposes only. Disability compensation would not be paid unless the condition were found directly service connected or arose within the one-year presumptive period provided for chronic diseases generally. At the time there were an estimated 9,000 World War II veterans awaiting hospitalization for nonservice-connected psychosis. The Senate Committee on Finance noted that psychosis "is not only an individual problem but involves broad social aspects as well." In view of this and other considerations, the Committee thought it important to provide priority care at VA facilities. **S. Rep. No. 749, 82d Cong., 2d Sess. 1952**
Enforce Congress's view. "[T]he reason we passed [the presumption statute] was because Congress did not agree with many of the medical findings [of VA doctors]. . . . Many doctors have [refused to service connect disabilities] . . . where nearly everyone would agree, [the veteran] should be given the benefit of the doubt. . . . The only way we can force proper administration is by setting up a presumptive right by law. . . . Otherwise they could disagree with us." **Olin E. Teague, Chairman, House Committee on Veterans' Affairs Hearings, 85th Cong., 1st Sess. 942 1957**

Arguments Favoring Presumptions
Association with risk factors. Since the amount of exposure of the "radiation-exposed veteran", as defined in the reported bill, is less than certain, the Committee has deliberately ignored the issue of level of exposure and has concentrated instead on the likelihood of relationship of disease entities to radiation exposure. The proposed legislation (later enacted as P.L. 100-321) includes those malignancies considered most likely to be related to ionizing radiation exposure. **H.R. Rep. No. 235, 100th Cong., 1st Sess. 4 1987**
Promote health. *Regarding extension of the presumptive period for active pulmonary tuberculosis from one year to three years after separation provided in Act of June 23,1950.* Extension of the presumption was "fully justified, in view of the nature of this particular chronic disease. . . . The entitlement to compensation and preference in hospitalization generally resulting will lessen the need of veterans to engage in labor injurious to their health, encourage them to take proper measures for recovery, and thus result in improving the health of the Nation generally." The report also noted that the World War Veterans' Act of 1924 provided a longer presumptive period for active tuberculosis in World I veterans. **Senate Report No. 1745, 81st Congress, Second Session 1950**

Appendix F

Tables: Summary of Presumptive Disability Decision-Making Legislative History

TABLE F-1 Summary of PDDM Legislative History (by Date)

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
August 9, 1921	Veterans' Bureau. Public Law 67-47. 1921. 67th Cong., 1st Sess. Ch. 57, Sec. 18, 42 Stat. 147, 153	**Chronic Diseases:** • Neuropsychiatric disease [later called psychoses] • Tuberculosis, pulmonary (active) [March 4, 1923 Act expanded the presumption to include all forms of active tuberculosis]	Disease contracted during active military service	On or after April 6, 1917 Or Discharged or resigned active service on or before November 11, 1918	Within 2 years after separation from active military or naval service Characteristic manifestations of the disease to 10 percent or more	
November 12, 1921 December 2, 1921	Internal Memorandum implementing Veterans' Bureau Regulation No. 11 Office Memorandum No. 36	**Chronic Constitutional Diseases:** • Anemia (primary) • Arteriosclerosis • Beriberi • Diabetes insipidus • Diabetes mellitus • Endocrinopathies • Gout • Hemochromatosis • Hemoglobinuria (paroxysmal) • Hemophilia • Hodgkin's disease • Leukemia (all types) • Ochronosis • Pellagra • Polycythemia (erythremia) • Purpura • Rickets • Scurvy	Chronic constitutional disease contracted during active military service		Within 1 year after the date of separation from service	November 12, 1921, stated connection to active military service And Constitutional diseases were defined on December 2, 1921

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
June 7, 1924	World War Veterans' Act, 1924. Public Law 68-242. 68th Cong., 1st Sess. Title II. Compensation and Treatment. Ch. 320, Sec. 200, 43 Stat. 607, 615	**Chronic Diseases:** • Dysentery (amebic) (*tropical disease added as chronic disease*) • Encephalitis lethargica • Neuropsychiatric disease • Paralysis agitans • Tuberculous (active)	Disease contracted during active military or naval service	Between April 6, 1917, and July 2, 1921 Or Discharged or resigned prior to July 2, 1921 Or Discharged or resigned on or before November 11, 1918, or on or after July 2, 1921	By January 1, 1925 Characteristic manifestations of the disease to 10 percent or more	
1925	Veterans' Bureau Schedule for Rating Disabilities (based upon the WW Veterans Act, 1924)	**Constitutional Diseases:** • Arthritis (deformans and chronic) • Carcinoma, sarcoma, and other tumors • Cardiovascular-renal disease, including hypertension • Endocarditis, chronic • Leprosy (*tropical disease added as a chronic disease*) • Myocarditis, chronic • Nephritis, chronic forms *(was not carried forward,* • *cholecystitis, chronic, proceeding to gall-stone formation*	Disease contracted during military or naval services in the World War I	During World War I	Characteristic manifestation within 1 year from date of separation from active service Or If medical evidence affirmatively establishes conclusive service connection after 1 year of separation	Amends list of constitutional diseases

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• *nephrolithiasis* • *valvulitis, chronic)*				
November 2, 1928	Veterans' Bureau Schedule of Disability Ratings, Extension 6	• Ulcers (gastric or duodenal)			Manifest within 6 months from discharge from military service and shown present within 1 year after discharge	Establishes service connection for ulcers
April 12, 1933	Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933	**Chronic Diseases** • Epilepsies • Organic diseases of the nervous system			**Tuberculosis:** Manifest to a degree of 10 percent within 1 year of discharge; second-year diagnoses presumptive if at 6 months for minimal cases, 9 months for moderately advanced cases, and 12 months for far advanced cases	Amends list of chronic diseases and presumption of tuberculosis Carried forward prior presumptions of chronic diseases *except* rickets, obesity, acidosis, beriberi, chronic cholecystitis, diabetes insipidus, gout, hemophilia, hemochromat-osis, hemoglobinuria, nephrolithiasis, ochronosis, pellagra, purpura, scurvy, polycythemia (erythremia), and chronic valvulitis

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
August 14, 1935	Executive Order 6089. Instruction No. 2-A, Implementing Vet. Reg. No. 1. August 14, 1935	**Chronic Diseases:** • Osteitis deformans (Paget's disease)				Amends list of chronic diseases
December 28, 1945	VA Circular No. 8, section I	**Tropical Diseases:** • Malaria	Disease contracted during active		Within 1 year after separation of active service military service	
January 3, 1947	Disability ratings for malaria and chronic diseases characteristically tropical in origin. *Veterans Administration Technical Bulletin 8-6.* Washington, DC: VA	**Tropical Diseases:** • Dysentery (amebic, bacillary) • Filariasis (Bancroft's type) • Leishmaniasis (including kala-azar) • Malaria • Schistosomiasis • Trypanosomiasis • Yaws	Disease contracted during wartime service	Service in the tropics or a place having a high incidence of the disease under consideration	Within 1 year after separation of active wartime service	Relapses of malaria (after the 1 year separation) need others, under oath to establish frequency of relapse over a period of time relating back to the 1-year period following discharge
June 24, 1948	Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess. Ch. 612, Sec. 1, 62 Stat. 581	**Chronic Diseases**: • Anemia (primary) • Arteriosclerosis • Arthritis • Bronchiectasis • Calculi of the kidney, bladder, or gall bladder • Cardiovascular-renal disease (hypertension, myocarditis, Buerger's disease, Raynaud's disease)	Disease contracted during active service		At least 6 months of service and honorably discharged Within 1 year after separation from active service or at a time when standard and accepted treatises indicate that the incubation period	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Cirrhosis of the liver • Coccidioidomycosis • Diabetes mellitus • Encephalitis lethargica residuals • Endocarditis • Endocrinopathies • Epilepsies • Hodgkin's disease • Leukemia (nephritis) • Organic diseases of the nervous system (tumors of the brain, cord, peripheral nerves) • Osteitis (deformans) • Osteomalacia • Peptic ulcers (gastric or duodenal) • Scleroderma • Tuberculosis (active) • Tumors (malignant) **Tropical Diseases:** • Black water fever • Cholera • Dracontiasis • Dysentery • Filariasis • Leishmaniasis • Leprosy • Loiasis • Malaria • Onchocerciasis			thereof commenced during active service	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Oroya fever • Pinta • Plague • Schistosomiasis • Yaws • Yellow fever				
February 9, 1949	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86(a), 3.95	**Chronic Diseases:** • Anemia (primary) • Arteriosclerosis • Arthritis • Atrophy, progressive muscular • Brain hemorrhage • Brain thrombosis • Bronchiectasis • Calculi of the kidney, bladder, or gall bladder • Cardiovascular-renal disease (hypertension) • Cirrhosis of the liver • Coccidioidomycosis • Diabetes mellitus • Encephalitis lethargica residuals • Endocarditis • Endocrinopathies • Epilepsies • Hodgkin's disease • Leprosy • Leukemia (nephritis) • Myasthenia gravis • Myelitis • Myocarditis	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947 **Tropical Diseases:** Service in the tropics or a place having a high incidence of the disease under consideration **Ulcer (peptic):** Within 6 months from date of active service or within 6 months of July 25, 1947; or if more than 6 months, then evidence of continuity of characteristic symptoms during the first 6 months after termination of active service	Within 1 year after separation from active wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic Disease:** Manifestations sufficient to identify the disease entity and sufficient observations to establish chronicity at the time **Tropical Disease:** When shown to exist at a time when standard and accepted treatises indicate that the	**Factual Basis:** Established by medical evidence, competent lay evidence, or both **Pulmonary Tuberculosis:** Specific assumptions for diagnosis in second year after service

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Nephritis • Organic diseases of the nervous system • Osteitis (deformans) • Osteomalacia • Palsy, bulbar • Paralysis agitans • Peptic ulcers (gastric or duodenal) • Psychoses • Raynaud's disease • Scleroderma • Sclerosis (amyotrophic lateral, multiple) • Syringomyelia • Thromboangiitis Obliterans (Buerger's disease) • Tuberculosis (active) • Tumors (malignant) of the brain or spinal cord or peripheral nerves **Tropical Diseases:** • Black water fever • Cholera • Dracontiasis • Dysentery • Filariasis • Leishmaniasis • Leprosy • Loiasis • Malaria			incubation period of the diseases commenced during active service Characteristic manifestations of the disease to 10 percent or more, except pulmonary tuberculosis	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Onchocerciasis • Oroya fever • Pinta • Plague • Schistosomiasis • Yaws • Yellow fever				
October 12, 1949	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(197):6174-6180. Former 38 CFR Sec. 3.86(a)	**Chronic Diseases:** Pupura idiopathic (hemorrhagic)	Military service			Amends list of chronic diseases
August 31, 1950	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 15(169):5902-5910. Former 38 CFR	**Chronic Disease:** Sarcoidosis **Tropical Disease:** Amebiasis	Disease contracted during military service	See Veterans Regulation 1 (38 USC Ch. 12)	See Veterans Regulation 1 (38 USC Ch. 12)	Added to list of chronic and tropical diseases
June 17, 1957	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th	**Chronic and Tropical Diseases:** Same diseases as above three entries (1949 and 1950	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with	**Tropical Diseases:** Serves 6 months or more and contracts	Summarizes previous rules and legislation and amends

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Cong., 1st Sess. Sec. 301(3 and 4). 71 Stat. 83, 95	entries)		a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947	tropical or disease because of therapy in connection with tropical disease Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period **Psychosis:** WWII or Korean service within 2 years after discharge or release and before July 26, 1949 (WWII) or February 1, 1957 (Korean)	dates/location of service and presumption
February 24, 1961	Disease subject to presumptive service connection. *Federal Register* 26(36):1581-1582	**Chronic and Tropical Diseases:** Same as June 17, 1957	Disease contracted during active military, naval, or air service			Lays out criteria for presumption wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence,

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						competent lay evidence or both
August 12, 1970	Public Law 91-376. Sec. 3. 91st Cong., 2d Sess., 1970. Sec 3. 84 Stat. 787, 788	**Former Prisoner of War Associated Diseases:** • Avitaminosis • Beriberi (including beriberi heart disease) • Chronic dysentery • Helminthiasis • Malnutrition (including optic atrophy associated with malnutrition) • Other nutritional deficiency • Pellagra • Psychosis	Active military, naval, or air service and was held prisoner of war	Held by Imperial Japanese Government or the German Government during World War II, Government of North Korea during the Korean conflict, or the Government of North Vietnam, or the Viet Cong during the Vietnam era	Detained or interned for not less than 6 months Characteristic manifestations of the disease (except psychosis) to 10 percent or more after service **Psychosis:** Characteristic manifestations of the disease to 10 percent or more within 2 years after separation from service	Service connection presumption for former prisoners of war
December 1, 1970	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-	**Diseases Associated with Former Prisoners of War** **Chronic and Tropical Diseases**	Active service **Former Prisons of War:** Held by an enemy government or its agents during WWII, Korean conflict, or the Vietnam era, suffered from dietary deficiencies,	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	18283. 38 CFR Part 3		forced labor, or inhumane treatment		service **Tropical Diseases:** Manifest to a degree of 10 percent or more within 1 year from date of separation from service or at a time when standard treatises indicate that the incubation period commenced during such service **Prisoners of War:** Manifest to a degree of 10 percent or more at any time after service, **except** psychosis, 10 percent within 2 years from date of separation from service	
September 26, 1974	Increase of disability compensation and dependency and indemnity compensation rates.	**Chronic, Tropical, or Former Prisoner of War Associated Diseases:** No new ones	Active service on or after January 1, 1947 **Chronic Before January 1, 1947:** No presumption	Service of 90 days or more during a war period on or after December 31, 1946	**Tropical Before January 1, 1947:** Manifest to a degree of 10 percent or more within 1 year after separation from	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Federal Register 39(188)34529-34533. 38 CFR Part 3		**Tropical: Before January 1, 1947:** Veteran with 6 or months of service		active service or at a time when standard and accepted treatises indicate that the incubation period commenced during active service	
December 23, 1976	Increased disability compensation and dependency and indemnity compensation; burial benefits. *Federal Register* 41(248):55872-55875. 38 CFR Part 3	**Chronic and Tropical Diseases:** • Hansen's disease			**Chronic Diseases:** Following service in a period of war or following peacetime service on or after January 1, 1947 **Tropical Diseases:** Tropical service following service in a period of war or following peacetime service	Used term Hansen's disease instead of leprosy
October 2, 1978	Pension, compensation, and dependence and indemnity. Final regulation. *Federal Register* 43(191):45347-45362. 38 CFR Part 3	**Chronic Disease:** • Pulmonary tuberculosis			Removes the presumptive period of 6, 9, and 12 months for minimally, moderately, and far advanced TB to developing within 3 years from the date of separation from active service	Amends presumptive period

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
August 28, 1979	Pension, compensation, and dependency and indemnity compensation, proximate results, secondary conditions. *Federal Register* 44(168):50339-50340. 38 CFR Part 3, Sec 3.310	**Diseases Associated with Service Amputation:** Ischemic heart disease (or other cardiovascular disease)	Service-connected amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles			
August 14, 1981	Former Prisoner of War Benefits Act of 1981. Public Law 97-37. 97th Cong., 1st Sess. Sec 4. 95 Stat. 935, 936	**Diseases Associated with Former Prisoner of War:** • Avitaminosis • Beriberi (including beriberi heart disease) • Chronic dysentery • Helminthiasis • Malnutrition (including optic atrophy associated with malnutrition) • Other nutritional deficiency • Pellagra • Psychosis • Any of the anxiety states	Former prisoner of war	While serving in active military, naval, or air service, was forcibly detained or interned in line of duty by an enemy government or its agents, or a hostile force during a period of war	Characteristic manifestations of the disease to 10 percent or more after service Detained or interned for not less than 30 days	The previous prisoner of war presumption is for the period of time not less than 6 months. This act changes that period of time to not less than 30 days
March 18, 1982	Veterans Benefits; Former Prisoners of War. Final regulations. *Federal Register* 47(53):11655-	**Former Prisoner of War** • Avitaminosis • Beriberi (including beriberi heart disease) • Chronic dysentery	Former prisoner of war	While serving in active military, naval, or air service, was forcibly detained or interned in line of	Characteristic manifestations of the disease to 10 percent or more after service	Implementing the new Former Prisoner of War Benefits Act of 1981

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	11656. 38 CFR Part 3	• Helminthiasis • Malnutrition (including optic atrophy associated with malnutrition) • Other nutritional deficiency • Pellagra • Psychosis • Any of the anxiety states		duty by an enemy government or its agents, or a hostile force during a period of war on or after January 1, 1947	Detained or interned for not less than 30 days	Amended period of detainment for presumption of disease
March 2, 1984	Veterans' Compensation and Program Improvements Amendments of 1984. Public Law 98-223. 98th Cong., 2d Sess. Sec 111 98 Stat. 37, 40	**Former Prisoner of War Diseases:** Dysthymic disorder (or depressive neurosis)	Prisoner of war			Amends list of diseases associated with former prisoner of war
August 26, 1985	Adjudication of claims based on exposure to dioxin or ionizing radiation. Final rules. *Federal Register* 50(165):34452-34461. 38 CFR Parts 1 and 3	**Diseases Associated with Herbicide Exposure:** Chloracne **Radiogenic Diseases:** • All forms of leukemia (except chronic lymphatic leukemia) • Cancer (bone, colon, esophageal, female breast, kidney, liver, lung, pancreatic, salivary gland, skin, stomach, thyroid, urinary bladder) • Multiple myeloma	**Herbicide** • Dioxin (2,3,7,8 tetrachlorodi-benzo-p-dioxin) **Radiation** • Ionizing	**Dioxin** Vietnam era **Ionizing** Hiroshima or Nagasaki, Japan (September 1945 until July 1946)	**Dioxin Exposure:** No later than 3 months from the date of exposure **Ionizing:** Leukemias and bone cancer must become manifest within 30 years after exposure; other forms of cancer must become manifest 5 years	**Dioxin:** Presumed to have been exposed if served in the Vietnam era **Ionizing:** Exposure at the highest level of the dose range estimated will be presumed; several factors to be considered in determining

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					or more after exposure	whether disease resulted from exposure during service
October 28, 1986	Veterans' Benefits Improvements and Health-Care Authorization Act of 1986. Public Law 99-576. 99th Cong., 2d Sess. Sec 108. 100 Stat. 3248, 3252	**Former Prisoner of War Associated Diseases:** • Organic residuals of frostbite • Posttraumatic osteoarthritis	Former prisoner of war			Amends list of associated diseases of former prisoners of war
May 20, 1988	Veterans' Benefits and Services Act of 1988. Public Law 100-322. 100th Cong., 2d Sess. Sec 312, 313. 102 Stat. 487, 535	**Chronic Diseases:** • Lupus erythematosus (systemic) **Diseases Associated with Former Prisoner of War:** • Irritable bowel syndrome • Peptic ulcer disease • Peripheral neuropathy (except where directly related to infectious causes)	• Chronic disease contracted during military service • Prisoner of war			Amended list of diseases related to former prisoners of war and service connection of chronic diseases
May 20, 1988	Radiation-Exposed Veterans Compensation Act of 1988. Public Law 100-321. 100th Cong., 2d Sess., Section 2, 102 Stat. 485	**Diseases Associated with Radiation Exposure (radiation-risk activity):** • Cancer (bile ducts, breast, esophagus, gall bladder, pharynx, primary liver, pancreas, small intestine, stomach, thyroid) • Leukemia (other than chronic lymphocytic	Radiation risk activity • Participation in a test involving atmospheric detonation of a nuclear device • Occupation of Hiroshima or	Japan WWI (August 6, 1945, to July 1, 1946) Others	40-year period beginning on the last date where the veteran participated in a radiation-risk activity **except leukemia** (30-year period after radiation-risk	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		leukemia) • Lymphomas (except Hodgkin's disease) • Multiple myeloma	Nagasaki, Japan (August 6, 1945, to July 1, 1946) • Prisoner of war in Japan during WWII exposure of ionizing radiation		activity)	
October 18, 1989	Claims based on exposure to ionizing radiation. Final regulations. *Federal Register* 54(200):42802-42803. 38 CFR Part 3	**Radiogenic Diseases:** • Cancer (breast, salivary gland) • Leukemia (other than chronic lymphatic [lymphocytic] leukemia) • Multiple myeloma • Nonmalignant thyroid nodular disease • Posterior subcapsular cataracts	Ionizing radiation		**Bone Cancer:** Manifest within 30 years after exposure **Leukemia:** Manifest any time after exposure **Posterior Subcapsular Cataracts:** Manifest 6 months or more after exposure **Other Diseases:** Manifest 5 years or more after exposure	Amended diseases considered to be radiogenic Withdrew proposed clarification concerning when service connection can be established based upon claimed exposure to ionizing radiation and herbicides containing dioxin
October 15, 1990	Radiation Exposure Compensation Act of 1990. Public	**Diseases Associated with Radiation Exposure:** Above-Ground Nuclear Tests	Radiation exposure • Above-ground nuclear tests	Government's above-ground nuclear tests in Nevada and lived	Childhood leukemia and other diseases (January 21, 1951, to	Individuals not in military • Uranium miners

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Law 101-426. 101st Cong., 2d Sess., 104 STAT 920	• Leukemia (not chronic lymphocytic) • Lymphomas (other than Hodgkin's disease • Multiple myeloma • Primary cancer of the: Bile ducts Esophagus Female breast Gall bladder Liver Pancreas Pharynx Small intestine Stomach Thyroid Uranium Miners • Lung cancer • Nonmalignant respiratory disease (fibrosis of the lung, pulmonary fibrosis, and corpulmonale)	• Uranium miners	downwind in Nevada, Utah, and Arizona Underground uranium mines	October 31, 1958, or June 30, 1962, to July 31, 1962) For miners: Any individual who was employed in a uranium mine located in Colorado, New Mexico, Arizona, Wyoming, or Utah at any time during the period beginning on January 1, 1947, and ending on December 31, 1971	• Downwind to nuclear tests
October 26, 1990	Claims based on service in Vietnam. Final regulations. *Federal Register* 55(208):43123-43125. 38 CFR Parts 3 and 4	**Diseases Associated with Vietnam Service:** • Non-Hodgkin's lymphoma	Service in Vietnam	Vietnam (includes waters offshore, or service in other locations if the conditions of service involved duty or visitation in Vietnam)		

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				During the Vietnam era		
February 6, 1991	Agent Orange Act of 1981. Public Law 102-4. 102d Cong., 1st Sess. 105 STAT. 11	**Diseases Associated with Herbicide Exposure:** • Chloracne (or another acneform disease) • Non-Hodgkin's lymphoma • Soft tissue sarcoma	Active military, naval, or air service Exposure to herbicide agent containing dioxin or 2,4-dichlorophenoxy-acetic acid or other chemical compound in an herbicide agent	Republic of Vietnam; Vietnam era	**Non-Hodgkin's Lymphoma and Soft Tissue Sarcoma (other than osteosarcoma, chondrosarcoma, kaposi's sarcoma, or mesothelioma):** Manifest 10 percent or more disability **Chloracne:** 10 percent or more disability within 1 year after the last date active duty in Republic of Vietnam	
August 14, 1991	Veterans' Benefits Programs Improvement Act of 1991. Public Law 102-86. 102d Cong., 1st Sess., Sec. 104,105. 105 Stat. 414	**Diseases Associated with Radiation Exposure:** • Leukemia (presumptive period)	Radiation exposure	Amends service to during active military, naval, or air service or reserve component of the Armed Forces, participated in a radiation-risk activity during a period of active duty for training or		Amends presumptive period for occurrence of leukemia and location of radiation exposure

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				inactive duty training		
October 15, 1991	Claims based on exposure to herbicides containing dioxin (soft tissue sarcomas). Final regulation. *Federal Register* 56(199):51651-51653. 38 CFR Parts 3 and 4	**Diseases Associated with Herbicide Exposure (containing dioxin):** • Chloracne • Soft-tissue sarcoma (adult fibrosarcoma; dermatofibrosarcoma protuberans; malignant fibrous histiocytoma; liposarcoma; leiomyosarcoma; epithelioid leiomyosarcoma; rhabdomyosarcoma; ectomesenchymoma; angiosarcoma; proliferating angioendotheliomatosis; malignant glomus tumor; malignant heman-giopericytoma; synovial sarcoma; malignant giant cell tumor of tendon sheath; malignant schwannoma; malignant mesenchymoma; malignant granular cell tumor; alveolar soft part sarcoma; epithelioid sarcoma; clear cell sarcoma of tendons and aponeuroses)	Exposure to herbicides containing dioxin	Republic of Vietnam; Vietnam era	**Chloracne:** Manifested not later than 3 months from the date of exposure **Soft-Tissue Sarcoma:** Manifest at any time after service	Lists diseases associated with exposure to herbicides containing dioxin

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
January 15, 1992	Claims based on chronic effects of exposure to mustard gas. Proposed rule. *Federal Register* 57(10):1699-1700. 38 CFR Part 3	**Diseases Associated with Exposure to Mustard Gas:** • Asthma • Bronchitis • Conjunctivitis • Corneal opacities • Emphysema • Keratitis • Laryngitis	Mustard gas exposure by participating in full-body, field, or chamber experiments to test protective clothing or equipment	During World War II; participating in full-body, field, or chamber experiments to test protective clothing or equipment	Chronic forms of the diseases manifested after exposure	Proposed rule for chronic effects of in-service exposure to mustard gas
January 21, 1992	Claims based on exposure to herbicides containing dioxin (peripheral neuropathy/lung cancer). Proposed rule. *Federal Register* 57(13):2236-2238. 38 CFR Part 3	**Diseases Associated with Exposure to Herbicides (containing dioxin):** • Peripheral neuropathy	Herbicide (containing dioxin) exposure Military service	Military service	**Peripheral Neuropathy:** Manifested not later than 10 years following the date of exposure	Proposed rule amends diseases associated with exposure to herbicides containing dioxin **Diseases NOT Associated with Exposure to Herbicides (containing dioxin):** • Lung cancer • Porphyria cutanea tarda
July 31, 1992	Claims based on chronic effects of exposure to mustard gas. Final rule. *Federal Register* 57(148):33875-33877. 38 CFR Part 3	**Diseases Associated with Exposure to Mustard Gas:** • Asthma • Bronchitis • Conjunctivitis • Corneal opacities • Emphysema • Keratitis • Laryngitis	Mustard gas exposure by participating in full-body, field, or chamber experiments to test protective clothing or equipment	During World War II; participating in full-body, field, or chamber experiments to test protective clothing or equipment	Chronic forms of the diseases manifested after exposure	Final rule from January 15, 1992

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
October 30, 1992	Veterans' Radiation Exposure Amendments of 1992. Public Law 102-578. 102d Cong., 2d Sess., Sec 2. 106 Stat. 4774	**Diseases Associated with Exposure to Radiation:** • Cancer of the: Salivary gland Urinary tract	Radiation exposure			Adds diseases to the list associated with exposure to radiation and elimination of latency-period limitations
March 26, 1993	Claims based on exposure to ionizing radiation. Final rule. *Federal Register* 58(57):16358-16359. 38 CFR Part 3	**Diseases Associated with Exposure to Radiation:** • Ovarian cancer • Parathyroid adenoma	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
April 27, 1993	Radiation Exposure Compensation Act of 1990. Final Rule. *Federal Register* 58(79):25564-25565. 38 CFR Part 3	**Diseases Associated with Exposure to Radiation: NONE**				Establishes compensation to any individual under the provisions of the Radiation Exposure Compensation Act of 1990
May 19, 1993a	Direct service connection (posttraumatic stress disorder). Final rule. *Federal Register* 58(95):29109-29110.	**Diseases Associated with Service:** • Posttraumatic stress disorder	Military service Stressor actually occurred in service (engaged in combat or evidence of the claimed in service	Military service or former prisoner of war		Amends list of diseases associated with military service

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	38 CFR Part 3		stressor) or prisoner of war experience			
May 19, 1993b	Republic of Vietnam. Final rule. *Federal Register* 58(95):29107-29109. 38 CFR Part 3 3.309(e)	**Diseases Associated with Service in the Republic of Vietnam:** • Chloracne • Congenital and infantile fibrosarcoma • Extraskeletal Ewing's sarcoma • Malignant ganglionar neuroma • Non-Hodgkin's lymphoma • Soft-tissue sarcoma (see October 19, 1991)	Wartime and service in the Republic of Vietnam	On or after January 1, 1947	Disease manifest to 10 percent or more at any time after service **Exception: Chloracne (or another acneform disease):** 10 percent or more within a year after the last date veteran performed active military, naval, or air service in the Republic of Vietnam	"Service in the Republic of Vietnam" includes service in the waters offshore and service in other locations if the conditions of service involved duty or visitation in the Republic of Vietnam
January 24, 1994	Claims based on chronic effects of exposure to vesicant agents. Proposed rule. *Federal Register* 59(15):3532-3534. 38 CFR Part 3	**Diseases Associated with Exposure to Mustard Gas and Other Vesicant Agents During Military Service:** • Asthma • Bronchitis • Cancers: Laryngeal Lung (except mesothelioma) Nasopharyngeal Squamous cell carcinoma of the skin	Mustard gas and other vesicant agents Full-body exposure to nitrogen or sulfur mustard or Lewisite Active military service	**Full-Body Exposure to Nitrogen or Sulfur Mustard:** Conjunctivitis, keratitis, corneal opacities, scar formation, or the following cancers: nasopharyngeal, laryngeal, lung (except mesothelioma), or	Chronic manifestation of the diseases after military service and either full-body exposure to nitrogen or sulfur mustard gas or Lewisite	Amends regulation concerning chronic diseases from exposure to mustard gas and other vesicant agents in response to NAS report

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Conjunctivitis (chronic) • Corneal opacities • Emphysema • Keratitis • Laryngitis • Nonlymphocytic leukemia (acute) • Obstructive pulmonary disease (chronic) • Scar formation		squamous cell carcinoma of the skin **Full-Body Exposure to Nitrogen or Sulfur Mustard or Lewisite:** Laryngitis, bronchitis, emphysema, asthma, or chronic obstructive pulmonary disease **Full-Body Exposure to Nitrogen Mustard:** Acute nonlymphocytic leukemia		
February 3, 1994	Disease associated with exposure to certain herbicide agents. Final rule. *Federal Register* 59(23):5106-5107. 38 CFR Part 3	**Diseases Associated with Exposure to Certain Herbicide Agents:** • Hodgkin's disease • Porphyria cutanea tarda	Herbicide agent exposure, specifically, 2,4-D; 2,4,5-T, and its contaminant TCDD; cacodylic acid; and picloram During active military, naval, or air service	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	Disease manifest to 10 percent or more at any time after service **Porphyria Cutanea Tarda:** 10 percent or more manifested within a year after the last date veteran was exposed to an	Amends list of diseases to other chronic, tropical, or prisoner-of-war related diseases or disease associated with exposure to certain herbicide agents; wartime and service on or after January 1, 1947

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					herbicide agent during active military, naval, or air service	
June 9, 1994	Disease associated with exposure to certain herbicide agents (multiple myeloma and respiratory cancers). Final rule. *Federal Register* 59(110):29723-29724. 38 CFR Part 3	**Diseases Associated with Exposure to Certain Herbicide Agents:** • Multiple myeloma • Respiratory cancers: Bronchus Larynx Lung Trachea	Herbicide agent exposure During active military, naval, or air service	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	**Multiple Myeloma:** Disease manifest to 10 percent or more at any time after service **Respiratory Cancers:** Within 30 years after the last date on which the veteran was exposed to an herbicide agent during active military, naval, or air service	Amends list of diseases associated with chronic, tropical, or prisoner of war, or exposure to certain herbicide agents
August 18, 1994	Claims based on chronic effects of exposure to mustard gas or lewisite. Final rule. *Federal Register* 59(159):42497-42500. 38 CFR Part 3	**Diseases Associated with Chronic Effects of Exposure to Mustard Gas or Lewisite During Military Service:** **Nitrogen or Sulfur Mustard (38 CFR 3.316[a][1])** • Chronic conjunctivitis • Corneal opacities • Keratitis	Mustard gas and other vesicant agents Active military service Full-body exposure to nitrogen or sulfur mustard or Lewisite	**Full-Body Exposure to Nitrogen or Sulfur Mustard:** Conjunctivitis, keratitis, corneal opacities, scar formation, or the following cancers: nasopharyngeal, laryngeal, lung (except	Chronic manifestation of the diseases after military service and either full-body exposure to nitrogen or sulfur mustard gas or Lewisite	Final rule based on NAS study and regulation on July 31, 1992, establishing service connection from exposure from field or chamber experiments during WWII

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Laryngeal cancer • Lung cancer (except mesothelioma) • Nasopharyngeal cancer • Scar formation • Squamous cell carcinoma of the skin **Nitrogen or Sulfur Mustard or Lewisite (38 CFR 3.316[a][2])** • Asthma • Chronic form of bronchitis • Chronic form of laryngitis • Chronic obstructive pulmonary disease • Emphysema **Nitrogen Mustard (38 CFR 3.316[a][3])** • Acute nonlymphocytic leukemia		mesothelioma), or squamous cell carcinoma of the skin **Full-Body Exposure to Nitrogen or Sulfur Mustard or Lewisite:** Laryngitis, bronchitis, emphysema, asthma, or chronic obstructive pulmonary disease **Full-Body Exposure to Nitrogen Mustard:** Acute nonlymphocytic leukemia		
September 6, 1994	Claims based on exposure to ionizing radiation. Final rule. *Federal Register* 59(171):45975. 38 CFR Part 3	**Diseases Associated with Exposure to Radiation:** • Tumors of the brain and central nervous system	Ionizing radiation			Amended diseases associated with exposure to ionizing radiation
November 2, 1994	Persian Gulf War Veterans' Benefits Act of 1994.	**Diseases Associated with Exposure to Certain Herbicide Agents:**	Herbicide agent exposure		**Hodgkin's Disease and Multiple**	Codified these diseases to the list of herbicide-

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Public Law 103-446. 103d Cong., 2d. Sess. 108 Stat. 4645	• Hodgkin's disease • Multiple myeloma • Porphyria cutanea tarda • Respiratory cancers (lung, bronchus, larynx, or trachea)	During active military, naval, or air service		**Myeloma:** Mnifest to 10 percent disability or more **Porphyria Cutanea Tarda:** 10 percent or more manifested within a year after the last date veteran was exposed to an herbicide agent during active military, naval, or air service **Respiratory Cancers:** Within 30 years after the last date on which the veteran was exposed to an herbicide agent during active military, naval, or air service	exposure presumptions
December 8, 1994	Compensation for certain undiagnosed illnesses. Proposed rule. *Federal Register* 59(235):63283-	**Diseases Associated with Undiagnosed Illnesses During the Persian Gulf War:** Signs or symptoms of: • Abnormal weight loss • Cardiovascular signs or	Active military, naval, or air service	Southwest Asia theatre during the Persian Gulf War (Iraq, Kuwait, Saudi Arabia, neutral zone between Iraq and	Chronic (6 months or more) disability resulting in one or more signs and symptoms and manifested either during active	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	63285. 38 CFR Part 3	symptoms • Fatigue • Gastrointestinal signs or symptoms • Headache • Joint pain • Menstrual disorders • Muscle pain • Neurologic signs or symptoms • Neuropsychological signs or symptoms • Signs or symptoms involving skin • Signs or symptoms involving the respiratory system (upper or lower) • Sleep disturbances		Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations	service or to a 10 percent degree or more no later than 2 years after the date the veteran last performed active service in the Southwest Asia theater of operations during the Persian Gulf War	
February 3, 1995	Compensation for certain undiagnosed illnesses. Final rule. *Federal Register* 60(23):6660-6666. 38 CFR Part 3	**Diseases Associated with Undiagnosed Illnesses During the Persian Gulf War:** Signs or symptoms of: • Abnormal weight loss • Cardiovascular signs or symptoms • Fatigue • Gastrointestinal signs or symptoms • Headache • Joint pain • Menstrual disorders • Muscle pain	Active military, naval, or air service	Southwest Asia theatre during the Persian Gulf War (Iraq, Kuwait, Saudi Arabia, neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and	Chronic (6 months or more or intermittent episodes of improvement and worsening over a 6-month period) disability resulting in one or more signs and symptoms and manifested either during active service or to a 10 percent degree or more no later than	Final rule for undiagnosed illnesses during service in the Persian Gulf War

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Neurologic signs or symptoms • Neuropsychological signs or symptoms • Signs or symptoms involving skin • Signs or symptoms involving the respiratory system (upper or lower) • Sleep disturbances		the airspace above these locations	2 years after the date the veteran last performed active service in the Southwest Asia theater of operations during the Persian Gulf War	
October 13, 1995	Claims based on exposure to ionizing radiation (lymphomas other than Hodgkin's disease and cancer of the rectum). Final rule. *Federal Register* 60(198):53276-53277. 38 CFR Part 3	**Diseases Associated with Exposure to Ionizing Radiation:** • Cancer of the rectum • Lymphomas other than Hodgkin's disease	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
October 9, 1996	Veterans' Benefits Improvements Act of 1996 Public Law 104-275. 104th Cong., 2d Sess., Sec. 505. 110 Stat. 3322	Expansion of period of Vietnam Era for certain veterans **NONE**			"Vietnam era" • For a Veteran who served in the Republic of Vietnam—February 28, 1961, to May 7, 1975 • In all other cases—August 5, 1964, to May 7, 1975	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
November 7, 1996	Diseases associated with exposure to certain herbicide agents (prostate cancer and acute and subacute peripheral neuropathy). Final rule. *Federal Register* 61(217):57586-57589. 38 CFR Part 3	**Diseases Associated with Exposure to Certain Herbicide Agents:** • Acute and subacute peripheral neuropathy • Prostate cancer	Herbicide agent exposure During active military, naval, or air service	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	Manifest to 10 percent disability or more after service **Note: acute and subacute peripheral neuropathy by definition** appears within weeks or months of exposure to a herbicide agent and resolves within 2 years of the date of onset	Amends list of diseases associated with exposure to certain herbicide agents
April 29, 1997	Compensation for certain undiagnosed illnesses. Interim rule with request for comments. *Federal Register* 62(82):23138-23139. 38 CFR Part 3	**Diseases Associated with Undiagnosed Illnesses:** Extension of the period of disease to manifest	Persian Gulf War service		Interim rule extending the period of disease to manifest from "two years after the date on which the veteran last performed active military, naval, or air service in the Southwest Asia theater of operations during the Persian Gulf War" to "December 31, 2001"	Interim rule to expand the period within diseases must manifest

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
July 1, 1997	Veterans' Benefits Improvements Act of 1996. Final rule. *Federal Register* 62(126):35421-35423. 38 CFR Part 3	Vietnam era inclusion dates **NONE**		"Vietnam era" February 28, 1961, to May 7, 1975, inclusive for a veteran who served in the Republic of Vietnam		
March 6, 1998	Compensation for certain undiagnosed illnesses. Final rule. *Federal Register* 63(44):11122-11123. 38 CFR Part 3	Persian Gulf Veterans presumptive period **NONE**			Extend the presumptive period (to December 31, 2001) in such a manner that no Persian Gulf veterans with qualifying disabilities would be denied compensation	Final rule for extending the presumptive period for Persian Gulf veterans
September 24, 1998	Claims based on exposure to ionizing radiation (prostate cancer and any other cancer). Final rule. *Federal Register* 63(185):50993-50995. 38 CFR Part 3	**Diseases Associated with Exposure to Radiation:** • Prostate cancer • Any other cancer	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
October 21, 1998	Persian Gulf War Veterans Act of 1998. Public Law	**Illnesses Associated with Persian Gulf War**	Establishes service connection for illnesses	Veteran who served on active duty in the Southwest Asia		

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	105-277. 105th Cong., 2d Sess., Sec. 1601, 1602, 1603	Language for the National Academy of Sciences report for presumption of service connection for illnesses associated with service in the Persian Gulf War	associated with the Persian Gulf War Diseases having an association with exposure to a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine	theater during the Persian Gulf War		
November 30, 1999	Veterans Millennium Health Care and Benefits Act of 1999. Public Law 106-117. 106th Cong., 1st Sess., Sec. 503. 113 Stat. 1545	**Diseases Associated with Radiation Exposure:** • Bronchiolo-alveolar carcinoma	Disease contracted during military service			
July 10, 2000	Radiation Exposure Compensation Act Amendments of 2000. Public Law 106-245. 106th Cong., 2d Sess. 114 Stat. 501	**Diseases Associated with Radiation Exposure:** **Nuclear Atmospheric Testing** • Brain cancer • Colon cancer • Gall bladder cancer • Male breast cancer • Ovary cancer	Nuclear atmospheric testing Uranium mining	**Leukemia:** Physically present in affected area for at least 1 year January 21, 1951, through October 31, 1958; or June 30, 1962, through July 31, 1962	**Lung Cancer:** Onset of disease at least 2 years after first exposure	Amends list of diseases associated to radiation exposure and manifestation of diseases Amends dates/location of

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• Salivary gland cancer • Urinary bladder cancer **Uranium Mining** • Lung cancer • Nonmalignant respiratory disease • Renal cancers • Other chronic renal disease (nephritis, kidney tubal tissue injury)				service for leukemia
July 14, 2000	Veterans Millennium Health Care and Benefits Act. Final rule. *Federal Register* 65(136):43699-43700. 38 CFR Part 3	**Diseases Associated with Exposure to Radiation and Service:** • Bronchiolo-alveolar carcinoma	Active military service Radiation exposure			Amended list of diseases related to exposure to radiation and active service
April 6, 2001	Claims based on the effects of tobacco products. Final rule. *Federal Register* 66(67):18195-18198. 38 CFR Part 3	**Diseases or Death NOT Associated with Military Service:** • Disease attributable to use of tobacco products	Active military, naval, or air service			Veterans' use of tobacco products are NOT considered to be service-connected
May 8, 2001	Disease associated with exposure to certain herbicide agents: Type 2 diabetes. Final	**Diseases Associated with Exposure to Herbicides:** • Type 2 diabetes	Herbicide exposure	In the Republic of Vietnam during the Vietnam Era Or active military	Illness manifest to a degree of 10 percent or more	Amends diseases associated to exposure to herbicides

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	rule. *Federal Register* 66(89):23166-23169. 38 CFR Part 3			service		
August 8, 2001	Diseases specific to radiation-exposed veterans. Proposed rule. *Federal Register* 66(153):41483-41485. 38 CFR Part 3	**Diseases Associated with Radiation-Risk Activity:** Add cancers: • Cancer of the bone • Cancer of the brain • Cancer of the colon • Cancer of the lung • Cancer of the ovary	Radiation-risk activity Ionizing radiation Military service	Total of at least 250 days before February 1, 1992 (Paducah, KY; Portsmouth, OH; K25 at Oak Ridge, TN) Service before January 1, 1974 (Amchitka Island, AL) and performance of duty related to Long Shot, Milrow, or Cannikin underground nuclear tests		Amends list of diseases associated with radiation-risk activities and date/location of service
November 9, 2001	Extension of the presumptive period for compensation for Gulf War veterans' undiagnosed illnesses. Interim final rule with request for comments. *Federal Register*	**Undiagnosed Illnesses:** Presumptive period extension	Persian Gulf War active military, naval, or air service	Veteran who served on active duty in the Southwest Asia theater during the Persian Gulf War	Undiagnosed illness manifest to a degree of 10 percent or more through December 31, 2006	Extension of presumptive period for compensation for Gulf War Veteran's undiagnosed illnesses

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	66(218):56614-56615. 38 CFR Part 3					
December 27, 2001	Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.	**Diseases Associated with Service-Connection or Herbicide Exposure:** • Diabetes mellitus (type 2) • Respiratory cancers **Diseases Associated with Persian Gulf War:** • Chronic multisymptom illness: Chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome • Undiagnosed illness or chronic multisymptom illness: Abnormal weight loss, cardiovascular signs or symptoms, fatigue, gastrointestinal signs or symptoms, headache, joint pain, menstrual disorders, muscle pain, neurological signs and symptoms, neuropsychological signs or symptoms, signs or symptoms involving the upper or lower	Herbicide exposure Military Service Vietnam Veteran active service **Persian Gulf Exposure:** Persian Gulf War service active military, naval, or air service	**Persian Gulf Exposure** Active duty in the Armed Forces in the Southwest Asia theatre of operations during the Persian Gulf War	***Herbicide Exposure*** **Additional diseases:** Up to September 30, 2015 **Respiratory cancers:** Presumptive period amended from "within 30 years" through "May 7, 1975" ***Persian Gulf Exposure*** **Additional diseases:** "On September 30, 2011"	Extension of presumptive period for respiratory cancers and additional diseases associated with herbicide exposure and Persian Gulf exposure Amended list of diseases associated with military service, Persian Gulf War

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		respiratory system, sleep disturbances, unexplained rashes or other dermatological signs or symptoms				
January 25, 2002	Diseases specific to radiation-exposed veterans. Final rule. *Federal Register* 67(17):3612-3616. 38 CFR Part 3	**Diseases Associated with Radiation-Risk Activity and Military Service:** Add cancers: • Cancer of the bone • Cancer of the brain • Cancer of the colon • Cancer of the lung • Cancer of the ovary	Ionizing radiation Military service Radiation-risk activity definition: Participation in a test involving atmospheric detonation of a nuclear device; occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946); or internment as a prisoner of war in Japan or service on active duty in Japan following such internment during WWII with opportunity for exposure to ionizing radiation	Total of at least 250 days before February 1, 1992 (Paducah, KY; Portsmouth, OH; K25 at Oak Ridge, TN) Service before January 1, 1974 (Amchitka Island, AL) and performance of duty related to Long Shot, Milrow, or Cannikin underground nuclear tests		Amends diseases associated with radiation-risk activity and military service Amends definition of radiation-risk activity
February 14, 2002	Claims based on exposure to	**Diseases Associated with Exposure to Radiation:**	Radiation exposure			Amends diseases from exposure to

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	ionizing radiation. Final rule. *Federal Register* 67(31):6870-6871. 38 CFR Part 3	• Polycythemia vera	Ionizing radiation			ionizing radiation; VA did not have evidence to add to the list of "radiogenic diseases," but the VA will consider a claim that polycythemia vera is a radiogenic disease as long as there is scientific or medical evidence to support the claim
November 7, 2002	Service connection by presumption of aggravation of a chronic preexisting disease. Final rule. *Federal Register* 67(216):67792-67793. 38 CFR Part 3	Preexisting chronic disease	Military service			Amended presumption of a preexisting disease that was aggravated by veteran's military service
December 27, 2002	Extension of the presumptive period for compensation for Gulf War veterans'	Undiagnosed illnesses associated with Persian Gulf War **NONE**		Southwest Asia theater of operations during the Persian Gulf War	Through December 31, 2006	Extends the period within which disabilities must become manifest for entitlement for

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	undiagnosed illnesses. Final rule. *Federal Register* 67(249):78979-78980. 38 CFR Part 3					compensation
February 10, 2003	Presumption of service connection for cirrhosis of the liver in former prisoners of war. Proposed rule. *Federal Register* 68(27):6679-6680. 38 CFR Part 3	**Diseases Associated with Prisoners of War:** • Cirrhosis of the liver	Former prisoners of war Evidence: Significantly higher risk of death from cirrhosis in former WWII POWs than the general population		Detained for at least 30 days	Amended list of diseases associated with prisoners of war
June 10, 2003	Compensation and pension provisions of the Veterans Education and Benefits Expansion Act of 2001. Final Rule. *Federal Register* 68(111):34539-34543. 38 CFR Parts 3 and 13	**Diseases Associated with the Persian Gulf Veterans:** • Undiagnosed illness • Chronic multisymptom illness: Chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome **Herbicide Exposure:** Amends date of presumption and exposure candidates				Amends what a "qualifying chronic disability" includes **Herbicide Exposure:** Eliminates respiratory cancer must manifest within 30 years of departure form Vietnam to qualify for presumption

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						based on herbicide exposure and expand presumption of exposure to herbicides to all Vietnam veterans
July 18, 2003	Presumption of service connection for cirrhosis of the liver in former prisoners of war. Final rule. *Federal Register* 68(138):42602-42603. 38 CFR Part 3	**Diseases Associated with Former Prisoners of War:** • Cirrhosis of the liver	Former prisoners of war			Amends list of diseases associated with former prisoners of war
October 16, 2003	Disease associated with exposure to certain herbicide agents: Chronic lymphocytic leukemia. Final rule. *Federal Register* 68(200):59540-59542. 38 CFR Part 3	**Disease Associated with Exposure to Herbicide:** • Chronic lymphocytic leukemia	Herbicide exposure Military service	Republic of Vietnam during the Vietnam era		Amends list of diseases associated with exposure to herbicide agents
October 21, 2003	Veterans Benefits Enhancement Act of 2003 S. Rep. No. 108-169. 108th Cong.	**Diseases Associated with Former Prisoners of War:** • Any of the anxiety states • *Any other nutritional deficiency	Former prisoners of war veteran active military, naval, or air service	Former prisoner of war	Disease to manifest to a degree of 10 percent or more after active service	Proposed Act that would amend the diseases associated with former prisoners

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	1st Sess. 11 **(proposed Act)**	• *Avitaminosis • *Beriberi (including beriberi heart disease) • *Chronic dysentery • *Cirrhosis of the liver • Dysthymic disorder (or depressive neurosis) • *Helminthiasis • *Irritable bowel syndrome • *Malnutrition (including optic atrophy associated with malnutrition) • Organic residuals of frostbite • *Pellagra • *Peptic ulcer disease • *Peripheral neuropathy (except where directly related to infectious causes) • Posttraumatic osteoarthritis • Psychosis			*Detained or interned for not less than 30 days	of war
December 16, 2003	Veterans Benefits Act of 2003. Public Law 108-183. 108th Cong., 1st Sess., Sec. 201. 117 Stat. 2651	**Diseases Associated with Former Prisoners of War:** • Any of the anxiety states • *Any other nutritional deficiency • *Avitaminosis • *Beriberi (including beriberi heart disease)	Former prisoners of war veteran active military, naval, or air service	Former prisoner of war	Disease to manifest to a degree of 10 percent or more after active service *Detained or interned for not less than 30 days	Final act amending list of diseases associated with former prisoners of war

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		• *Chronic dysentery • *Cirrhosis of the liver • Dysthymic disorder (or depressive neurosis) • *Helminthiasis • *Irritable bowel syndrome • *Malnutrition (including optic atrophy associated with malnutrition) • Organic residuals of frostbite • *Pellagra • *Peptic ulcer disease • *Peripheral neuropathy (except where directly related to infectious causes) • Posttraumatic osteoarthritis • Psychosis				
June 8, 2004	Change of effect-tive date of rule adding a disease associated with exposure to certain herbicide agents: Type 2 diabetes. Final rule. *Federal Register* 69(110): 31882-31883. 38 CFR Part 3	**Disease Associated with Exposure to Certain Herbicides:** • Type 2 diabetes				Change of effective date of presumption to May 8, 2001

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
October 7, 2004	Presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. Interim final rule. *Federal Register* 69(194):60083-60090. 38 CFR Parts 1 and 3	**Diseases Associated with Former Prisoner of War:** • Atherosclerotic disease or hypertensive vascular disease (including hypertensive heart disease) and their complications (including myocardial infarction, congestive heart failure, arrhythmia) • Stroke and its complications	Former prisoner of war		Eliminated the 30-day detained requirement for psychosis, any anxiety state, dysthymic disorders, organic residuals of frostbite, and posttraumatic osteoarthritis The new diseases in this rule are presumed to be service connected following any period of prisoner of war activity	Amended diseases associated with former prisoner of war and amended the 30-day requirement for some of the related diseases Defines the evidence necessary to determine presumption of service connection
December 10, 2004	Veterans Benefits Improvement Act of 2004. Public Law 108-454. 108th Cong., 2d Sess., Sec. 306. 118 Stat 3598	**Diseases Associated with Radiation-Risk Activity and Military Service:** Add cancers: • Cancer of the bone • Cancer of the brain • Cancer of the colon • Cancer of the lung • Cancer of the ovary	Radiation-risk activity Ionizing Military service			Amended "radiation-risk activity" to include service in a capacity if performed as an employee of the Department of Energy (DOE) would qualify inclusion as a member of the Special Exposure Cohort

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
June 20, 2005	Prisoner of War Benefits Act of 2005. 109th Cong., 1st Sess. Senate Bill 1271 **(proposed act)**	**Diseases Associated with Former Prisoners of War:** • Diabetes (type 2) • Heart disease • Osteoporosis • Stroke	Former prisoners of war			Proposed act to amend the list of diseases associated with former prisoners of war
June 28, 2005	Presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. Affirmation of interim final rule as final rule. *Federal Register* 70(123):37040-37042. 38 CFR Parts 1 and 3	**Diseases Associated with Former Prisoners of War:** • Atherosclerotic disease or hypertensive heart disease (including hypertensive vascular disease) and their complications (including myocardial infarction, congestive heart failure, arrhythmia) • Stroke and its complications				Final rule without change from October 7, 2004, interim rule
December 18, 2006	Extension of the presumptive period for compensation for Gulf War veterans. Interim final rule. *Federal Register* 7(242):75669-75672. 38 CFR Part 3	Undiagnosed illnesses associated with Persian Gulf War **NONE**		Southwest Asia theater of operations during the Persian Gulf War	Through December 31, 2011	Extends the period within which disabilities must become manifest for entitlement for compensation

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	U.S. Code Title 38. Veterans' Benefits Part II. General Benefits. **Title 42. The Public Health and Welfare Chapter 23.**					
Approved February 27, 2006	38 USC § 101	**NONE** Definitions: Veteran Spanish-American War World War I World War II Korean conflict Armed Forces Veteran of any war Service-connected Non-service-connected Active duty Active duty for training Inactive duty training Active military, naval, or air service Former prisoner of war Reserve Vietnam era Persian Gulf war				
Approved February 27, 2006	38 USC § 108	Death			7-year absence	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Approved February 27, 2006	38 USC § 501	**NONE** Secretary has authority to prescribe rules and regulations to carry out laws administered by the VA				
Approved February 27, 2006	38 USC § 1110	Entitlement to compensation for disability resulting from diseases contracted in line of duty in the active military, naval, or air service, during a period of war				
Approved February 27, 2006	38 USC § 1111	Presumption of sound condition at the time of examination, acceptance, and enrollment into service				
Approved February 27, 2006	38 USC § 1112	**Presumptions Relating to Certain Diseases and Disabilities:** • Chronic disease • Tropical disease • Tuberculous (active) • Multiple sclerosis • Hansen's disease • **Prisoner of war-related diseases** Any of the anxiety states, *any other nutritional deficiency, *avitaminosis, *beriberi (including beriberi heart disease), *chronic dysentery, *cirrhosis of the liver, *helminthiasis, *irritable bowel	Active military service **Tropical Disease:** Disorders or disease originating because of therapy, administered in connection with such disease, or as a preventative **Radiation-Exposed Veteran:** Radiation risk activity	Veteran who served for 90 days or more during a period of war ***Prisoner of War Associated Diseases:** Not less than 30 days as a prisoner of war **Radiation-Exposed Veteran:** Participation in a test involving atmospheric detonation of a nuclear device; occupation of	**Chronic Disease:** Disease manifest to 10 percent or more within 1 year from separation of such service **Tropical Disease:** Disease manifest to 10 percent or more within 1 year from separation of such service **Or** Standard or accepted incubation periods	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		syndrome,*malnutrition, organic residuals of frostbite, *pellagra, *peptic ulcer disease, *peripheral neuropathy dysthymic disorder (or depressive neurosis), posttraumatic osteoarthritis, psychosis • **Radiation-Exposed Veteran-Related Diseases:** Bronchiolo-alveolar carcinoma; cancer: bile ducts, bone, brain, breast, colon, esophagus, gall bladder, lung, ovary, pancreas, pharynx, primary liver, salivary gland, small intestine, stomach, thyroid, urinary tract; leukemia; lymphomas (except Hodgkin's disease); multiple myeloma		Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946); internment as a prisoner of war in Japan or service on active duty in Japan following such internment during WWII with opportunity for exposure to ionizing radiation; **Or** Performed as an employee of the DOE	**Tuberculous Disease (active) and Hansen's Disease:** Disease manifest to 10 percent or more within 3 years from separation of such service **Multiple Sclerosis:** Disease manifest to 10 percent or more within 7 years from separation of such service **Prisoner of War:** Disease manifest to 10 percent or more after active military, naval, or air service **Radiation-Exposed Veterans:** Disease manifest after active military, naval, or air service	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Approved February 27, 2006	38 USC § 1116	Presumptions of service connection for diseases associated with **exposure to certain herbicide agents** Presumption of exposure for veterans who **served in the Republic of Vietnam** • Chloracne • Diabetes mellitus (type 2) • Hodgkin's disease • Multiple myeloma • Non-Hodgkin's lymphoma • Porphyria cutanea tarda • Respiratory cancers (bronchus, larynx, lung, or trachea) • Soft tissue sarcoma	Active military naval, or air service Herbicide agent (containing dioxin or 2,4-dichlorophenoxy-acetic acid)	Republic of Vietnam (January 9, 1962, to May 7, 1975)	**Republic of Vietnam Diseases:** Manifest disease 10 percent disability or more, except for diabetes mellitus In addition: **Porphyria cutanea tarda and chloracne:** within 1 year from active military service	
Approved February 27, 2006	38 USC § 1117	Compensation for disabilities occurring in the **Persian Gulf War:** • Undiagnosed illness (abnormal weight loss; cardiovascular signs or symptoms; fatigue; gastrointestinal signs or symptoms; headache; joint pain; menstrual disorders; muscle pain; neurological signs and symptoms; neuropsychological signs	Active duty in the Armed Forces during the Persian Gulf War	Southwest Asia theater during the Persian Gulf War	Medical or scientific evidence and historical treatment of manifestation periods that have been established	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		or symptoms; signs or symptoms involving the upper or lower respiratory system; sleep disturbances; unexplained rashes or other dermatological signs or symptoms) • Chronic multisymptom illness (chronic fatigue syndrome; fibromyalgia; irritable bowel syndrome)				
Approved February 27, 2006	38 USC § 1118	Presumptions of service connection for illness associated with service in the Persian Gulf War (see 38 USC § 1117 for diseases)	Association with exposure to a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine	Service in the Armed Forces in the Southwest Asia theater of operations during the Persian Gulf War	Within a period (if any) that is prescribed in a regulation	
Approved February 27, 2006	38 USC § 1153	Aggravation to a preexisting injury or disease	Increase in disability during active military, naval, or air service, unless the increase is due to the natural progress of the disease			
Approved February 27,	38 USC § 1521	Veteran's service requirements for non-	Active military, naval, or air	Service requirements:		

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
2006		service-connected disability	service	• 90 days or more during a period of war • Period of war and was discharged or released for a service-connected disability • 90 consecutive days or more and began or ended during a period of war • Aggregate of 90 days or more in two or more separate periods of service during more than one period of war		
	Code of Federal Regulations					
	38 CFR 1.18	Guidelines for establishing presumptions of service connection for former prisoners of war	Former prisoners of war		May give a minimum duration of detention or internment for application of the presumption Defines "evidence"	Secretary may establish a presumption of service connection for a disease when there is at least limited/suggestive evidence that an increased risk of

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						such disease is associated with service involving detention or internment as a prisoner of war and an association between the two is biologically plausible
	38 CFR 3.307	Presumptive service connection for chronic, tropical, or prisoner-of-war related disease or disease associated with exposure to certain herbicide agents	Former prisoners of war Herbicide agent exposure (specifically 2,4, D; 2,4,5-T and its contaminant TCDD; cacodylic acid; and picloram) Military service	**Herbicide Agent Exposure:** Republic of Vietnam (January 9, 1962, to May 7, 1975) active military, naval, or air service (including the waters off-shore and service in other locations involving duty or visitation in the Republic of Vietnam	Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Chronic:** manifest to degree of 10 percent or more within 1 year (for Hansen's disease; and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service **Tropical:** Manifest to a	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					degree of 10 percent or more within 1 year from separation of service or time when standard accepted treatises indicate incubation period; diseases resulting from therapy administered **Former Prisoners of War:** Manifest to a degree of 10 percent or more after discharge or release for active service **Herbicide Agent Exposure:** Manifest to a degree of 10 percent or more at any time after service except chloracne, porphyria cutanea tarda, and acute and subacute peripheral neuropathy	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					manifest to a degree of 10 percent or more within 1 year after last date veteran was exposed to an herbicide agent	
	38 CFR 3.309	Disease subject to presumptive service connection • **Chronic Diseases:** Anemia, primary; arteriosclerosis; arthritis; atrophy, progressive muscular; brain hemorrhage; brain thrombosis; bronchiectasis; calculi of the kidney, bladder, or gallbladder; cardiovascular-renal disease, including hypertension; cirrhosis of the liver; coccidioidomycosis; diabetes mellitus; encephalitis lethargica residuals; endocarditis; endocrinopathies; epilepsies; Hansen's disease; Hodgkin's disease; leukemia; lupus erythematosus, systemic; myasthenia gravis;	Military Service Former Prisoner of War **Radiation-Exposed Veteran:** Serving active duty or Armed Forces active duty or training or inactive duty training and participated in a "radiation-risk activity"	**Chronic Diseases:** On or after January 1, 1947, following service in a period of war or peacetime service **Radiation-Exposed Veteran:** • Participation in test atmospheric detonation of nuclear device • Occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946) • Prisoner of war in Japan exposure of ionizing radiation comparable to above exposure	**Chronic Diseases:** see section 3.307 above **Tropical Diseases:** See section 3.307 above **Radiation-Exposed Veteran:** See section 3.307 above **Exposure to Herbicide agents:** See section 3.307 above **Former Prisoner of War:** Manifest to a degree of 10 percent or more after release or discharge from active military,	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		myelitis; myocarditis; nephritis; osteitis deformans (Paget's disease); osteomalacia; other organic diseases of the nervous system; palsy, bulbar; paralysis agitans; psychoses; purpura idiopathic, hemorrhagic; Raynaud's disease; sarcoidosis; scleroderma; sclerosis, amyotrophic lateral; sclerosis, multiple; syringomyelia; thromboangiitis obliterans (Buerger's disease); tuberculosis, active; tumors, malignant; ulcers, peptic (gastric or duodenal) • **Tropical Diseases:** Amebiasis; backwater fever; cholera; dracontiasis; dysentery; filariasis; leishmaniasis, including kala-azar; loiasis; malaria; onchocerciasis; oroya fever; pinta; plague; schistosomiasis; yaws; yellow fever • **Prisoners of War:** Any of the anxiety		• Total of 250 days before February 1, 1992, on grounds of gaseous diffusion plant (Paducah, KY; Portsmouth OH; K25 Oak Ridge, TN) • Service before January 1, 1974, on Amchitka Island, AL, and exposed to underground nuclear tests at Long Shot, Milrow, or Cannikin	naval, or air service *Indicate only for veteran that was detained or interned for not less than 30 days	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		states; *any other nutritional deficiency; *avitaminosis; *beriberi (including beriberi heart disease; *chronic dysentery; *cirrhosis of the liver; dysthymic disorder (or depressive neurosis); *helmin-thiasis; *irritable bowel syndrome; *malnutrition; organic residuals of frostbite; *pellagra; *peptic ulcer disease; *peripheral neuropathy atherosclerotic heart disease or hypertensive vascular disease; posttraumatic osteoarthritis; psychosis; stroke and its complications • **Radiation-Exposed Veterans:** Bronchiolo-alveolar carcinoma; cancer of the bile ducts, bone, brain, breast, colon, esophagus, gall bladder, lung, ovary, pancreas, pharynx, salivary gland, small intestine, stomach, thyroid, urinary tract;				

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		leukemia; lymphomas; multiple myeloma; primary liver cancer • **Exposure to Certain Herbicide Agents:** Acute and subacute peripheral neuropathy; chloracne or other acneform disease; chronic lymphocytic leukemia; Hodgkin's disease; multiple myeloma; non-Hodgkin's lymphoma; porphyria cutanea tarda; prostate cancer; respiratory cancers (lung, bronchus, larynx, or trachea); soft tissue sarcoma (adult fibrosarcoma; dermatofibrosarcoma protuberans; malignant fibrous histocytoma; liposarcoma; leiomyosarcoma; epithelioid leiomyosarcoma; rhabdomyosarcoma; ectomesenchymoma; angiosarcoma; proliferating angioendotheliomatosis; malignant glomus tumor;				

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		malignant hemangiopericytoma; synovial sarcoma; malignant giant cell tumor of tendon sheath; malignant schwannoma; malignant mesenchymoma; malignant granular cell tumor; alveolar soft part sarcoma; epithelioid sarcoma; clear cell sarcoma of tendons and aponeuroses; extraskeletal Ewing's sarcoma; congenital and infantile fibrosarcoma; malignant ganglionar neuroma); type 2 diabetes				
	38 CFR 3.310	Secondary condition established as service connection of the original condition • Cardiovascular disease for service-connected amputation	Service-connected amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles			
	38 CFR 3.311	Claims based on exposure to ionizing radiation: Cancer of the breast, bone, colon, esophageal,	Ionizing radiation Service	Occupation of Hiroshima or Nagasaki, Japan (September 1945 to	Manifest 5 years or more after exposure	

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		kidney, liver, lung, ovarian, pancreatic, prostate, rectum, salivary gland, skin, stomach, thyroid, urinary bladder; any other cancer; leukemia; lymphomas; multiple myeloma; non-malignant thyroid nodular disease; parathyroid adenoma; posterior subcapsular cataracts; tumors of the brain and central nervous system		July 1946) or other activities where they participated in atmospheric testing of nuclear weapons	**Bone Cancer:** Manifest within 30 years after exposure **Leukemia:** Manifest any time after exposure **Posterior Subcapsular Cataracts:** Manifest 6 months or more after exposure	
	38 CFR 3.313	Service in Vietnam • Non-Hodgkin's lymphoma	Service in Vietnam	Service in Vietnam during the Vietnam Era	Subsequent to service	
	38 CFR 3.316	Claims based on chronic effects of exposure to mustard gas • **Nitrogen or Sulfur Mustard:** Cancers: lung (except mesothelioma), nasopharyngeal, laryngeal, squamous cell carcinoma of the skin; chronic conjunctivitis; corneal opacities; keratitis; scar formation • **Nitrogen or Sulfur Mustard or Lewisite:** Chronic form of asthma,	Exposure to nitrogen or sulfur mustard or Lewisite	Active military service		

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		bronchitis, emphysema, laryngitis, chronic obstructive pulmonary disease • **Nitrogen Mustard:** Acute nonlymphocytic leukemia				
	38 CFR 3.317	Compensation for certain disabilities due to **undiagnosed illnesses** during Persian Gulf War • Undiagnosed illness • Medically unexplained chronic multisymptom illnesses defined by a cluster of signs or symptoms: chronic fatigue syndrome; fibromyalgia; irritable bowel syndrome • Signs or symptoms which may be manifestations of undiagnosed illness or medially unexplained chronic multisymptom illness: abnormal weight loss; cardiovascular signs or symptoms; fatigue; gastrointestinal signs or symptoms; headache; joint pain; menstrual disorders; muscle pain;		Southwest Asia Theater during the Persian Gulf War Southwest Asia Theater includes Iraq, Kuwait, Saudi Arabia, neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, United Arab Emirates, Oman, Gulf of Aden, Gulf of Oman, Persian Gulf, Arabian Sea, Red Sea, and air space above these locations)	Manifest either during active military, naval, or air service or to a degree of 10 percent or more not later than December 31, 2006	Chronic disabilities for a period of 6 months or more or intermittent episodes of improvement and worsening over a 6-month period

Date	Legislation or Regulation	Presumptive Disease	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
		neurological signs and symptoms; neuropsychological signs or symptoms; signs or symptoms involving skin; signs or symptoms involving the respiratory system (upper and lower); sleep disturbances				

TABLE F-2 Summary of PDDM Legislative History (by Health Outcome)

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Chronic Constitutional Diseases						
• Anemia (primary) • Arteriosclerosis • Beriberi • Diabetes insipidus • Diabetes mellitus • Endocrinopathies • Gout • Haemochromatosis • Hemoglobinuria (paroxysmal) • Hemophilia • Hodgkin's disease • Leukemia (all types) • Ochronosis • Pellagra • Polycythemia (Erythremia) • Purpura • Rickets • Scurvy	Internal Memorandum implementing Veterans' Bureau Regulation No. 11	November 12, 1921	Chronic constitutional disease contracted during active military service		Within 1 year after the date of separation from service	November 12, 1921, stated connection to active military service
	Office Memorandum No. 36	December 2, 1921				Constitutional diseases were defined on December 2, 1921
• Arthritis (deformans and chronic) • Carcinoma, sarcoma, and other tumors • Cardiovascular-renal disease, including hypertension • Endocarditis, chronic • Leprosy (*tropical disease added as a chronic disease*)	Veterans' Bureau Schedule for Rating Disabilities (based upon the WW Veterans Act, 1924)	1925	Disease contracted during military or naval services in World War I	During World War I	Characteristic manifestation within 1 year from date of separation from active service Or If medical evidence affirmatively	Amends list of constitutional diseases

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Myocarditis, chronic • Nephritis, chronic forms (*was not carried forward,* • *cholecystitis, chronic, proceeding to gall-stone formation* • *nephrolithiasis* • *valvulitis, chronic*)					establishes conclusive service connection after 1 year of separation	
Chronic Diseases						
• Dysentery (amoebic) • Encephalitis lethargica • Paralysis agitans • Psychoses (originally called neuropsychiatric disease) • Tuberculous (active)	World War Veterans' Act, 1924. Public Law 68-242. 68th Cong., 1st Sess. Title II. Compensation and Treatment Ch. 320, Sec. 200, 43 Stat. 607, 615	June 7, 1924	Disease contracted during active military or naval service	Between April 6, 1917, and July 2, 1921 Or Discharged or resigned prior to July 2, 1921 Or Discharged or resigned on or before November 11, 1918, or on or after July 2, 1921	By January 1, 1925 Characteristic manifestations of the disease to 10 percent or more	
• Anemia (primary) • Arteriosclerosis • Arthritis • Cardiovascular-renal disease (including hypertension) • Diabetes mellitus	Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933	April 12, 1933				Amends list of chronic diseases and presumption of tuberculosis

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Encephalitis lethargica • Endocarditis • Endocrinopathies • Epilepsies • Hodgkin's disease • Leukemia • Myocarditis • Nephritis • Organic diseases of the nervous system • Tumors, malignant, or of the brain						
• Bronchiectasis • Calculi of the kidney, bladder, or gall bladder • Cirrhosis of the liver • Coccidioidomycosis • Osteitis (deformans) (also called Paget's disease) • Osteomalacia • Raynaud's disease • Scleroderma • Thromboangiitis obliterans (Buerger's disease)	Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess. Ch. 612, Sec 1, 62 Stat. 581.	June 24, 1948	Disease contracted during active service		At least 6 months of service and honorably discharged Within 1 year after separation from active service or at a time when standard and accepted treatises indicate that the incubation period thereof commenced during active service	
• Atrophy, progressive muscular • Brain hemorrhage	Pensions, bonuses, and veterans' relief.	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25,	Within 1 year after separation from active	**Factual Basis:** Established by medical evidence,

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Brain thrombosis • Myasthenia gravis • Myelitis • Palsy, bulbar • Paralysis agitans • Sclerosis (amyotrophic lateral, multiple) • Syringomyelia	Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95			1947	wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic disease:** Manifestations sufficient to identify the disease entity and sufficient observations to establish chronicity at the time	competent lay evidence, or both
• Sarcoidosis	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301(3 and 4). 71 Stat. 83, 95.	June 17, 1957	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and	Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period	Summarizes previous rules and legislation and amends dates/location of service and presumption

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947		
	Disease subject to presumptive service connection. *Federal Register* 26(36):1581-1582.	February 24, 1961	Disease contracted during active military, naval, or air service			Lays out criteria for presumption wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence, competent lay evidence, or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation,	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3				tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from service	
	Increase of disability compensation and dependency and indemnity compensation rates. *Federal Register* 39(188):34529-34533. 38 CFR Part 3	September 26, 1974	No new ones	Active service on or after January 1, 1947 **Chronic Before January 1, 1947:** No presumption	Service of 90 days or more during a war period on or after December 31, 1946	
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Chronic:** manifest to degree of 10 percent or more within 1 year (for Hansen's disease;	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service	
	38 CFR 3.309		Military service	**Chronic Diseases:** On or after January 1, 1947, following service in a period of war or peacetime service	**Chronic Diseases:** See section 3.307 above	
Leprosy (also called Hansen's disease)	Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933	April 12, 1933				Amends list of chronic diseases and presumption of tuberculosis
	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947	Within 1 year after separation from active wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic Disease:** Manifestations	**Factual Basis:** Established by medical evidence, competent lay evidence, or both

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					sufficient to identify the disease entity and sufficient observations to establish chronicity at the time	
	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301(3 and 4). 71 Stat. 83, 95	June 17, 1957	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if	Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period	Summarizes previous rules and legislation and amends dates/location of service and presumption

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				period began before January 1, 1947		
	Disease subject to presumptive service connection. *Federal Register* 26(36):1581-1582	February 24, 1961	Disease contracted during active military, naval, or air service			Lays out criteria for presumption wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence, competent lay evidence or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from service	
	Increased disability compensation and dependency and	December 23, 1976			**Chronic Diseases:** Following service in a period of war	Used term Hansen's disease instead of leprosy

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	indemnity compensation; burial benefits. *Federal Register* 41(248):55872-55875. 38 CFR Part 3				or following peacetime service on or after January 1, 1947	
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Chronic:** Manifest to degree of 10 percent or more within 1 year (for Hansen's disease; and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service	
	38 CFR 3.309	Military service	**Chronic Diseases:** On or after January 1, 1947, following service in a period of	**Chronic Diseases:** See section 3.307 above		

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
			war or peacetime service			
	38 USC § 1112	Approved February 27, 2006	Active military service	Veteran who served for 90 days or more during a period of war	**Chronic Disease:** Disease manifest to 10 percent or more within 1 year from separation of such service **Tuberculous Disease (active) and Hansen's Disease:** Disease manifest to 10 percent or more within 3 years from separation of such service	
Lupus erythematosus (systemic)	Veterans' Benefits and Services Act of 1988. Public Law 100-322. 100th Cong., 2d Sess. Sec 312, 313. 102 Stat. 487, 535	May 20, 1988	Chronic disease contracted during military service			Amended list of diseases related to service connection of chronic diseases
Osteitis (deformans) (also called Paget's disease)	Executive Order 6089. Instruction No. 2-A, Implementing Vet. Reg. No. 1. August 14, 1935	August 14, 1935				Amends list of chronic diseases

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Psychoses (originally called neuropsychiatric disease)	Veterans' Bureau. Public Law 67-47. 1921. 67th Cong., 1st Sess. Ch. 57, Sec. 18, 42 Stat. 147, 153	August 9, 1921	Disease contracted during active military service	On or after April 6, 1917 Or Discharged or resigned active service on or before November 11, 1918	Within 2 years after separation from active military or naval service Characteristic manifestations of the disease to 10 percent or more	
	Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933	April 12, 1933				Amends list of chronic diseases and presumption of tuberculosis
	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947	Within 1 year after separation from active wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic Disease:** Manifestations sufficient to identify the disease entity and sufficient	**Factual Basis:** Established by medical evidence, competent lay evidence, or both

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					observations to establish chronicity at the time	
	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301 (3 and 4). 71 Stat. 83, 95	June 17, 1957	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947	Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period	Summarizes previous rules and legislation and amends dates/location of service and presumption

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Disease subject to presumptive service connection. *Federal Register* 26(36):1581-1582	February 24, 1961	Disease contracted during active military, naval, or air service			Lays out criteria for presumption wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence, competent lay evidence or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from service	
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					December 31, 1946 **Chronic:** Manifest to degree of 10 percent or more within 1 year (for Hansen's disease; and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service	
	38 CFR 3.309		Military service	**Chronic Diseases:** On or after January 1, 1947, following service in a period of war or peacetime service	**Chronic Diseases:** See section 3.307 above	
Pupura idiopathic (hemorrhagic)	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(197): 6174-6180. Former 38 CFR Sec. 3.86 (a)	October 12, 1949	Military service			Amends list of chronic diseases

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Sarcoidosis	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 15(169):5902-5910. Former 38 CFR	August 31, 1950	Disease contracted during military service	See Veterans Regulation 1 (38 USC Ch. 12)	See Veterans Regulation 1 (38 USC Ch. 12)	Added to list of chronic and tropical diseases
Tuberculous (active)	Veterans' Bureau. Public Law 67-47. 1921. 67th Cong., 1st Sess. Ch. 57, Sec. 18, 42 Stat. 147, 153	August 9, 1921	Disease contracted during active military service during service	On or after April 6, 1917 Or discharged or resigned active service on or before November 11, 1918	Within 2 years after separation from active military or naval service Characteristic manifestations of the disease to 10 percent or more	March 4, 1923, Act expanded the presumption to include all forms of tuberculosis
	Executive Order 6089. Instruction No. 2, Implementing Vet. Reg. No. 1. April 12, 1933	April 12, 1933			**Tuberculosis:** Manifest to a degree of 10 percent within 1 year of discharge; second-year diagnoses presumptive if at 6 months for minimal cases, 9 months moderately advanced cases,	Amends list of chronic diseases and presumption of tuberculosis

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					and 12 months far advanced cases	
	Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess. Ch. 612, Sec 1, 62 Stat. 581.	June 24, 1948	Disease contracted during active service	Within 1 year after separation from active service or at a time when standard and accepted treatises indicate that the incubation period thereof commenced during active service	At least 6 months of service and honorably discharged	
	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947	Within 1 year after separation from active wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic Disease:** Manifestations sufficient to identify the disease entity and sufficient observations to	**Factual Basis:** Established by medical evidence, competent lay evidence, or both **Pulmonary Tuberculosis:** Specific assumptions for diagnosis in second year after service

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					establish chronicity at the time	
	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301(3 and 4). 71 Stat. 83, 95	June 17, 1957	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947	Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period	Summarizes previous rules and legislation and amends dates/location of service and presumption
	Disease subject to presumptive	February 24, 1961	Disease contracted during active military,			Lays out criteria for presumption

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	service connection. *Federal Register* 26(36):1581-1582.		naval, or air service			wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence, competent lay evidence or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from service	
	Pension, compensation, and dependence and indemnity. Final regulation. *Federal Register* 43(191):45347-45362. 38 CFR Part 3	October 2, 1978			Removes the presumptive period of 6, 9, and 12 months for minimally, moderately, and far advanced tuberculosis to:	Amends presumptive period

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					Developing within 3 years from the date of separation from active service	
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Chronic:** Manifest to degree of 10 percent or more within 1 year (for Hansen's disease; and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service	
	38 CFR 3.309		Military service	**Chronic Diseases:** On or after January 1, 1947, following service in a period of war or peacetime service	**Chronic Diseases:** See section 3.307 above	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	38 USC § 1112	Approved February 27, 2006	Active military service	Veteran who served for 90 days or more during a period of war	**Chronic Disease:** Disease manifest to 10 percent or more within 1 year from separation of such service **Tuberculous Disease (active) and Hansen's Disease:** Disease manifest to 10 percent or more within 3 years from separation of such service	
Ulcers, peptic (gastric or duodenal)	Veterans' Bureau Schedule of Disability Ratings Extension 6	November 2, 1928			Manifest within 6 months from discharge from military service and shown present within 1 year after discharge	Establishes service connection for ulcers
	Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess. Ch. 612, Sec 1, 62 Stat. 581	June 24, 1948	Disease contracted during active service		At least 6 months of service and honorably discharged Within 1 year after separation from active	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					service or at a time when standard and accepted treatises indicate that the incubation period thereof commenced during active service	
	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947 **Ulcer (peptic):** within 6 months form date of active service or within 6 months of July 25, 1947; or more than 6 months then evidence of continuity of characteristic symptoms during the first 6 months after termination of active service	Within 1 year after separation from active wartime service Within 1 year after the date prior to which a disability must have been incurred **Chronic disease:** Manifestations sufficient to identify the disease entity and sufficient observations to establish chronicity at the time	**Factual Basis:** Established by medical evidence, competent lay evidence, or both
	Veterans' Benefits Act of	June 17, 1957	Disease contracted during active military,	Veteran who engaged in	Within 1 year after separation	Summarizes previous rules and

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301(3 and 4). 71 Stat. 83, 95.		naval, or air service	combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947	from active service or when standard and accepted treatises indicate incubation period	legislation and amends dates/location of service and presumption
	Disease subject to presumptive service connection. *Federal Register* 26(36):1581-1582	February 24, 1961	Disease contracted during active military, naval, or air service			Lays out criteria for presumption wartime service connection for chronic or tropical disease

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						Factual Basis: May be established by medical evidence, competent lay evidence, or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Chronic Diseases:** Manifest to a degree of 10 percent or more within 1 year for Hansen's disease (leprosy) and tuberculosis within 3 years; multiple sclerosis within 7 years from date of separation from service	
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Chronic:** Manifest to degree of 10 percent or more	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					within 1 year (for Hansen's disease; and tuberculosis within 3 years; multiple sclerosis within 7 years) from separation of service	
	38 CFR 3.309		Military service	**Chronic Diseases:** On or after January 1, 1947, following service in a period of war or peacetime service	**Chronic Diseases:** See section 3.307 above	
Preexisting chronic disease before entry into service. Assumption any disease considered chronic because does not specify diseases	Service connection by presumption of aggravation of a chronic preexisting disease. Final rule. *Federal Register* 67(216):67792-67793. 38 CFR Part 3	November 7, 2002	Military service		**Chronic Disease:** Manifests to a 10 percent degree of disability within a specified period after service. Aggravated by the veteran's military service	Made ruling based on the decision of the United States Court of Appeals for the Federal Circuit. Splane v. West, 216 F. 3d 1058 (2000) Amends 38 CFR Part 3
Tropical Diseases						
• Malaria	VA Circular No. 8, section I	December 28, 1945	Disease contracted during active service		Within 1 year after separation of active service military service	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Dysentery (amebic, bacillary) • Filariasis (Bancroft's type) • Leishmaniasis (including kala-azar) • Malaria • Schistosomiasis • Trypanosomiasis • Yaws	Disability ratings for malaria and chronic diseases characteristically tropical in origin. *Veterans Administration Technical Bulletin 8-6.* Washington, DC: VA	January 3, 1947	Disease contracted during wartime service	Service in the tropics or a place having a high incidence of the disease under consideration	Within 1 year after separation of active wartime service	Relapses of malaria (after the 1 year separation) need others, under oath to establish frequency of relapse over a period of time relating back to the 1-year period following discharge
• Black water fever • Cholera • Dracontiasis • Dysentery • Filariasis • Leishmaniasis • Leprosy • Loiasis • Malaria • Onchocerciasis • Oroya fever • Pinta • Plague • Schistosomiasis • Yaws • Yellow fever	Act of June 24, 1948. Public Law 80-748. 80th Cong., 2d Sess. Ch. 612, Sec 1, 62 Stat. 581	June 24, 1948	Disease contracted during active service		At least 6 months of service and honorably discharged Within 1 year after separation from active service or at a time when standard and accepted treatises indicate that the incubation period thereof commenced during active service	
	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims;	February 9, 1949	Disease contracted during military service	Wartime service prior to January 1, 1947, to July 25, 1947	Within one year after separation from active wartime service	**Factual Basis:** Established by medical evidence, competent lay evidence, or both

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	miscellaneous amendments. *Federal Register* 14(26):568-578. Former 39 CFR Sec. 3.80; Sec. 3.86 (a), 3.95			**Tropical Diseases:** Service in the tropics or a place having a high incidence of the disease under consideration	Within 1 year after the date prior to which a disability must have been incurred **Tropical Disease:** When shown to exist at a time when standard and accepted treatises indicate that the incubation period of the diseases commenced during active service Characteristic manifestations of the disease to 10 percent or more, except pulmonary tuberculosis	
• Amebiasis	Pensions, bonuses, and veterans' relief. Part 3: Veterans' claims; miscellaneous amendments. *Federal Register*	August 31, 1950	Disease contracted during military service	See Veterans Regulation 1 (38 USC Ch. 12)	See Veterans Regulation 1 (38 USC Ch. 12)	Added to list of chronic and tropical diseases

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	15(169):5902-5910. Former 38 CFR					
	Veterans' Benefits Act of 1957. Public Law 85-56. Sec. 301. 85th Cong., 1st Sess. Sec 301(3 and 4). 71 Stat. 83, 95	June 17, 1957	Disease contracted during active military, naval, or air service	Veteran who engaged in combat with the enemy in active service with a military, naval, or air organization of the U.S. during a period of war, campaign, or expedition Period of service after November 11, 1918, and before July 2, 1921, if served after April 5, 1917, and before November 12, 1918 Period after December 31, 1946, and before July 26, 1947, if period began before January 1, 1947	**Tropical Diseases:** Serves 6 months or more and contracts tropical or disease because of therapy in connection with tropical disease Within 1 year after separation from active service or when standard and accepted treatises indicate incubation period	Summarizes previous rules and legislation and amends dates/location of service and presumption
	Disease subject to presumptive	February 24, 1961	Disease contracted during active military,			Lays out criteria for presumption

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	service connection. *Federal Register* 26(36):1581-1582		naval, or air service			wartime service connection for chronic or tropical disease **Factual Basis:** May be established by medical evidence, competent lay evidence or both
	Pensions, bonuses, and veterans' relief. Part 3: Adjudication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service	Service of 90 days or more during a war period on or after January 31, 1955	**Tropical Diseases:** Manifest to a degree of 10 percent or more within 1 year from date of separation from service or at a time when standard treatises indicate that the incubation period commenced during such service	
	Increase of disability compensation and dependency and indemnity compensation rates. *Federal Register*	September 26, 1974	Active service on or after January 1, 1947 **Tropical Before January 1, 1947:** Veteran with 6 or months of service	Service of 90 days or more during a war period on or after December 31, 1946	**Tropical Before January 1, 1947:** Manifest to a degree of 10 percent or more within 1 year after separation from active service or	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	39(188):34529-34533. 38 CFR Part 3				at a time when standard and accepted treatises indicate that the incubation period commenced during active service	
• Hansen's disease	Increased disability compensation and dependency and indemnity compensation; burial benefits. *Federal Register* 41(248):55872-55875. 38 CFR Part 3	December 23, 1976			**Tropical Diseases:** Tropical service following service in a period of war or following peacetime service	Used term Hansen's disease instead of leprosy
All tropical diseases listed.	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Tropical:** Manifest to a degree of 10 percent or more within 1 year	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					from separation of service or time when standard accepted treatises indicate incubation period; diseases resulting from therapy administered	
	38 CFR 3.309		Military service		**Tropical Diseases:** See section 3.307 above	
	38 USC § 1112	Approved February 27, 2006	Active military service **Tropical Disease:** Disorders or disease originating because of therapy, administered in connection with such disease, or as a preventative	Veteran who served for 90 days or more during a period of war	**Tropical Disease:** Disease manifest to 10 percent or more within 1 year from separation of such service Or Standard or accepted incubation periods **Hansen's Disease:** Disease manifest to 10 percent or more within 3 years from separation of such service	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Prisoner of War Diseases						
• Avitaminosis • Beriberi (including beriberi heart disease) • Chronic dysentery • Helminthiasis • Malnutrition (including optic atrophy associated with malnutrition) • Other nutritional deficiency • Pellagra • Psychosis	Public Law 91-376. Sec. 3. 91st Cong., 2d Sess., 1970. Sec 3. 84 Stat. 787, 788	August 12, 1970	Active military, naval, or air service and was held prisoner of war	Held by Imperial Japanese government or the German government during World War II, government of North Korea during the Korean conflict, or the government of North Vietnam, or the Viet Cong during the Vietnam era	Detained or interned for not less than 6 months Characteristic manifestations of the disease (except psychosis) to 10 percent or more after service **Psychosis:** Characteristic manifestations of the disease to 10 percent or more within 2 years after separation from service	Service connection presumption for former prisoners of war
	Pensions, bonuses, and veterans' relief. Part 3: Adjud-ication. Subpart A: Pension, compensation, and dependency and indemnity compensation. *Federal Register* 35(232):18280-18283. 38 CFR Part 3	December 1, 1970	Active service **Former Prisoners of War:** Held by an enemy government or its agents during WWII, Korean conflict, or the Vietnam era, suffered from dietary deficiencies, forced labor, or inhumane treatment	Service of 90 days or more during a war period on or after January 31, 1955	**Prisoners of War:** Manifest to a degree of 10 percent or more at any time after service, **except** psychosis, 10 percent within 2 years from date of separation from service	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Any of the anxiety states	Increase of disability compensation and dependency and indemnity compensation rates. *Federal Register* 39(188):34529-34533. 38 CFR Part 3	September 26, 1974	Active service on or after January 1, 1947	Service of 90 days or more during a war period on or after December 31, 1946		
	Former Prisoner of War Benefits Act of 1981. Public Law 97-37. 97th Cong., 1st Sess. Sec 4. 95 Stat. 935, 936	August 14, 1981	Former prisoner of war	While serving in active military, naval, or air service, was forcibly detained or interned in line of duty by an enemy government or its agents, or a hostile force during a period of war	Characteristic manifestations of the disease to 10 percent or more after service Detained or interned for not less than 30 days	Amends list of associated diseases of former prisoners of war The previous prisoner of war presumption is for the period of time not less than 6 months. This act changes that period of time to not less than 30 days
	Veterans Benefits; Former Prisoners of War. Final regulations. *Federal Register* 47(53):11655-11656. 38 CFR Part 3	March 18, 1982	Former prisoner of war	While serving in active military, naval, or air service, was forcibly detained or interned in line of duty by an enemy government or its	Characteristic manifestations of the disease to 10 percent or more after service Detained or interned for not less than 30 days	Implementing the new Former Prisoner of War Benefits Act of 1981 Amended period of detainment for presumption of

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				agents, or a hostile force during a period of war on or after January 1, 1947		disease
• Dysthymic disorder (or depressive neurosis)	Veterans' Compensation and Program Improvements Amendments of 1984, Public Law 98-223. 98th Cong., 2d Sess. Sec. 111 98 Stat. 37, 40	March 2, 1984	Prisoner of war			Amends list of diseases associated with former prisoner of war
• Organic residuals of frostbite • Posttraumatic osteoarthritis	Veterans' Benefits Improvements and Health-Care Authorization Act of 1986. Public Law 99-576. 99th Cong., 2d Sess. Sec 108. 100 Stat. 3248, 3252	October 28, 1986	Former prisoner of war			Amends list of associated diseases of former prisoners of war
• Irritable bowel syndrome • Peptic ulcer disease • Peripheral neuropathy (except where directly related to infectious causes)	Veterans' Benefits and Services Act of 1988. Public Law 100-322. 100th Cong., 2d Sess. Sec 312, 313. 102 Stat. 487, 535	May 20, 1988	Prisoner of war			Amended list of diseases related to Former prisoners of war and service connection of chronic diseases
• Cirrhosis of the liver	Presumption of	February 10,	Former prisoners of		Detained for at	Amended list of

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	service connection for cirrhosis of the liver in former prisoners of war. Proposed rule. *Federal Register* 68(27):6679-6680. 38 CFR Part 3	2003	war Evidence: Significantly higher risk of death from cirrhosis in former WWII prisoners of war than the general population		least 30 days	diseases associated with prisoners of war
	Presumption of service connection for cirrhosis of the liver in former prisoners of war. Final rule. *Federal Register* 68(138):42602-42603. 38 CFR Part 3	July 18, 2003				No change from proposed rule
	Veterans Benefits Enhancement Act of 2003 S. Rep. No. 108-169 108th Cong. 1st Sess. 11 **(proposed Act)**	October 21, 2003	Former prisoners of war veteran active military, naval, or air service	Former prisoner of war	Disease to manifest to a degree of 10 percent or more after active service	Proposed act that would amend the diseases associated with former prisoners of war
	Veterans Benefits Act of 2003. Public Law 108-183. 108th Cong.,	December 16, 2003			Detained or interned for not less than 30 days (for following	No change from proposed act

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	1st Sess., Sec. 201. 117 Stat. 2651				diseases: any other nutritional deficiency, avitaminosis, beriberi, chronic dysentery, cirrhosis of the liver, helminthiasis, irritable bowel syndrome, malnutrition, pellagra, peptic ulcer disease, peripheral neuropathy)	
• Atherosclerotic disease or Hypertensive vascular disease (including hypertensive heart disease and their complications [including myocardial infarction, congestive heart failure, arrhythmia]) • Stroke and its complications	Presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. Interim final rule. *Federal Register* 69(194):60083-60090. 38 CFR Parts 1 and 3	October 7, 2004	Former prisoner of war		Eliminated the 30-day detained requirement for psychosis, any anxiety state, dysthymic disorders, organic residuals of frostbite, and posttraumatic osteoarthritis The new diseases in this rule are presumed to be service connected following any period of prisoner-of-war	Amended diseases associated with former prisoner of war and amended the 30-day requirement for some of the related diseases Defines the evidence necessary to determine presumption of service connection

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					activity	
	Presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. Affirmation of interim final rule as final rule. *Federal Register* 70(123):37040-37042. 38 CFR Parts 1 and 3	June 28, 2005				Final rule without change from October 7, 2004 interim rule
• Diabetes (type 2) • Heart disease • Osteoporosis • Stroke	Prisoner of War Benefits Act of 2005 **(proposed act)**. 109th Cong. 1st Sess. Senate Bill 1271	June 20, 2005	Former prisoners of war			Proposed act to amend the list of diseases associated with former prisoners of war
	38 CFR 3.307		Former prisoners of war Military service		Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					Former Prisoners of War: Manifest to a degree of 10 percent or more after discharge or release for active service	
	38 CFR 3.309		Former prisoner of war		**Former Prisoner of War:** Manifest to a degree of 10 percent or more after release or discharge from active military, naval, or air service Prisoner of war associated diseases: not less than 30 days as a prisoner of war (for the following diseases: any other nutritional deficiency, avitaminosis, beriberi, chronic dysentery, cirrhosis of the liver, helminthiasis, irritable bowel	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					syndrome, malnutrition, pellagra, peptic ulcer disease, peripheral neuropathy)	
	38 USC § 1112	Approved February 27, 2006	Active military service	Veteran who served for 90 days or more during a period of war **Prisoner of War Associated Diseases:** Not less than 30 days as a prisoner of war (for the following diseases: any other nutritional deficiency, avitaminosis, beriberi, chronic dysentery, cirrhosis of the liver, helminthiasis, irritable bowel syndrome, malnutrition, pellagra, peptic ulcer disease, peripheral neuropathy)	**Prisoner of War:** Disease manifest to 10 percent or more after active military, naval, or air service	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Diseases Associated with Service Amputation						
Ischemic heart disease (or other cardiovascular disease)	Pension, compensation, and dependency and indemnity compensation, proximate results, secondary conditions. *Federal Register* 44(168):50339-50340. 38 CFR Part 3, Sec. 3.310	August 28, 1979	Service-connected amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles			
Diseases Associated with Herbicide Exposure						
• Chloracne	Adjudication of claims based on exposure to dioxin or ionizing radiation. Final rules. *Federal Register* 50(165):34452-34461. 38 CFR Parts 1 and 3	August 26, 1985	**Herbicide** • Dioxin (2,3,7,8 tetrachlorodibenzo -p-dioxin)	**Dioxin** Vietnam era	**Dioxin Exposure:** No later than 3 months from the date of exposure	**Dioxin:** Presumed to have been exposed if served in the Vietnam era
• Chloracne (or another acneform disease) • Non-Hodgkin's lymphoma • Soft tissue sarcoma	Agent Orange Act of 1981. Public Law 102-4. 102d Cong., 1st Sess. 105 Stat. 11	February 6, 1991	Active military, naval, or air service Exposure to herbicide agent containing dioxin or 2,4-dichlorophenoxyacetic acid or other chemical	Republic of Vietnam; Vietnam era	**Non-Hodgkin's Lymphoma and Soft Tissue Sarcoma (other than osteosarcoma, chondrosarcoma, kaposi's**	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
			compound in an herbicide agent		**sarcoma, or mesothelioma):** Manifest 10 percent or more disability **Chloracne:** 10 percent or more disability within 1 year after the last date active duty in Republic of Vietnam	
• Chloracne • Soft tissue sarcoma (adult fibrosarcoma; dermatofibrosarcoma protuberans; malignant fibrous histocytoma; liposarcoma; leiomyosarcoma; epithelioid leiomyosarcoma; rhabdomyosarcoma; ectomesenchymoma; angiosarcoma; proliferating angioendotheliomato-sis; malignant glomus tumor; malignant hemangiopericytoma; synovial sarcoma; malignant giant cell tumor of tendon sheath;	Claims based on exposure to herbicides containing dioxin (soft tissue sarcomas). Final regulation. *Federal Register* 56(199):51651-51653. 38 CFR Parts 3 and 4	October 15, 1991	Exposure to herbicides containing dioxin	Republic of Vietnam; Vietnam era	**Chloracne:** Manifested not later than 3 months from the date of exposure **Soft Tissue Sarcoma:** Manifest at any time after service	Lists diseases associated with exposure to herbicides containing dioxin

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
malignant schwannoma; malignant mesenchymoma; malignant granular cell tumor; alveolar soft part sarcoma; epithelioid sarcoma; clear cell sarcoma of tendons and aponeuroses)						
• Peripheral neuropathy	Claims based on exposure to herbicides containing dioxin (peripheral neuropathy/lung cancer). Proposed rule. *Federal Register* 57(13):2236-2238. 38 CFR Part 3	January 21, 1992	Herbicide (containing dioxin) exposure Military service	Military service	**Peripheral Neuropathy:** Manifested not later than 10 years following the date of exposure	Proposed rule amends diseases associated with exposure to herbicides containing dioxin **Diseases NOT Associated with Exposure to Herbicides (containing dioxin):** • Lung cancer • Porphyria cutanea tarda
• Hodgkin's disease • Porphyria cutanea tarda	Disease associated with exposure to certain herbicide agents. Final rule. *Federal Register* 59(23):5106-5107. 38 CFR Part 3	February 3, 1994	Herbicide agent exposure: specifically, 2,4-D; 2,4,5-T, and its contaminant TCDD; cacodylic acid; and picloram During active	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	Disease manifest to 10 percent or more at any time after service **Porphyria Cutanea Tarda:** 10 percent or more manifested	Amends list of diseases to other chronic, tropical, or prisoner-of-war related diseases or disease associated with exposure to certain herbicide agents; wartime and

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
			military, naval, or air service		within a year after the last date veteran was exposed to an herbicide agent during active military, naval, or air service	service on or after January 1, 1947
• Multiple myeloma • Respiratory cancers: Bronchus Larynx Lung Trachea	Disease associated with exposure to certain herbicide agents (multiple myeloma and respiratory cancers). Final rule. *Federal Register* 59(110):29723-29724. 38 CFR Part 3	June 9, 1994	Herbicide agent exposure During active military, naval, or air service	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	**Multiple Myeloma:** Disease manifest to 10 percent or more at any time after service **Respiratory Cancers:** Within 30 years after the last date on which the veteran was exposed to an herbicide agent during active military, naval, or air service	Amends list of diseases associated with chronic, tropical or prisoner of war, or exposure to certain herbicide agents
• Hodgkin's disease • Multiple myeloma • Porphyria cutanea tarda • Respiratory cancers: Bronchus Larynx Lung	Persian Gulf War Veterans' Benefits Act of 1994. Public Law 103-446. 103d Cong., 2d. Sess. 108 Stat. 4645	November 2, 1994	Herbicide agent exposure During active military, naval, or air service		**Hodgkin's Disease and Multiple Myeloma:** Manifest to 10 percent disability or more	Codified these diseases to the list of herbicide-exposure presumptions

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Trachea					**Porphyria Cutanea Tarda:** 10 percent or more manifested within a year after the last date veteran was exposed to an herbicide agent during active military, naval, or air service **Respiratory Cancers:** Within 30 years after the last date on which the veteran was exposed to an herbicide agent during active military, naval, or air service	
• Acute and subacute peripheral neuropathy • Prostate cancer	Diseases associated with exposure to certain herbicide agents (prostate cancer and acute and subacute peripheral neuropathy). Final rule.	November 7, 1996	Herbicide agent exposure During active military, naval, or air service	Republic of Vietnam; Vietnam era And wartime and service on or after January 1, 1947	Manifest to 10 percent disability or more after service **Note: Acute and subacute peripheral neuropathy by definition** appears	Amends list of diseases associated with exposure to certain herbicide agents

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Federal Register 61(217):57586-57589. 38 CFR Part 3				within weeks or months of exposure to a herbicide agent and resolves within 2 years of the date of onset	
• Type 2 Diabetes	Disease associated with exposure to certain herbicide agents: Type 2 diabetes. Final rule. *Federal Register* 66(89):23166-23169. 38 CFR Part 3	May 8, 2001	Herbicide exposure	In the Republic of Vietnam during the Vietnam Era Or active military service	Illness manifest to a degree of 10 percent or more	Amends diseases associated to exposure to herbicides
• Diabetes mellitus (type 2) • Respiratory cancers	Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.	December 27, 2001	Herbicide exposure Military service Vietnam Veteran active service		***Herbicide Exposure*** **Additional Diseases:** Up to September 30, 2015 **Respiratory Cancers:** Presumptive period amended from "within 30 years" through "May 7, 1975"	Extension of presumptive period for respiratory cancers and additional diseases associated with herbicide exposure and Persian Gulf exposure
Amends date of presumption and exposure candidates	Compensation and pension provisions of the	June 10, 2003				**Herbicide Exposure:** Eliminates

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Veterans Education and Benefits Expansion Act of 2001. Final Rule. *Federal Register* 68(111):34539-34543. 38 CFR Parts 3 and 13					respiratory cancer, must manifest within 30 years of departure from Vietnam to qualify for presumption based on herbicide exposure and expand presumption of exposure to herbicides to all Vietnam veterans
• Chronic lymphocytic leukemia	Disease associated with exposure to certain herbicide agents: Chronic lymphocytic leukemia. Final rule. *Federal Register* 68(200):59540-59542. 38 CFR Part 3	October 16, 2003	Herbicide exposure Military service	Republic of Vietnam during the Vietnam era		Amends list of diseases associated with exposure to herbicide agents
• Type 2 diabetes	Change of effective date of rule adding a disease associated with exposure to certain herbicide agents: Type 2 diabetes. Final rule. *Federal Register*	June 8, 2004				Change of effective date of presumption to May 8, 2001

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	69(110):31882-31883. 38 CFR Part 3					
Presumptions of service connection for diseases associated with **exposure to certain herbicide agents**	38 USC § 1116	Approved February 27, 2006	Active military naval, or air service Herbicide agent (containing dioxin or 2,4-dichlorophenoxyacetic acid)	Republic of Vietnam (January 9, 1962, to May 7, 1975)	**Republic of Vietnam Diseases:** Manifest disease 10 percent disability or more In addition: **Porphyria cutanea tarda and Chloracne:** within 1 year from active military service	
Presumptive service connection for chronic, tropical, or prisoner-of-war related disease or disease associated with exposure to certain herbicide agents	38 CFR 3.307		Former prisoners of war Herbicide agent exposure (specifically 2,4, D; 2,4,5-T and its contaminant TCDD; cacodylic acid; and picloram) Military service	**Herbicide Agent Exposure:** Republic of Vietnam (January 9, 1962, to May 7, 1975) active military, naval, or air service (including the waters offshore and service in other locations involving duty or visitation in the Republic of Vietnam	Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946 **Herbicide Agent Exposure:** Manifest to a degree of 10 percent or more at any time after service except	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
					chloracne, porphyria cutanea tarda, and acute and subacute peripheral neuropathy manifest to a degree of 10 percent or more within 1 year after last date veteran was exposed to an herbicide agent	
	38 CFR 3.309		Military service Former prisoner of war		**Exposure to Herbicide Agents:** See section 3.307 above	
Radiogenic Disease						
• All forms of leukemia (except chronic lymphatic leukemia) • Cancer (bone, colon, esophageal, female breast, kidney, liver, lung, pancreatic, salivary gland, skin, stomach, thyroid, urinary bladder) • Multiple myeloma	Adjudication of claims based on exposure to dioxin or ionizing radiation. Final rules. *Federal Register* 50(165):34452-34461. 38 CFR Parts 1 and 3	August 26, 1985	**Radiation** • Ionizing	**Ionizing** Hiroshima or Nagasaki, Japan (September 1945 until July 1946)	**Ionizing:** Leukemias and bone cancer must become manifest within 30 years after exposure; other forms of cancer must become manifest 5 years or more after exposure	**Ionizing:** Exposure at the highest level of the dose range estimated will be presumed; several factors to be considered in determining whether disease resulted from exposure during service
• Cancer (breast, salivary gland) • Leukemia (other than	Claims based on exposure to ionizing	October 18, 1989	Ionizing radiation		**Bone Cancer:** Manifest within 30 years after	Amended diseases considered to be radiogenic

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
chronic lymphatic [lymphocytic] leukemia) • Multiple myeloma • Nonmalignant thyroid nodular disease • Posterior subcapsular cataracts	radiation. Final regulations. *Federal Register* 54(200):42802-42803. 38 CFR Part 3				exposure **Leukemia:** Manifest any time after exposure **Posterior Subcapsular Cataracts:** Manifest 6 months or more after exposure **Other Diseases:** Manifest 5 years or more after exposure	Withdrew proposed clarification concerning when service connection can be established based upon claimed exposure to ionizing radiation and herbicides containing dioxin
Diseases Associated with Radiation Exposure						
• Cancer (bile ducts, breast, esophagus, gall bladder, pancreas, pharynx, primary liver, small intestine, stomach, thyroid) • Leukemia (other than chronic lymphocytic leukemia) • Lymphomas (except Hodgkin's disease) • Multiple myeloma	Radiation-Exposed Veterans Compensation Act of 1988. Public Law 100-321. 100th Cong., 2d Sess., Section 2, 102 Stat. 485	May 20, 1988	Radiation-risk activity • Participation in a test involving atmospheric detonation of a nuclear device • Occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946) • Prisoner of war in Japan during WWII exposure of ionizing radiation	Japan WWI August 6, 1945, to July 1, 1946 Others	40-year period beginning on the last date where the veteran participated in a radiation-risk activity **except leukemia** (30-year period after radiation-risk activity)	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Radiation Exposure Compensation Act of 1990. Public Law 101-426. 101st Cong., 2d Sess., 104 Stat. 920	October 15, 1990	Radiation exposure • Above-ground nuclear tests • Uranium miners	Government's above-ground nuclear tests in Nevada and lived downwind in Nevada, Utah, and Arizona Underground uranium mines	Childhood leukemia and other diseases (January 21, 1951, to October 31, 1958; or June 30, 1962, to July 31, 1962) For miners: Any individual who was employed in a uranium mine located in Colorado, New Mexico, Arizona, Wyoming, or Utah at any time during the period beginning on January 1,1947, and ending on December 31, 1971	Individuals not in military • Uranium miners • Downwind to nuclear tests
Leukemia (presumptive period)	Veterans' Benefits Programs Improvement Act of 1991. Public Law 102-86. 102d Cong., 1st Sess., Sec. 104, 105. 105 Stat. 414	August 14, 1991	Radiation exposure	Amends service to during active military, naval, or air service or reserve component of the Armed Forces, participated in a radiation-risk activity during a		Amends presumptive period for occurrence of leukemia and location of radiation exposure

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				period of active duty for training or inactive duty training		
• Cancer of the: salivary gland urinary tract	Veterans' Radiation Exposure Amendments of 1992. Public Law 102-578. 102d Cong., 2d Sess., Sec 2. 106 Stat. 4774	October 30, 1992	Radiation exposure			Adds diseases to the list associated with exposure to radiation and elimination of latency-period limitations
• Ovarian cancer • Parathyroid adenoma	Claims based on exposure to ionizing radiation. Final rule. *Federal Register* 58(57):16358-16359. 38 CFR Part 3	March 26, 1993	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
	Radiation Exposure Compensation Act of 1990. Final Rule. *Federal Register* 58(79):25564-25565. 38 CFR Part 3	April 27, 1993				Establishes compensation to any individual under the provisions of the Radiation Exposure Compensation Act of 1990
• Tumors of the brain and central nervous system	Claims based on exposure to ionizing	September 6, 1994	Ionizing radiation			Amended diseases associated with exposure to ionizing

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	radiation. Final rule. *Federal Register* 59(171):45975. 38 CFR Part 3					radiation
• Cancer of the rectum • Lymphomas other than Hodgkin's disease	Claims based on exposure to ionizing radiation (lymphomas other than Hodgkin's disease and cancer of the rectum). Final rule. *Federal Register* 60(198):53276-53277. 38 CFR Part 3	October 13, 1995	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
• Prostate cancer • Any other cancer	Claims based on exposure to ionizing radiation (prostate cancer and any other cancer). Final rule. *Federal Register* 63(185):50993-50995. 38 CFR Part 3	September 24, 1998	Ionizing radiation			Amends diseases associated with exposure to ionizing radiation
Nuclear Atmospheric Testing: • Brain cancer • Colon cancer	Radiation Exposure Compensation Act Amendments	July 10, 2000	Nuclear atmospheric testing Uranium mining	**Leukemia:** Physically present in affected area for at least 1 year	**Lung Cancer:** Onset of disease at least 2 years after first	Amends list of diseases associated to radiation exposure and

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Gall bladder cancer • Male breast cancer • Ovary cancer • Salivary gland cancer • Urinary bladder cancer **Uranium Mining** • Lung cancer • Nonmalignant respiratory disease • Renal cancers • Other chronic renal disease (nephritis, kidney tubal tissue injury)	of 2000. Public Law 106-245. 106th Cong., 2d Sess. 114 Stat. 501			January 21, 1951, through October 31, 1958; or June 30, 1962, through July 31, 1962	exposure	manifestation of diseases Amends dates/location of service for leukemia
• Bronchiolo-alveolar carcinoma	Veterans Millennium Health Care and Benefits Act. Final rule. *Federal Register* 65(136):43699-43700. 38 CFR Part 3	July 14, 2000	Active military service Radiation exposure			Amended list of diseases related to exposure to radiation and active service
• Polycythemia vera	Claims based on exposure to ionizing radiation. Final rule. *Federal Register* 67(31):6870-	February 14, 2002	Radiation exposure Ionizing			Amends diseases from exposure to ionizing radiation; VA did not have evidence to add to the list of "radiogenic

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	6871. 38 CFR Part 3					diseases," but the VA will consider a claim that polycythemia vera is a radiogenic disease as long as there is scientific or medical evidence to support the claim
All diseases listed above	38 USC § 1112	Approved February 27, 2006	Active military service **Radiation-Exposed Veteran:** Radiation-risk activity	Veteran who served for 90 days or more during a period of war **Radiation-Exposed Veteran:** Participation in a test involving atmospheric detonation of a nuclear device; Occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946); Internment as a prisoner of war in Japan or service on active duty in Japan following	**Radiation-Exposed Veterans:** Disease manifest after active military, naval, or air service	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				such internment during WWII with opportunity for exposure to ionizing radiation; or Performed as an employee of the DOE		
All diseases listed above	38 CFR 3.309		Military Service **Radiation-Exposed Veteran:** Serving active duty or Armed Forces active duty or training or inactive duty training and participated in a "radiation-risk activity"	**Radiation-Exposed Veteran:** • Participation in test atmospheric detonation of nuclear device • Occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946) • Prisoner of War in Japan exposure of ionizing radiation comparable to above exposure • Total of 250 days before	Wartime and service on or after January 1, 1947 90 days or more during a war period or after December 31, 1946	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				February 1, 1992, on grounds of gaseous diffusion plant (Paducah, KY; Portsmouth OH; K25 Oak Ridge, TN) • Service before January 1, 1974 on Amchitka Island, Alaska, and exposed to underground nuclear tests at Long Shot, Milrow, or Cannikin		
• Cancer of the bone, breast, colon, esophageal, kidney, liver, lung, ovarian, pancreatic, prostate, rectum, salivary gland, skin, stomach, thyroid, urinary bladder, any other cancer • Nonmalignant	38 CFR 3.311		Ionizing radiation Service	Occupation of Hiroshima or Nagasaki, Japan (September 1945 to July 1946) or other activities where they participated in atmospheric testing of nuclear weapons	Manifest 5 years or more after exposure **Bone Cancer:** Manifest within 30 years after exposure **Leukemia:** Manifest any time	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
thyroid nodular disease • Parathyroid adenoma • Posterior subcapsular cataracts • Tumors of the brain and central nervous system					after exposure **Posterior Subcapsular Cataracts:** Manifest 6 months or more after exposure	
Diseases Associated with Vietnam Service						
• Non-Hodgkin's lymphoma	38 CFR 3.313		Service in Vietnam	Service in Vietnam during the Vietnam Era	Subsequent to service	
	Claims based on service in Vietnam. Final regulations. *Federal Register* 55(208):43123-43125. 38 CFR Parts 3 and 4	October 26, 1990	Service in Vietnam	Vietnam (includes waters offshore, or service in other locations if the conditions of service involved duty or visitation in Vietnam During the Vietnam era		
• Chloracne • Congenital and	Republic of Vietnam. Final	May 19, 1993	Wartime and service in the Republic of	On or after January 1, 1947	Disease manifest to 10 percent or	"Service in the Republic of

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
infantile fibrosarcoma • Extraskeletal Ewing's sarcoma • Malignant ganglioneuroma • Soft tissue sarcoma (see October 19, 1991)	rule. *Federal Register* 58(95):29107-29109. 38 CFR Part 3 3.309(e)		Vietnam		more at any time after service **Except: Chloracne (or another acneform disease):** 10 percent or more within a year after the last date veteran performed active military, naval, or air service in the Republic of Vietnam	Vietnam" includes service in the waters offshore and service in other locations if the conditions of service involved duty or visitation in the Republic of Vietnam
Expansion of Period of Vietnam Era for Certain Veterans	Veterans' Benefits Improvements Act of 1996 Public Law 104-275. 104th Cong., 2d Sess., Sec. 1711	October 9, 1996			"Vietnam era" • For a Veteran who served in the Republic of Vietnam—February 28, 1961, to May 7, 1975 • In all other cases—August 5, 1964, to May 7, 1975	
Vietnam era inclusion dates	Veterans' Benefits Improvements	July 1, 1997		"Vietnam era" February 28, 1961, to May 7,		

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Act of 1996, Final rule. *Federal Register* 62(126):35421-35423. 38 CFR Part 3			1975, inclusive who served in the Republic of Vietnam		
• Diabetes mellitus (type 2) • Hodgkin's disease • Multiple myeloma • Porphyria cutanea tarda • Respiratory cancers (bronchus, larynx, lung, or trachea)	38 USC § 1116	Approved February 27, 2006	Active military naval, or air service Herbicide agent (containing dioxin or 2,4-dichlorophenoxyacetic acid)	Republic of Vietnam (January 9, 1962, to May 7, 1975)	**Republic of Vietnam Diseases:** Manifest disease 10 percent disability or more In addition: **Porphyria cutanea tarda and chloracne:** within 1 year from active military service	Amends list of diseases associated with Vietnam service
Diseases Associated with Exposure to Mustard Gas						
• Asthma • Bronchitis • Conjunctivitis • Corneal opacities • Emphysema • Keratitis • Laryngitis	Claims based on chronic effects of exposure to mustard gas. Proposed rule. *Federal Register* 57(10):1699-1700. 38 CFR Part 3	January 15, 1992	Mustard gas exposure by participating in full-body, field, or chamber experiments to test protective clothing or equipment	During World War II; participating in full-body, field, or chamber experiments to test protective clothing or equipment	Chronic forms of the diseases manifested after exposure	Proposed rule for chronic effects of in-service exposure to mustard gas
	Claims based on chronic effects of exposure to mustard gas.	July 31, 1992				No change from proposed rule

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Final rule. *Federal Register* 57(148):33875-33877. 38 CFR Part 3					
Nitrogen or sulfur mustard: • Cancers: carcinoma of the skin, lung, laryngeal, nasopharyngeal, squamous cell • Chronic conjunctivitis • Corneal opacities • Keratitis • Scar formation **Nitrogen or sulfur mustard or Lewisite:** • Chronic form of: asthma, bronchitis, emphysema, laryngitis • Chronic obstructive pulmonary disease **Nitrogen mustard:** • Acute nonlymphocytic leukemia	38 CFR 3.316		Exposure to nitrogen or sulfur mustard or Lewisite	Active military service		
Diseases Associated with Service						
• Posttraumatic stress disorder	Direct service connection (post-	May 19, 1993	Military service	Military service or former prisoner		Amends list of diseases associated

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	traumatic stress disorder). Final rule. *Federal Register* 58(95):29109-29110. 38 CFR Part 3		Stressor actually occurred in service (engaged in combat or evidence of the claimed in service stressor) or prisoner of war experience	of war		with military service
• Bronchiolo-alveolar carcinoma	Veterans Millennium Health Care and Benefits Act of 1999. Public Law 106-117. 106th Cong., 1st Sess., Sec. 503. 113 Stat. 1545	November 30, 1999	Disease contracted during military service			
Diseases Associated with Chronic Effects of Exposure to Mustard Gas or Lewisite During Military Service						
Nitrogen or Sulfur Mustard (38 CFR 3.316[a][1]) • Chronic conjunctivitis • Corneal opacities • Keratitis • Laryngeal cancer • Lung cancer (except mesothelioma) • Nasopharyngeal cancer • Scar formation • Squamous cell carcinoma of the skin	Claims based on chronic effects of exposure to vesicant agents. Proposed rule. *Federal Register* 59(15):3532-3534. 38 CFR Part 3	January 24, 1994	Mustard gas and other vesicant agents Full-body exposure to nitrogen or sulfur mustard or Lewisite Active military service	**Conjunctivitis, Keratitis, Corneal Opacities, Scar Formation, or the Following Cancers: Nasopharyngeal, Laryngeal, Lung (except mesothelioma), or Squamous Cell Carcinoma of the Skin:** Full-body exposure to nitrogen or sulfur mustard	Chronic manifestation of the diseases after military service and either full-body exposure to nitrogen or sulfur mustard gas or Lewisite	Amends regulation concerning chronic diseases from exposure to mustard gas and other vesicant agents in response to NAS report

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Nitrogen or Sulfur Mustard or Lewisite (38 CFR 3.316[a][2]) • Asthma • Chronic form of bronchitis • Chronic form of laryngitis • Chronic obstructive pulmonary disease • Emphysema **Nitrogen Mustard (38 CFR 3.316[a][3])** • Acute nonlymphocytic leukemia	Claims based on chronic effects of exposure to mustard gas or lewisite. Final rule. *Federal Register* 59(159):42497-42500. 38 CFR Part 3	August 18, 1994		**Laryngitis, Bronchitis, Emphysema, Asthma, or Chronic Obstructive Pulmonary Disease:** Full-body exposure to nitrogen or sulfur mustard or Lewisite **Acute nonlymphocytic leukemia:** Full-body exposure to nitrogen mustard		Final rule based on NAS study and regulation on July 31, 1992, establishing service connection from exposure from field or chamber experiments during WWII. No change from proposed rule
Diseases Associated with Undiagnosed Illnesses During the Persian Gulf War						
Undiagnosed Illness Signs or Symptoms of: • Abnormal weight loss • Cardiovascular signs or symptoms • Fatigue • Gastrointestinal signs or symptoms • Headache • Joint pain • Menstrual disorders • Muscle pain	Compensation for certain undiagnosed illnesses. Proposed rule. *Federal Register* 59(235):63283-63285. 38 CFR Part 3	December 8, 1994	Active military, naval, or air service	Southwest Asia theatre during the Persian Gulf War (Iraq, Kuwait, Saudi Arabia, neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf,	Chronic (6 months or more) disability resulting in one or more signs and symptoms and manifested either during active service or to a 10 percent degree or more no later than 2 years after the date the veteran last performed	

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Neurologic signs or symptoms • Neuropsychological signs or symptoms • Signs or symptoms involving skin • Signs or symptoms involving the respiratory system (upper or lower) • Sleep disturbances				the Arabian Sea, the Red Sea, and the airspace above these locations	active service in the Southwest Asia theater of operations during the Persian Gulf War	
	Compensation for certain undiagnosed illnesses. Final rule. *Federal Register* 60(23):6660-6666. 38 CFR Part 3	February 3, 1995				Final rule for undiagnosed illnesses during service in the Persian Gulf War
	Compensation for certain undiagnosed illnesses. Interim rule with request for comments. *Federal Register* 62(82):23138-23139. 38 CFR Part 3	April 29, 1997	Persian Gulf War service		Interim rule extending the period of disease to manifest from "two years after the date on which the veteran last performed active military, naval, or air service in the Southwest Asia theater of operations during the Persian Gulf War" to "December 31, 2001"	Interim rule to expand the period within diseases must manifest
	Compensation for certain	March 6, 1998			Extend the presumptive	Final rule for extending the

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	undiagnosed illnesses. Final rule. *Federal Register* 63(44):11122-11123. 38 CFR Part 3				period (to December 31, 2001) in such a manner that no Persian Gulf veterans with qualifying disabilities would be denied compensation (no specific dates)	presumptive period for Persian Gulf veterans
• Chronic multisymptom illness: chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome	Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.	December 27, 2001	Military service Vietnam Veteran active service ***Persian Gulf Exposure:*** Persian Gulf War service active military, naval, or air service	***Persian Gulf Exposure:*** Active duty in the Armed Forces in the Southwest Asia theater of operations during the Persian Gulf War	***Persian Gulf Exposure*** **Additional Diseases:** "On September 30, 2011"	Extension of presumptive period for respiratory cancers and additional diseases associated with herbicide exposure and Persian Gulf exposure Amended list of diseases associated with military service, Persian Gulf War
	Extension of the presumptive period for compensation for Gulf War veterans' undiagnosed illnesses. Interim	November 9, 2001	Persian Gulf War active military, naval, or air service	Veteran who served on active duty in the Southwest Asia theater during the Persian Gulf War	Undiagnosed illness manifest to a degree of 10 percent or more through December 31, 2006	Extension of presumptive period for compensation for Gulf War veteran's undiagnosed illnesses

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	final rule with request for comments. *Federal Register* 66(218):56614-56615. 38 CFR Part 3					
	Extension of the presumptive period for compensation for Gulf War veterans' undiagnosed illnesses. Final rule. *Federal Register* 67(249):78979-78980. 38 CFR Part 3	December 27, 2002		Southwest Asia theater of operations during the Persian Gulf War	Through December 31, 2006	Extends the period within which disabilities must become manifest for entitlement for compensation
	Compensation and pension provisions of the Veterans Education and Benefits Expansion Act of 2001. Final Rule. *Federal Register* 68(111):34539-34543. 38 CFR Parts 3 and 13	June 10, 2003				Amends what a "qualifying chronic disability" includes

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
	Extension of the presumptive period for compensation for Gulf War veterans. Interim final rule. *Federal Register* 7(242):75669-75672. 38 CFR Part 3	December 18, 2006		Southwest Asia theater of operations during the Persian Gulf War	Through December 31, 2011	Extends the period within which disabilities must become manifest for entitlement for compensation
	38 USC § 1117	Approved February 27, 2006	Active duty in the Armed Forces during the Persian Gulf War	Southwest Asia theater during the Persian Gulf War	Medical or scientific evidence and historical treatment of manifestation periods that have been established	
	38 USC § 1118	Approved February 27, 2006	Association with exposure to a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine	Service in the Armed Forces in the Southwest Asia theater of operations during the Persian Gulf War	Within a period (if any) that is prescribed in a regulation	
	38 CFR 3.317			Southwest Asia theater during the Persian Gulf War Southwest Asia theater includes	Manifest either during active military, naval, or air service or to a degree of 10 percent or more	Chronic disabilities for a period of 6 months or more or intermittent episodes of improvement and

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				Iraq, Kuwait, Saudi Arabia, neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, United Arab Emirates, Oman, Gulf of Aden, Gulf of Oman, Persian Gulf, Arabian Sea, Red Sea, and air space above these locations	not later than December 31, 2006	worsening over a 6-month period
Language for the National Academy of Sciences report for presumption of service connection for illnesses associated with service in the Persian Gulf War	Persian Gulf War Veterans Act of 1998. Public Law 105-277. 105th Cong., 2d Sess., Sec. 1601, 1602, 1603	October 21, 1998	Establishes service connection for illnesses associated with the Persian Gulf War Diseases having an association with exposure to a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine	Veteran who served on active duty in the Southwest Asia theater during the Persian Gulf War		
Diseases Associated with Radiation-Risk Activity						
• Cancer of the bone • Cancer of the brain	Diseases specific to radiation-exposed veterans.	August 8, 2001	Radiation-risk activity Ionizing radiation	Total of at least 250 days before February 1, 1992		Amends list of diseases associated with radiation-risk

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
• Cancer of the colon • Cancer of the lung • Cancer of the ovary	Proposed rule. *Federal Register* 66(153):41483-41485. 38 CFR Part 3		Military service	(Paducah, KY; Portsmouth, OH; K25 at Oak Ridge, TN)		activities and date/location of service
	Diseases specific to radiation-exposed veterans. Final rule. *Federal Register* 67(17):3612-3616. 38 CFR Part 3	January 25, 2002	Radiation-risk activity Definition: Participation in a test involving atmospheric detonation of a nuclear device; occupation of Hiroshima or Nagasaki, Japan (August 6, 1945, to July 1, 1946); or internment as a prisoner of war in Japan or service on active duty in Japan following such internment during WWII with opportunity for exposure to ionizing radiation	Service before January 1, 1974 (Amchitka Island, AL) and performance of duty related to Long Shot, Milrow, or Cannikin underground nuclear tests		Amends definition of radiation-risk activity
	Veterans Benefits Improvement Act of 2004. Public Law 108-454. 108th Cong., 2d Sess., Sec. 306. 118 Stat. 3598	December 10, 2004	Radiation-risk activity Ionizing Military service			Amended "radiation-risk activity" to include service in a capacity if performed as an employee of the DOE would qualify inclusion as a

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						member of the Special Exposure Cohort
Diseases or Death NOT Associated with Military Service						
Disease attributable to use of tobacco products	Claims based on the effects of tobacco products. Final rule. *Federal Register* 66(67):18195-18198. 38 CFR Part 3	April 6, 2001	Active military, naval, or air service			Veterans' use of tobacco products are NOT considered to be service connected
Miscellaneous						
Definitions: Veteran Spanish-American War World War I World War II Korean conflict Armed Forces Veteran of any war Service-connected Non-service-connected Active duty Active duty for training Inactive duty training Active military, naval, or air service Former prisoner of war Reserve Vietnam era Persian Gulf war	38 USC § 101	Approved February 27, 2006				

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
Death	38 USC § 108	Approved February 27, 2006			7-year absence	
Secretary has authority to prescribe rules and regulations to carry out laws administered by the VA	38 USC § 501	Approved February 27, 2006				
Entitlement to compensation for disability resulting from diseases contracted in line of duty in the active military, naval, or air service, during a period of war	38 USC § 1110	Approved February 27, 2006				
Presumption of sound condition at the time of examination, acceptance, and enrollment into service	38 USC § 1111	Approved February 27, 2006				
Aggravation to a preexisting injury or disease	38 USC § 1153	Approved February 27, 2006	Increase in disability during active military, naval, or air service, unless the increase is due to the natural progress of the disease			
Veteran's service requirements for non-service-connected disability	38 USC § 1521	Approved February 27, 2006	Active military, naval, or air service	Service requirements: • 90 days or more during a period of war • Period of war		

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
				and was discharged or released for a service-connected disability • 90 consecutive days or more and began or ended during a period of war • Aggregate of 90 days or more in two or more separate periods of service during more than one period of war		
Guidelines for establishing presumptions of service connection for former prisoners of war	38 CFR 1.18		Former prisoners of war		May give a minimum duration of detention or internment for application of the presumption Defines "evidence"	Secretary may establish a presumption of service connection for a disease when there is at least limited/suggestive evidence that an increased risk of such disease is associated with

Presumptive Disease	Legislation or Regulation	Date	Etiology of Disease	Location/Date of Service	Presumptive Period	Additional Information
						service involving detention or internment as a prisoner of war and an association between the two is biologically plausible
Secondary condition established as service connection of the original condition • Cardiovascular disease for service-connected amputation	38 CFR 3.310		Service-connected amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles			

Appendix G

VA's White Paper on the Presumptive Disability Decision-Making Process

Internal VA Process for Reviewing Reports of the Institute of Medicine Under the Agent Orange Act of 1991 and the Persian Gulf War Veterans Act of 1998

BACKGROUND

The Agent Orange Act of 1991, Pub. L. No 102-4 (codified in part at 38 U.S.C. § 1116) and the Persian Gulf War Veterans Act of 1998, Pub. L. No. 105-277, title XVI (codified in part at 38 U.S.C. § 1118), direct the Secretary of Veterans Affairs to contract with the National Academy of Sciences (NAS) to evaluate the available evidence concerning the health effects of exposure to herbicides and exposure to certain hazards suspected to be associated with Gulf War service and to prepare biennial reports to the Secretary summarizing its findings based on such evidence. Pursuant to those statutes, NAS's Institute of Medicine (IOM) prepares such reports and provides them to the Secretary.

Upon receipt of each such report, the Secretary is required to determine whether a presumption of service connection is warranted for any diseases discussed in the report, based on the Secretary's finding that there is a "positive association" between the exposure in question and the development of the disease. For this purpose, a "positive association" exists if the credible evidence for an association is equal to or outweighs the credible evidence against the association. In making those determinations, the Secretary is required to take into account the IOM's report and all other sound scientific and medical evidence available to the Secretary. Additionally, in evaluating any study for this purpose, the Secretary is directed to consider "whether the results are statistically significant, are capable of replication, and withstand peer review."

If the Secretary determines that a presumption is warranted for any disease, the Secretary must issue rules through notice-and-comment rule-making procedures to establish the presumption. Additionally, if the Secretary determines that presumptions are not warranted for certain diseases discussed in the IOM report, the Secretary must publish in the Federal Register a notice explaining the scientific bases for such determination.

The IOM reports prepared pursuant to these two laws typically state conclusions for each disease with reference to one of four or five general categories describing the strength of the available evidence for an association between the disease and the exposure under investigation.

The four categories used in the IOM reports under both laws are "sufficient evidence of an association," "limited/suggestive evidence of an association," "inadequate/insufficient evidence to determine whether an association exists," and "limited/suggestive evidence of no association." The IOM reports under the Persian Gulf War Veterans Act include a fifth category, "sufficient evidence of a causal relationship." The IOM categories intentionally do not address the central issue in the Secretary's determination, i.e., the existence of a "positive association." Accordingly, the Secretary is ultimately responsible for determining how the IOM's findings, together with any other evidence available to the Secretary, bear upon the resolution of that ultimate question.

This paper describes the process by which the Department of Veterans Affairs (VA) evaluates the IOM reports in order to assist the Secretary in making the determinations described above.

RECEIPT OF REPORT AND IOM COMMITTEE BRIEFING

VA ordinarily receives an embargoed copy of the IOM report a short period (about one week) prior to the date of the report's public release. On or about the day of the public release, a representative of the IOM committee ordinarily provides VA a briefing on the report. The briefing typically identifies any significant findings in the report, any changes in the IOM's categorization of specific diseases in comparison to prior reports, and any significant changes in the scope or methodology of the IOM's investigation in comparison to prior reports, and responds to any questions from VA participants. The briefing is ordinarily attended by the members of VA's Working Group (described below) and other interested VA personnel.

SUMMARY OF VA'S REVIEW PROCESS

VA has not adopted formal procedures governing its internal review of IOM reports under the two statutes discussed above. However, a general practice has developed that VA usually, though not always, follows in conducting its internal review. The general practice involves a three-tiered review. In the first tier, a "Working Group" of VA employees from different operational elements of VA reviews the IOM report and any other relevant evidence and prepares a summary of its assessment and a statement of recommendations or options. This summary is intended for the benefit of a "Task Force" composed of high-level VA officials. In the second tier, the Task Force, based on the Working Group's input, provides recommendations to the Secretary, usually in the form of a separate written report. In the third tier, the Secretary determines, based on the Task Force's input, whether a presumption of service connection is warranted for any disease.

VA WORKING GROUP

The Working Group ordinarily consists of members of the Office of Public Health and Environmental Hazards (OPHEH) of the Veterans Health Administration (VHA), the Compensation and Pension Service (C&P Service) of the Veterans Benefits Administration (VBA), and Professional Staff Group II (PSG II) of the Office of the General Counsel (OGC). Additionally, the Working Group often includes other VHA personnel with specialized medical training or experience concerning a health issue implicated by a particular IOM report. The members generally are assigned to the Working Group by supervisory personnel within VHA, VBA, and OGC.

The Working Group generally convenes within a short time after receiving the briefing from the IOM committee. Prior to the meeting, VHA personnel usually will seek to identify, based on the IOM report and the committee briefing, the diseases that may warrant special consideration because the IOM's findings with respect to those diseases appear to be potentially significant. Prior to or at the initial Working Group meeting, VHA generally provides the Working Group members with additional information concerning those diseases, including copies of any significant scientific studies identified in the IOM report and other information concerning matters such as the course of the disease, known causes or risk factors, related conditions or health effects, latency periods (if any), and any other known relevant information.

At the initial Working Group meeting, the OGC representative briefs the Working Group on the legal standard governing the Secretary's decision. Members of the Working Group generally will discuss whether any of the IOM's findings appear to be potentially significant, in that they might warrant a presumption of service connection for a particular disease or diseases, and will discuss the strength of the scientific evidence with respect to such diseases. The Working Group will try to reach consensus as to whether the scientific evidence appears to warrant a presumption of service connection for any diseases under the applicable legal standard. If the Working Group reaches agreement that a presumption is or is not warranted on the basis of the scientific evidence and the legal standard, it will agree to put forth a recommendation based on that conclusion. In arriving at such recommendations, the Working Group relies on scientific evidence and the legal standard, and generally does not consider matters of governmental policy or cost.

If the Working Group concludes that the scientific evidence and legal standard do not provide a clear basis for recommending for or against establishing a presumption, but permit a range of options, the Working Group generally will agree to set forth a range of options for decision by VA policy-making officials. In those circumstances, the Working Group will discuss the factors that preclude a clear recommendation, which may include ambiguity in the governing statutory standard as applied to certain IOM findings, the limited or conditional nature of the IOM's findings with respect to certain diseases, or other factors. The Working Group will discuss the decisional options available to the Secretary and may also discuss the factors that may be relevant to the Secretary's decision among those options. To this extent, the Working Group may discuss the policy considerations that would be relevant to the Secretary's choice among permissible courses of action.

Once the Working Group has reached agreement concerning its recommendations or presentation of options, members of the group will prepare a written report. The Working Group Report typically will contain (1) a summary of the issues to be decided under applicable law and the IOM report, (2) a summary of the findings contained in the IOM report, (3) a summary of the legal standard governing VA's decision, (4) a summary of the Working Group's analysis of the medical evidence in relation to the legal standard, particularly with respect to any potentially significant findings in the IOM report, and (5) a statement of the Working Group's recommendations or of the options identified by the Working Group. The Working Group does not prepare or obtain a cost estimate for the options, although it may provide general information concerning, e.g., the prevalence rates of certain diseases under consideration. If the Working Group report lists a range of options available to the Secretary, it ordinarily would identify the scientific and legal considerations relevant to the Secretary's choice among those options, and may also identify policy implications associated with various options.

VA TASK FORCE

The Task Force ordinarily consists of the Under Secretary for Health, the Under Secretary for Benefits, the General Counsel, and the Assistant Secretary for Policy and Planning. There is no generally established procedure for the Task Force's deliberations. Task Force members generally receive a copy of the Working Group report and, based on that report, provide advice to the Secretary concerning the Secretary's determination, which may include recommendations based upon the options, if any, outlined by the Working Group. The Task Force often, though not always, provides a separate report to the Secretary, which is based largely upon the Working Group's report and is usually similar to the Working Group's report in format and content. As a practical matter, these Task Force reports are usually drafted by members of the Working Group, based on guidance from members of the Task Force. Once the report is drafted, it is circulated to the Task Force members for signature and is then transmitted to the Secretary.

SECRETARY

Based on the Task Force's report, the Secretary determines whether to establish presumptions for any diseases discussed in the IOM report and directs appropriate action to implement the decision.

ESTABLISHMENT OF PRESUMPTIONS

If the Secretary determines that a presumption of service connection is warranted for any disease, VBA (through the C&P Service staff) will prepare proposed rules to establish such presumptions. The preamble to the proposed rule will explain the scientific and legal basis for the presumption and will invite comments from the public on the rule. VBA staff will prepare an estimate of the costs associated with the rule, as required by executive order. Once drafted, the proposed rule will be circulated to appropriate VA offices, including VHA and OGC, for review and concurrence. Once all offices concur, VA will transmit the proposed rule and cost estimate to the Office of Management and Budget (OMB) for review. If OMB approves the proposed rule, it will be transmitted to the Secretary for signature. VA will then transmit the rule to the Federal Register for publication. Once the period for providing public comments on the rule has ended, VBA will prepare a final rule. Subject to the same process described above for internal concurrence, OMB review, and the Secretary's signature, VA will submit the final rule to the Federal Register for publication.

In certain circumstances, additional review procedures may be required. For example, if a proposed or final rule would have an annual budgetary impact of $100 million or more, VA must provide a copy of the rule to Congress for review prior to publication of the rule.

NOTICE OF DECISION NOT TO ESTABLISH PRESUMPTIONS

If the Secretary determines that a presumption of service connection is not warranted for certain diseases, VBA will prepare a notice explaining the scientific basis for that decision with respect to each such disease. The notice is circulated for concurrence within VA in the same manner as a proposed rule, although VA does not prepare cost estimates with respect to the diseases concerned in this notice. The notice also may be subject to review by OMB prior to publication. Once the Secretary has signed the notice, VA will transmit it to the Federal Register for publication.

Appendix H

IOM's Statements of Task and Conclusions for Agent Orange and Gulf War Reports

APPENDIX H-1

Statements of Task for IOM Reports on Agent Orange

1994. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides
Statement of Task:

Review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and each disease or condition suspected to be associated with such exposure. Determine, if possible:

1. Whether there is a statistical association between the suspect diseases and herbicide use, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association;
2. The increased risk of disease among individuals exposed to herbicides during service in Vietnam; and
3. Whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a disease.

The committee was also asked to make recommendations concerning the need, if any, for additional scientific studies to resolve areas of continuing scientific uncertainty and to comment on four particular programs mandated in Public Law 102-4 (the Agent Orange Act of 1991).

1996. Veterans and Agent Orange: Update 1996
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides
Statement of Task:

Conduct a comprehensive review of the evidence that has become available since the previous (Veterans and Agent Orange) IOM committee report and reassess its determinations and

estimates of statistical association, risk, and biological plausibility. For each disease, determine, to the extent that available data permitted meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
2. The increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. Whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The committee was also asked to address the following specific areas of concern as requested by the Department of Veterans Affairs (VA):

- The relationship between exposure to herbicides and the development of acute and subacute peripheral neuropathy;
- The relationship between exposure to herbicides and the development of prostate cancer, hepatobiliary cancer, and nasopharyngeal cancer; and
- The relationship between the length of time since first exposed and the possible risk of cancer development.

1999. Veterans and Agent Orange: Update 1998
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Second Biannual Update)
Statement of Task:

Conduct a second review and evaluation of the newly published scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. For each disease, determine, to the extent that available data permitted meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. The increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. Whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The committee also addressed the following specific areas of interest as identified by VA:

- The relationship between exposure to herbicides and the subsequent development of diabetes;
- The issue of the latency between exposure to herbicides and development of adverse health outcomes;
- The classification of chondrosarcomas of the skull;

- Herbicide exposure assessment for Vietnam veterans; and
- The potential for using data combination methodologies to informatively reexamine existing data on the health effects of herbicide or dioxin exposure.

2000. Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes
Committee to Review the Evidence Regarding the Link Between Exposure to Agent Orange and Diabetes
Statement of Task:

Conduct a focused review of the scientific evidence regarding the association, if any, between type 2 diabetes and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. Determine, to the extent that available data permitted meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. The increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. Whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

2001. Veterans and Agent Orange: Update 2000
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Third Biennial Update)
Statement of Task:

Conduct a third review and evaluation of the newly published scientific evidence regarding associations between health outcomes and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. For each disease, determine, to the extent that available data permitted meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. The increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. Whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

At VA's request, the committee also examined the possible association between the herbicides of concern in this report and AL-type primary amyloidosis, a condition not examined in previous Veterans and Agent Orange reports.

2002. Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides
Statement of Task:

Conduct a review of the scientific evidence regarding the association between exposure to dioxin and other chemical compounds in herbicides used in Vietnam and acute myelogenous leukemia in the offspring of Vietnam veterans. Determine, to the extent that available data permitted meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. The increased risk of the disease associated with exposure to herbicides during Vietnam service; and
3. Whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

2003. Veterans and Agent Orange: Update 2002
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Fourth Biennial Update)
Statement of Task:

Conduct a fourth review and evaluation of the newly published scientific evidence regarding the association between exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other chemical compounds contained in herbicides used in Vietnam and a wide range of health effects. Determine, to the extent that available data permit meaningful determinations:

1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
2. The increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
3. Whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

2004. Veterans and Agent Orange: Length of Presumptive Period for Association Between Exposure and Respiratory Cancer
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides
Statement of Task:

Undertake a review and evaluation of the evidence regarding the period between cessation of exposure to herbicides used in Vietnam and their contaminants (2,4-D; 2,4,5-T and its contaminant TCDD; cacodylic acid; and picloram) and the occurrence of respiratory cancer.

2005. Veterans and Agent Orange: Update 2004
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Fifth Biennial Update)
Statement of Task:

> Determine (to the extent that available scientific data permit meaningful determinations) the following regarding associations between specific health outcomes and exposure to TCDD and other chemical compounds in herbicides:
>
> 1. Whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
> 2. The increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
> 3. Whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

2007. Veterans and Agent Orange: Update 2006. The Sixth Biennial Update report on Veterans and Agent Orange was released at the end of July 2007. The report was in development at the same time as and independent of the Committee's report, and therefore, was unavailable to the Committee during their deliberations.

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APPENDIX H-2

Statements of Task for IOM Reports on Gulf War

2000. Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines
Committee on Health Effects Associated with Exposures During the Gulf War
Summary of Charge:

The purpose of this study was to conduct a review of the scientific and medical literature regarding adverse health effects associated with exposures experienced during the Persian Gulf War. The review included assessments of biological plausibility that exposures, or synergistic effects of combinations of exposures, are associated with illnesses experienced by Gulf War veterans. The review also included recommendations for additional scientific studies to resolve areas of continued scientific uncertainty related to the health consequences of Gulf War service. Exposures considered included depleted uranium, chemical warfare agents (sarin and cyclosarin), pyridostigmine bromide, and vaccines (anthrax and botulinum toxoid).

2003. Gulf War and Health, Volume 2: Insecticides and Solvents
Committee on Gulf War and Health: Literature Review of Pesticides and Solvents
Summary of Charge:

This committee reviewed the peer-reviewed literature on long-term health outcomes associated with exposure to classes of insecticides (such as organophosphorous compounds) identified as having been used in the Persian Gulf, as well as 53 specific solvents. The committee's review focused primarily on epidemiologic studies of humans who had been exposed to these insecticides and solvents in occupational settings. Where available, studies of Gulf War veterans were included as well. Information on plausible biologic mechanisms of health outcomes came from toxicological and experimental data studies of both humans and animals.

2004. Gulf War and Health: Updated Literature Review of Sarin
Committee on Gulf War and Health: Updated Literature Review of Sarin
Summary of Charge:

Following publication of studies of sarin exposure from terrorist attacks in Japan, toxicological studies of low-dose exposure to sarin, and possible sarin exposure of veterans during the Gulf War, this ad hoc committee was formed and tasked with conducting an updated assessment of the literature on health outcomes associated with exposure to sarin and cyclosarin. The review built upon the information previously developed by earlier IOM reports on health outcomes associated with exposure to sarin and related compounds. In its final report, the committee also outlined recommendations for additional studies to resolve areas of continued scientific uncertainty.

2005. Gulf War and Health, Volume 3: Fuels, Combustion Products, and Propellants
Committee on Gulf War and Health: Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds
Summary of Charge:

This committee reviewed the scientific literature to examine the health effects of hydrazines, red fuming nitric acid, hydrogen sulfide, oil-fire by-products, diesel-heater fumes, and fuels (for example, jet fuel and gasoline). The committee's review focused on epidemiologic studies but included other relevant literature with regard to chronic medical effects of exposure, including studies of Gulf War veterans. The committee was also charged with determining, to the extent permitted by available scientific data, the increased risk of illness among people exposed to the putative agents during service in the Persian Gulf.

2006a. Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War
Committee on Gulf War and Health: A Review of the Medical Literature Relative to Gulf War Veterans' Health
Summary of Charge:

The work of this committee was different from that of prior Gulf War and Health committees in that this study was an attempt to summarize health outcomes associated with deployment, rather than health outcomes associated with a specific biologic or chemical agent believed to have been present in the Gulf. This study was developed to inform the VA of illnesses among Gulf War veterans that might not have been evident at the time. The committee's specific charge was to review, evaluate, and summarize the peer-reviewed scientific and medical literature addressing the health status of Gulf War veterans. The committee reviewed epidemiologic studies to draw conclusions regarding long-term health outcomes (such as cancer, cardiovascular disease, and nervous system disorders) associated with serving in the Gulf War.

2006b. Posttraumatic Stress Disorder: Diagnosis and Assessment
Subcommittee on Posttraumatic Stress Disorder of the Committee on Gulf War and Health: Physiologic, Psychologic, and Psychosocial Effects of Deployment-Related Stress
Summary of Charge:

This committee's task was to review the scientific and medical literature related to the diagnosis and assessment of posttraumatic stress disorder (PTSD). The committee was also given a series of specific questions from VA regarding diagnosis and assessment of PTSD. These included, among others, questions regarding accepted diagnostic criteria for PTSD, how best to diagnose and document stressful events, and the components of an evidence-based diagnosis of PTSD. The committee relied primarily on reviews and other well-documented sources to form conclusions regarding diagnosis and assessment of PTSD. The committee will, at a later date, deliver a second report on PTSD treatments and their efficacy, and also comment on the chronicity of PTSD, the potential for recovery, and the value of early intervention.

2007. Gulf War and Health, Volume 5: Infectious Diseases
Committee on Gulf War and Health: Infectious Diseases
Summary of Charge:

This committee evaluated the scientific and medical literature on long-term adverse human health outcomes associated with nine infectious diseases potentially acquired by veterans during the Gulf War. These infectious diseases included brucellosis, campylobacteriosis, leishmaniasis, malaria, Q fever, salmonellosis, shigellosis, tuberculosis, and West Nile fever.

The committee's report also included information on specific diseases and agents reported in the published literature or popular press to have infectious agents and to have caused illnesses in veterans of the Gulf War, Operation Iraqi Freedom, and Operation Enduring Freedom.

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APPENDIX H-3

Conclusions from IOM's Agent Orange Biennial Reports[1]

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association.

- Chloracne (1994)
- Chronic lymphocytic leukemia (CLL) (2003)[2]
- Hodgkin's disease (1994)
- Non-Hodgkin's lymphoma (1994)
- Porphyria cutanea tarda (in genetically susceptible individuals) (1994)
- Soft tissue sarcoma (1994)

[1] NOTE: "Herbicides" refers to the major herbicides used in Vietnam, which include 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)—2,4,5-T contaminant, cacodylic acid, picloram. The evidence regarding association was drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

[2] Previously listed under Inadequate/Insufficient Evidence category (as leukemia).

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent.

- Acute and subacute peripheral neuropathy (1996); acute and subacute transient peripheral neuropathy (1999); early-onset transient peripheral neuropathy (2005)
- Acute myelogenous leukemia (AML) in the children of veterans (2001)
- Multiple myeloma (1994)
- Porphyria cutanea tarda (1996)[3]
- Prostate cancer (1994)
- Respiratory cancers (lung, larynx, trachea) (1994); respiratory cancers (lung/bronchus, larynx, trachea) (1999); respiratory cancer (of lung and bronchus, larynx, and trachea) (2003)
- Spina bifida (1996); spina bifida in the children of veterans (1999); spina bifida in the offspring of exposed individuals (2005)
- Type 2 diabetes (2000)[4]

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency.

- Abnormal sperm parameters and infertility (1994); abnormal sperm characteristics and infertility (2003)
- AL-type primary amyloidosis (2001)
- Birth defects (1994); birth defects (other than spina bifida) (1996); birth defects (other than spina bifida) in the offspring of exposed individuals (2005)
- Bone cancer (1994); bone and joint cancer (2005)
- Breast cancer (1994)
- Childhood cancer in offspring (1994); childhood cancer in offspring, other than AML (2001); childhood cancer in offspring, including AML (2003); childhood cancer (including AML) in offspring of exposed individuals (2005)
- Circulatory disorders (1994)
- Cognitive and neuropsychiatric disorders (1994); neurobehavioral disorders (cognitive and neuropsychiatric) (2005)
- Effects on thyroid homeostasis (2003)
- Endometriosis (2003)

[3] Previously listed under Sufficient Evidence of an Association category (as porphyria cutanea tarda [in genetically susceptible individuals]).
[4] Previously listed under Inadequate/Insufficient Evidence category (within metabolic and digestive disorders [diabetes, changes in liver enzymes, lipid abnormalities, ulcers]).

- Female reproductive cancers (cervical, uterine, ovarian) (1994)
- Hepatobiliary cancers (1994)
- Immune system disorders (immune modulation and autoimmunity) (1994); immune system disorders (immune suppression and autoimmunity) (1996)
- Leukemia (1994); leukemia (other than CLL) (2003)
- Low birthweight (1994); low birthweight in offspring of exposed individuals (2005)
- Metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, ulcers) (1994); gastrointestinal, metabolic and digestive disorders (changes in liver enzymes, lipid abnormalities, ulcers) (2001)
- Motor/coordination dysfunction (1994); movement disorders, including Parkinson's disease and amyotrophic lateral sclerosis (ALS) (2005)
- Nasal/nasopharyngeal cancer (1994); oral, nasal, and pharyngeal cancer (2005)
- Neonatal/infant death and stillbirths (1994); neonatal or infant death and stillbirth in offspring of exposed individuals (2005)
- Peripheral nervous system disorders (1994); chronic peripheral nervous system disorders (1996)
- Renal cancer (1994)
- Respiratory disorders (1994)
- Skin cancers (1996);[5] skin cancers (melanoma, basal, and squamous) (2001); skin cancers (melanoma, basal cell, and squamous cell) (2005)
- Spontaneous abortion (1994)
- Testicular cancer (1994)
- Urinary bladder cancer (1999)[6]

Limited/Suggestive Evidence of No Association

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

- Bladder cancer (1994)
- Brain tumors (1994)
- Gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, rectal cancer) (1994); gastrointestinal tumors (esophagus, stomach, pancreas, colon, rectum) (2005)
- Skin cancer (1994)

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[5] Previously listed under Limited/Suggestive Evidence of No Association category.
[6] Previously listed under Limited/Suggestive Evidence of No Association category (as bladder cancer).

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APPENDIX H-4

Conclusions from IOM's Gulf War and Health Series Volumes 1, 2, 3, 5, and Updated Literature Review of Sarin[7]

Sufficient Evidence of a Causal Relationship

Evidence is sufficient to conclude that there is a causal association between exposure to a specific agent and a specific health outcome in humans. The evidence is supported by experimental data and fulfills 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 a temporal relationship.

- Benzene and
  - acute leukemia (2003)
  - aplastic anemia (2003)
- *Coxiella burnettii* infection (Q fever) and osteomyelitis (2007)
- Malarial infection and ophthamologic, hematologic, and renal manifestations as well as later presentation of or relapse of disease months to years after acute infection (2007)
- *Mycobacterium tuberculosis* infection and occurrence of active (tuberculosis) TB months to decades after infection (2007)
- Sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months (2000)

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive

[7] The *Gulf War Volume 4* summary of evidence is not included in this review because that committee's charge was to examine health outcomes related to deployment in general, rather than the specific biological or chemical agents believed to have been present in the Gulf region (IOM, 2006).

associations, and the studies are sufficiently free of bias, including adequate control for confounding.

- Active TB and long-term adverse health outcomes due to irreversible tissue damage from severe forms of pulmonary and extrapulmonary TB (2007)
- Anthrax vaccination and transient acute local and systemic effects (2000)
- Benzene and adult leukemia (2003)
- Botulinum toxoid vaccination and transient acute local and systemic effects (2000)
- Brucellosis and
  - arthritis and spondylitis (2007)
  - cardiovascular, nervous, and respiratory system infections (2007)
  - chronic meningitis and meningoencephalitis (2007)
  - hepatic abnormalities, including granulomatous hepatitis (2007)
  - orchioepididymitis and infections of the genitourinary system (2007)
  - uveitis (2007)
- *Campylobacter* infection and reactive arthritis (ReA) if ReA is manifest within 3 months of the infection (2007)
- *Campylobacter jejuni* infection and Guillain-Barre syndrome (GBS) if GBS is manifest within 2 months of infection (2007)
- Combustion products and lung cancer (2005)
- *Coxiella burnetii* infection (Q fever) and
  - chronic hepatitis years after primary infection (2007)
  - endocarditis years after primary infection (2007)
  - vascular infection years after primary infection (2007)
- Nontyphoid *Salmonella* infection and ReA if ReA is manifest within 3 months of the infection (2007)
- *Plasmodium falciparum* infection with recrudescence weeks to months after the primary infection, but only in the case of inadequate therapy (2007)
- *Plasmodium malariae* infection and manifestation of immune-complex glomerulonephritis years to decades later (2007)
- Propylene glycol and allergic contact dermatitis (2003)
- Pyridostigmine bromide and transient acute cholinergic effects in doses normally used in treatment and for diagnostic purposes (2000)
- *Shigella* infection and
  - hemolytic-uremia syndrome (HUS) if HUS is manifest within 1 month of the infection (2007)
  - ReA if ReA is manifest within 3 months of the infection (2007)
- Solvents and acute leukemia (2003)
- Visceral leishmaniasis (kala-azar) and
  - delayed presentation of the acute clinical syndrome (2007)
  - Post-kala-azar dermal leishmaniasis (PKDL) if PKDL occurs generally within 2 years of the initial infection (2007)

  - reactivation of visceral leishmaniasis in the context of future immunosuppression (2007)
- West Nile virus infection and variable physical, functional, or cognitive disability, which may persist for months or years or be permanent (2007)

Limited/Suggestive Evidence of an Association

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

Cancers

- Benzene and non-Hodgkin's lymphoma (2003)
- Carbamates and non-Hodgkin's lymphoma (2003)
- Combustion products and
  - bladder cancer (2005)
  - cancers of the nasal cavity and nasopharynx (2005)
  - cancers of the oral cavity and oropharynx (2005)
  - laryngeal cancer (2005)
- Hydrazines and lung cancer (2005)
- Organophosphorus insecticides and
  - adult leukemia (2003)
  - non-Hodgkin's lymphoma (2003)
- Solvents and
  - adult leukemia (2003)
  - bladder cancer (2003)
  - multiple myeloma (2003)
  - myelodysplastic syndromes (2003)
- Tetrachloroethylene and dry-cleaning solvents and
  - bladder cancer (2003)
  - kidney cancer (2003)

Neurologic Effects

- Organophosphorus (OP) insecticide exposure with OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings) (2003)

- *Plasmodium falciparum* infection and neurologic disease, neuropsychiatric disease, or both months to years after the acute infection (2007)
- *Plasmodium vivax* and *Plasmodium falciparum* infections and demyelinating polyneuropathy and GBS (2007)
- Sarin at doses sufficient to cause acute cholinergic signs and symptoms and a variety of subsequent long-term neurological effects (2004)
- Solvents and neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings) (2003)

Other Health Effects

- Brucellosis and
  - fatigue, inattention, amnesia, and depression (2007)
  - myelitis-radiculoneuritis, demyelinating meningovascular syndromes, deafness, sensorineural hearing loss, and GBS (2007)
  - papilledema, optic neuritis, episcleritis, nummular keratitis, and multifocal choroiditis (2007)
- *Campylobacter jejuni* infection and development of uveitis if uveitis is manifest within 1 month of infection (2007)
- *Coxiella burnetii* infection and post–Q fever chronic fatigue syndrome years after the primary infection (2007)
- Insecticides and allergic contact dermatitis (2003)
- Sarin at doses sufficient to cause acute cholinergic signs and symptoms and subsequent long-term health effects (2000)
- Solvents and
  - chronic glomerulonephritis (2003)
  - hepatic steatosis (2003)
  - reactive airways dysfunction syndrome, which would be evident with exposure and could persist for months or years (2003)

Reproductive Effects

- Combustion products and
  - low birthweight/intrauterine growth retardation and exposure during pregnancy (2005)
  - preterm birth and exposure during pregnancy (2005)

Respiratory Effects

- Combustion products and incident asthma (2005)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

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

Cancers

- Benzene and myelodysplastic syndromes (2003)
- Combustion products and
  - colon cancer (2005)
  - esophageal cancer (2005)
  - female breast cancer (2005)
  - female genital cancers (cervical, endometrial, uterine, and ovarian cancers) (2005)
  - hepatic cancer (2005)
  - Hodgkin's disease (2005)
  - kidney cancer (2005)
  - leukemia (2005)
  - male breast cancer (2005)
  - melanoma (2005)
  - multiple myeloma (2005)
  - nervous system cancers (2005)
  - non-Hodgkin's lymphoma (2005)
  - ocular melanoma (2005)
  - pancreatic cancer (2005)
  - prostatic cancer (2005)
  - rectal cancer (2005)
  - stomach cancer (2005)
  - testicular cancer (2005)
- Fuels and
  - bladder cancer (2005)
  - cancers of the nasal cavity and nasopharynx (2005)
  - cancers of the oral cavity and oropharynx (2005)
  - colon cancer (2005)
  - esophageal cancer (2005)
  - female breast cancer (2005)
  - female genital cancers (cervical, endometrial, uterine, and ovarian cancers) (2005)
  - hepatic cancer (2005)
  - Hodgkin's disease (2005)
  - kidney cancer (2005)
  - laryngeal cancer (2005)
  - lung cancer (2005)

  - male breast cancer (2005)
  - melanoma (2005)
  - multiple myeloma (2005)
  - myelodysplastic syndromes (2005)
  - nervous system cancers (2005)
  - non-Hodgkin's lymphoma (2005)
  - nonmelanoma skin cancer (2005)
  - pancreatic cancer (2005)
  - prostatic cancer (2005)
  - rectal cancer (2005)
  - stomach cancer (2005)
  - testicular cancer (2005)
- Hydrazines and
  - bladder cancer (2005)
  - digestive tract cancers (2005)
  - hematopoietic and lymphopoietic cancers (2005)
  - kidney cancer (2005)
  - pancreatic cancer (2005)
- Insecticides and
  - brain and other central nervous system (CNS) cancers (2003)
  - lung cancer (2003)
  - pancreatic cancer (2003)
  - prostate, testicular, bladder, or kidney cancers (2003)
  - soft tissue sarcomas (2003)
- Insecticides and solvents and
  - hepatobiliary cancers (2003)
  - Hodgkin's disease (2003)
  - multiple myeloma (2003)
- Insecticides, parental preconception exposure, and childhood leukemias, brain and other CNS cancers, and non-Hodgkin's lymphoma (2003)
- Lindane and solvents and breast cancer (2003)
- Nitric acid and
  - bladder cancer (2005)
  - laryngeal cancer (2005)
  - lung cancer (2005)
  - lymphopoietic cancers (2005)
  - melanoma (2005)
  - multiple myeloma (2005)
  - pancreatic cancer (2005)
  - stomach cancer (2005)

- Solvents and
  - bone cancer (2003)
  - melanoma or nonmelanoma skin cancer (2003)
  - oral, nasal, or laryngeal cancer (2003)
  - ovarian or uterine cancer (2003)
  - prostate cancer (2003)
  - stomach, rectal, or pancreatic cancer (2003)
- Solvents other than tetrachloroethylene and dry-cleaning solvents and
  - bladder cancer (2003)
  - esophageal cancer (2003)
  - kidney cancer (2003)
  - lung cancer (2003)
- Solvents other than trichloroethylene and cervical cancer (2003)
- Solvents other than trichloroethylene and mixtures of benzene, toluene, and xylene and colon cancer (2003)
- Solvents, parental preconception exposure to solvents and neuroblastoma and childhood brain cancers (2003)
- Specific solvents other than benzene and
  - acute and adult leukemia (2003)
  - brain and other central nervous system cancers (2003)
  - non-Hodgkin's lymphoma (2003)
- Uranium and
  - bone cancer (2000)
  - lung cancer at higher levels of cumulative exposure (>200 mSv or 25 cGy) (2000)
  - lymphatic cancer (2000)

Cardiovascular Effects

- Combustion products and ischemic heart disease or myocardial infarction (less than 2 years of exposure) (2005)
- Hydrazines and ischemic heart disease or myocardial infarction (2005)
- Nitric acid and cardiovascular diseases (2005)
- Sarin and subsequent long-term cardiovascular effects (2004)
- Uranium and cardiovascular effects (2000)

Dermal Effects

- Combustion products and dermatitis—irritant and allergic (2005)
- Fuels and dermatitis—irritant and allergic (2005)
- Uranium and dermal effects (2000)

Neurologic Effects

- Combustion products and
  - Multiple Chemical Sensitivity symptoms (2005)
  - nervous system subgroupings (or individual nervous system diseases) (2005)
  - neurobehavioral effects (2005)
  - posttraumatic stress disorder (2005)
- Fuels and
  - Multiple Chemical Sensitivity symptoms (2005)
  - neurobehavioral effects (2005)
  - peripheral neuropathy (2005)
- Insecticides and solvents and
  - ALS (2003)
  - Alzheimer's disease (2003)
  - Parkinson's disease (2003)
  - peripheral neuropathy (2003)
- Sarin at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse neurological health effects (2004)
- Solvents and
  - long-term hearing loss (2003)
  - long-term reduction in color discrimination (2003)
  - long-term reduction in olfactory function (2003)
  - multiple sclerosis (2003)
- Uranium and nervous system disease (2000)

Reproductive Effects

- Combustion products and
  - all childhood cancers identified, including acute lymphocytic leukemia, leukemia, neuroblastoma, and brain cancer (2005)
  - low birthweight and intrauterine growth retardation and exposure before gestation or during any specific period during pregnancy (for example, the first trimester) (2005)
  - preterm births and exposure during any specific time period during pregnancy (for example, the first trimester) (2005)
  - specific birth defects, including cardiac effects, and exposure before conception (maternal and paternal) or during early pregnancy (maternal) (2005)
- Fuels and adverse reproductive or developmental outcomes (including infertility, spontaneous abortion, childhood leukemia, CNS tumors, neuroblastoma, and Prader-Willi syndrome) (2005)
- Insecticides and solvents and male or female infertility after cessation of exposure (2003)
- Insecticides or solvents, parental preconception exposure, and

  - congenital malformations (2003)
  - spontaneous abortion or other adverse pregnancy outcomes (2003)
- Uranium and reproductive or developmental dysfunction (2000)

Respiratory Effects

- Combustion products and
  - chronic bronchitis (less than 1 year of exposure) (2005)
  - chronic obstructive pulmonary disease (2005)
  - emphysema (2005)
- Fuels and
  - asthma (2005)
  - chronic bronchitis (2005)
  - emphysema (2005)
  - nonmalignant respiratory disease (2005)
- Hydrazines and emphysema (2005)
- Uranium and nonmalignant respiratory disease (2000)

Other Health Effects

- Anthrax vaccination and long-term adverse health effects (2000)
- Botulinum toxoid vaccination and long-term adverse health effects (2000)
- Combustion products and sarcoidosis (2005)
- Fuels and sarcoidosis (2005)
- Hydrazines and hepatic disease (2005)
- Insecticides and aplastic anemia (2003)
- Insecticides and solvents and
  - irreversible cardiovascular outcomes (2003)
  - persistent respiratory symptoms or impairment after cessation of exposure (2003)
- Multiple vaccinations and long-term adverse health effects (2000)
- Pyridostigmine bromide and long-term adverse health effects (2000)
- Sarin, exposure at low doses insufficient to cause acute cholinergic signs and symptoms and subsequent long-term adverse health effects (2000)
- Solvents and
  - alterations in liver function tests after cessation of exposure (2003)
  - chronic pancreatitis and other persistent gastrointestinal outcomes (2003)
  - cirrhosis (2003)
  - the systemic rheumatic diseases: scleroderma, rheumatoid arthritis, undifferentiated connective tissue disorders, and systemic lupus erythematosus (2003)
- Solvents other than benzene and aplastic anemia (2003)

- Uranium and
  - effects on hematological parameters (2000)
  - gastrointestinal disease (2000)
  - genotoxic effects (2000)
  - hepatic disease (2000)
  - immune-mediated disease (2000)
  - musculoskeletal effects (2000)
  - ocular effects (2000)

Limited/Suggestive Evidence of No Association

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

- Exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy (2000)
- Uranium and clinically significant renal dysfunction (2000)

Consensus Not Reached on Category of Association

- Benzene and solvents and brain and other CNS cancers (2003)
- Mixtures of benzene, toluene, and xylene and colon cancer (2003)
- OP insecticide exposure without OP poisoning and long-term neurobehavioral effects (that is, abnormal results on neurobehavioral test batteries and symptom findings) (2003)
- Parental preconception exposure to solvents and childhood leukemia (2003)
- Solvents and kidney cancer (2003)
- Tetrachloroethylene and dry-cleaning solvents and esophageal cancer (2003)
- Tetrachloroethylene and dry-cleaning solvents and lung cancer (2003)
- Trichloroethylene and cervical cancer (2003)
- Trichloroethylene and colon cancer (2003)

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Appendix I

Case Studies

CASE STUDY 1: MENTAL DISORDERS' PRESUMPTIONS

War and combat have long been considered to have acute and chronic impacts on the emotional well-being and mental health of those exposed. Indeed, of the two initial presumptive disabilities recognized in 1921, one was "neuropsychiatric disease," a mental disorder (Veterans' Bureau Act. 1921. Public Law 67-47. 67th Cong., 1st Sess., p. 154). The scientific understanding of mental disorders, as well as the role of war and combat in triggering them, have evolved over time. These factors have influenced the inclusion of mental disorders as presumptive disabilities among U.S. veterans. This case study is intended to review factors influencing the inclusion of various mental disorders as presumptive disabilities among U.S. veterans to date.

Scientific and Legislative History

Following World War I, two of the most common causes for hospitalizations identified among U.S. veterans were "neuropsychiatric disease" and tuberculosis. At that time, neuropsychiatric disease was considered to consist of a combination of delusions, hallucinations, and illogical thinking. Because of the lack of effective treatments at the time, neuropsychiatric disease was considered to be chronic (VA, 2006). In 1921, Senator Walsh of Massachusetts proposed an amendment to pending legislation, which was adopted and later modified, that removed the burden of proof for connecting military service and the development of a disorder from the veteran by granting presumptions of service connection for veterans diagnosed with neuropsychiatric disease or tuberculosis causing at least 10 percent disability within 2 years of military service (Veterans' Bureau Act. 1921. Public Law 67-47. 67th Cong., 1st Sess., p. 154). In support of these presumptions, Senator Walsh stated that

> It is very apparent to me that this wave of tuberculosis and of nervous and mental disease that has taken such a deadly hold and grip of late upon our ex-servicemen must have been contracted in the service. I feel, therefore, that we ought not continue this requirement of endless affidavits, necessarily involving long delay, in demonstrating the fact that their illness is of service origin.
>
> (61 Cong. Rec. 4105 [daily ed. July 20, 1921], as referenced in VA, 1993a, p. 8)

To emphasize the difficulty in particular for veterans with neuropsychiatric disease he added that

> I think really that the most human feature of this amendment is the assistance it will render to those afflicted with nervous and mental disease in obtaining their compensation. When it is considered that the most important proof, the essential proof, to establish a claim for compensation must come from the man himself, and when it is realized that he is mentally afflicted and therefore can not, for instance, file affidavits from officers and servicemen with whom he served—since memory is usually defective and he can not remember whom his officers or comrades were—it becomes apparent how important is the change made by the bill.
>
> (61 Cong. Rec. 4105 [daily ed. July 20, 1921], as referenced in VA, 1993a, p. 9)

At the time the legislation was enacted in 1921, there were few scientific studies to support or refute these assertions, and a flood of demands for presumptions for other disorders and for enhancement of those already approved followed soon thereafter.

By early 1923, the 2-year period from the time of discharge within which the neuropsychiatric disorder had to manifest itself was extended to 3 years despite administration objections that the extension was not supported by scientific evidence (VA, 1993a, p. 12). Later that same year veterans groups, including the Disabled American Veterans, the Veterans for Foreign Wars, and the American Legion, began calling to extend the period from 3 to 5 years. The lack of scientific evidence to justify the extension was noted by Dr. Earl Holt of the Veterans Bureau. In testimony to Congress, Dr. Holt stated that available statistics showed that neuropsychiatric disorder was just as common among the civilian population as among the military population, and that the extension of presumptions was unwarranted due to uncertainty over the causes of psychiatric disabilities arising after service (VA, 1993a, p. 14). In response to the Depression, the Economy Act of 1933 eliminated all benefits based on presumptive service connection. In its place the President was given broad authority to prescribe rules concerning eligibility for disability compensation including "the nature and extent of proofs, and *presumptions*" (emphasis added) for various classes of veterans (Economy Act of 1933 ch. 3 § 4, 48 Stat. at 9, as referenced in VA, 1993a, p. 17).

Following strong protests from World War I veterans, Congress subsequently moved to reenact presumptive service-connection conditions. President Roosevelt vetoed the legislation stating that he thought the Economy Act had settled the issue that a service-connected disability was a "question of fact rather than a question of law" in which each individual case would be "considered on its merits" rather than by

> legislative dicta which, contrary to fact, provide that thousands of individual cases of sickness that commenced 4, 5, or 6 years after the termination of the war were caused by war services.
>
> (VA, 1993a, p. 19)

Congress overrode the veto, and the measure was enacted into law (Independent Offices Appropriations Act. 1935. Public Law 141. 73rd Cong., 2d Sess.). The tension between those intent on being inclusive and generous in presumptive benefits to veterans and those wanting presumptions to be more firmly grounded by evidence of causation continues today.

The pertinent provisions of that 1935 Act are now found in 38 USC § 1702, "Presumption Relating to Psychosis," and provide that eligible veterans who developed an active psychosis

within 2 years of military discharge "shall be deemed to have incurred such a disability in the active military, naval, or air service." That language has remained essentially unchanged except for the expansion of eligibility for veterans of subsequent periods of military conflict up to and including those serving in today's current war. The Committee was unable to obtain information as to how many veterans rated for mental disabilities have been service connected by use of the presumption set forth in section 1702.

Additional legislation concerning psychiatric presumptions has been confined to former prisoners of war (POWs). These psychiatric presumptions were the result of strong concern about the well-being of a group of veterans who suffered extreme privations and of POW studies undertaken to ascertain the effect of their captivity.

Psychiatric disorders, by their very nature, have created challenges for decision making on presumptions. For many of these disorders, symptoms can only be obtained by self-reporting methods, making it more difficult to distinguish those who truly exhibit symptoms and those who do not. Many early studies focused on excessive hospitalizations for mental disorders among veterans and associations of these disorders with military service rather than causation (Beebe, 1975; Cohen and Cooper, 1954). In addition, as the medical community's understanding of mental disorders has evolved over time so have the definitions of various mental disorders. Congress, the Department of Veterans Affairs (VA), the National Academy of Sciences (NAS), and a large collection of veterans groups and scientists have all been involved in questions related to presumptions and psychiatric disorders in veterans.

The first legislation to create statutory presumptions specifically applicable to POWs was enacted in 1970 (Veterans Disability Compensation Increase Act. 1970. Public Law 91-376. 91st Cong., 2d Sess.). Under Public Law 91-376, *psychosis* was to be considered a service-connected disability provided it became manifest within 2 years of separation from service in the military. In justifying the statutory presumptions, the accompanying report said that because of the conditions of captivity and the "kinds of long-range harm that may have been caused," it was "sometimes difficult for a former prisoner of war to establish some time after completion of military service" that a disability is related to military service (U.S. Congress, House of Representatives, Committee on Veterans' Affairs, 1970, p. 7).

From October 1972 through August 1976, VA issued a number of program guides with respect to Public Law 91-376. These guides were characterized as suggestions for the guidance of personnel in the handling of disability claims filed by former POWs. The program guides instructed that in light of the "frequent paucity of records" in POW claims, special attention should be given to POW experiences in determining the relationship of the disability to service (VA, 1980, p. 118). The duration and circumstances of imprisonment were to be associated with pertinent medical principles in making determinations.

The burden of proof as to the occurrence of a POW episode was shifted from the claimant to the government. The "unusual hardship and isolation from society" resulting from POW life meant that an "extended period of readjustment to ordinary conditions of life is essential." Claims for individual unemployability (IU) were to receive liberal construction, and if the threshold disability percentage for the IU benefit was not met, the claim was to be submitted to the VA central office for further consideration. Finally, it was emphasized that presumptions were rebuttable only where there was "affirmative evidence to the contrary" (VA, 1980, p. 119).

In 1975, the second phase of the *Follow-Up Studies of World War II and Korean War Prisoners*, entitled *Morbidity, Disability, and Maladjustment*, was issued (Beebe, 1975). Its author, Gilbert W. Beebe, observed at the outset that studies of the long-term effects of catastrophic

stress are "difficult to make and the frequently multidimensional character of such stress severely limits inferences about the etiologic role of specific components, such as malnutrition, social isolation, sensory deprivation, physical punishment, compulsory reeducation, and the like." He further noted that recent studies of survivors of World War II German concentration camps provided useful information on a persistent defective state marked by "severe permanent psychiatric residuals and by nonspecific somatic symptoms" (Beebe, 1975, pp. 400-401).

Beebe's findings were that morbidity, some types of maladjustment, and disability were elevated in POWs relative to controls especially for Pacific theater veterans. Beebe stated that the "most remarkable and long-lasting differentials" were seen in hospitalization for psychoneurosis and for psychosis (schizophrenia). Data obtained supported a finding that many Pacific theater and Korean War POWs had "permanent psychologic impairments." Beebe also noted that European theater POWs did not go "unscathed" with respect to psychoneurosis hospitalization (Beebe, 1975, p. 421).

In the Veterans Disability Compensation and Survivor Benefits Act of 1978 (Public Law 95-479. 95th Cong., 2d Sess.), Congress included provisions requiring VA to carry out a "comprehensive study on the compensation awarded to, and the health-care needs of" former POWs. The results of the study were to include such administrative and legislative recommendations as "may be necessary to assure that former prisoners of war receive compensation and health-care benefits for all disabilities which may *reasonably be attributed to their internment*" (Public Law 95-479, sec. 305; emphasis added). The legislative history indicates that the study was prompted by questions about the adequacy of repatriation examinations and by concerns that health conditions that may have appeared minor at the time were becoming progressively more debilitating. It also cited Beebe's 1975 follow-up study for the proposition that POWs had excess morbidity, and many were suffering from what was termed a "POW syndrome" (VA, 1993a, p. 51).

As VA was preparing its study, the third phase of the follow-up studies entitled *Mortality to January 1, 1976*, authored by Robert J. Keehn (1980), was issued. That study continued to find increased risks of mortality among World War II Pacific theater and Korean War POWs, though the excess diminished over time. For Pacific theater veterans the principal cause for the mortality increase was tuberculosis and trauma, while for former Korean War POWs it was trauma. In describing this trauma, the report found that for Pacific theater POWs suicide was responsible for two-thirds and accidents one-third of the excess deaths (Keehn, 1980). The study also reported that anxiety neurosis accounted for 12.7 percent of all service-connected conditions for former POWs, compared to a rate of approximately 4 percent for all veterans receiving compensation.

Given a consistent finding of persistent psychologic impairment and reported problems of adjustment to civilian life, the report concluded that

> The finding of increased mortality due to trauma, both accidental (including cases of masked suicide) and suicide, in former prisoners of war is not surprising. Increased feelings of frustration, anger, and tension lead to impatience and impulsive actions that are likely to contribute to both the risk and severity of accidental and self-inflicted injury.
>
> (Keehn, 1980, p. 209)

Shortly thereafter VA delivered its *Study of Former Prisoners of War* (VA, 1980) to Congress as required by Public Law 95-479. The principal finding that VA stated was "essential to the entire study" was that

> [T]he POW experience—characterized by starvation diet, poor quality or nonexistent medical care, "death marches," executions, and tortures—has historically been an extremely harsh and brutal experience.
>
> (VA, 1980, p. 161)

Concerning the quality of POW repatriation procedures, exams, and resultant medical records, the study found that the prescribed procedures were generally well designed and reflected "state-of-the art medical knowledge and technique at the time they were designed," which "if followed would have provided former POWs with adequate records" (VA, 1980, p. 71). Examination of VA claims folders, however, found that less than 20 percent of European theater POWs who filed disability claims had evidence of a repatriation examination. For Pacific theater and Korean War veterans, records of repatriation examinations were located in 60 percent and 85 percent of their files, respectively. In those cases where records were located, VA reviewer physicians judged 67 percent of World War II and 85 percent of Korean War POW repatriation exams as "providing a good or adequate basis for evaluating physical or psychiatric conditions." The limitations were that over half of the examinations contained either no medical history or poor history of health status prior to capture. In addition, about one-third of the examinations had "inadequate evaluations of the POW's mental status and psychiatric conditions" (VA, 1980, p. 72).

The "most remarkable finding" of the study, according to VA, was that anxiety neurosis was "the most prevalent service-connected condition of the former POWs under study, from the time of their repatriation to the present." Anxiety neurosis accounted for 12.7 percent of all service-connected conditions of former POWs, which was three times the rate of all veterans receiving compensation (VA, 1980, p. 95). VA stated that

> The significance of this disability relative to veterans controls remains regardless of the length of internment. This is especially apparent among former European theater POWs, in which those POWs interned less as well as more than 6 months exhibit significantly higher rates of anxiety neurosis compared to other service-connected World War II veterans.
>
> (VA, 1980, p. 95)

The study had also required VA to analyze procedures used to determine eligibility for benefits with a particular emphasis on the statutory and regulatory provisions unique to POWs. VA concluded that

> Former POWs generally have received special consideration in keeping with statutory and procedural provisions in terms of medical evaluations and disability compensation. Limitations in knowledge as to the long-term effects of the stresses and deprivations experienced by prisoners of war is a major obstacle for decision makers.
>
> (VA, 1980, p. 128)

VA also reported that over the years it had changed its approach to the adjudication of POW claims by gradually developing flexibility in such areas as substantiation of claims in the absence of medical records for periods of internment and in the presumption of service incurrence for certain disabilities. This changed approach reflected the "evolution of the law," and the degree of flexibility roughly coincided with "advancements in medical knowledge" concerning the serious effects of imprisonment on health (VA, 1980, p. 121).

The literature review of health problems of former POWs, a fourth requirement of the study, included eyewitness accounts of disabilities during captivity, epidemiologic follow-up studies, analysis of concentration camp populations, and discussions of former POW family and social problems. VA said that its review showed that the higher rate of health problems experienced were "related to the malnutrition, torture, climatic exposure, and other deprivations of internment." The epidemiologic follow-up studies indicated that "residuals of these and other disabilities have persisted until the present time." According to VA, it was particularly noteworthy that the psychological problems of former POWs, especially those of World War II, "closely resemble[d]" those of concentration camp survivors of the same period (VA, 1980, p. 154). The K-Z syndrome, as discussed in Beebe's 1975 report, included the symptoms:

> General anxiety and nervousness, "startle" reaction, insomnia and nightmares, phobias, psychosomatic complaints, memory lapses, moodiness, inferiority complex, obsession with the past, depression, apathy, and survivor guilt.
>
> (VA, 1980, p. 154)

The psychological literature on K-Z syndrome and what VA termed "other forms of psychic stress" revealed a significantly higher amount of family and social maladjustment as evidenced by inadequate functioning in father and parent roles, and higher rates of unemployment and disability compensation among POWs (VA, 1980, p. 154).

Two major legislative recommendations were contained in the study submitted to Congress. First, VA recommended that the law be amended to authorize eligibility for VA health care to former POWs for any disease or neuropsychiatric disability. VA observed that studies by the National Research Council (NRC) and NAS showed former POWs generally had higher mortality and morbidity rates and that this was reflected in their higher rates of service-connected disabilities. Yet, despite the special consideration given to POW claims, their adjudication was complicated by the frequent absence of medical information at the time of repatriation and by the fact that "*medical science cannot, at this time, conclusively determine on an individual basis the origins of some disabilities particularly prevalent among former POWs*" (emphasis added). Authorizing comprehensive VA inpatient and outpatient medical care for any disease or neuropsychiatric condition "would remove access barriers to VA medical care for those former POWs currently classified in a lower than 50 percent service-connected priority category" (VA, 1980, pp. 163-164).

The second legislative recommendation was to modify the existing statutory presumption of service connection for psychosis. VA proposed to "eliminate the requirement that psychoses suffered by POWs must become manifest within 2 years following service separation before the rebuttable presumption of service connection arises" (VA, 1980, p. 164). VA said that its literature review indicated that psychosis related to the POW experience "frequently appears years after service, not just immediately after separation," citing NAS/NRC follow-up studies published between 1946 and 1980 in support thereof (VA, 1980, p. 164).

VA also reported that it was undertaking several administrative actions as a result of its study. First, forthcoming guidelines on "post-traumatic stress neurosis" would have "explicit reference to former POWs as well as other combat veterans." *Post-traumatic stress neurosis* was a term scheduled on October 1, 1980, to become part of VA's official diagnostic classification system to describe this anxiety neurosis. The guidelines would "specifically be used to *diagnose, treat, and rate* former POWs with anxiety neurosis or similar neurotic disorders" (emphasis added). VA said this change was justified because former POWs had experienced a wide

range of psychological problems. In addition, anxiety neurosis had been the most prevalent disability among former POWs according to NRC epidemiologic studies and VA compensation data. VA also added that an analysis comparing anxiety neurosis and length of internment demonstrated that it remained a "statistically significant service-connected disability among former POWs *regardless of the amount of time in prison camp*" (VA, 1980, pp. 165-166; emphasis added).

VA announced that it would adopt a standardized protocol for disability compensation examinations for all former POWs similar to that developed by the military for former Vietnam POWs (VA, 1980).

Congressional hearings followed the receipt of VA's study of POWs in both 1980 and 1981. Legislation was reported in June 1981 and enacted into law on August 14 as the Former Prisoner of War Benefits Act of 1981 (Public Law 97-37. 97th Cong., 1st Sess.). Among its provisions, the requirement that psychosis manifests itself within 2 years of separation of service in order to qualify for a service-connection presumption was deleted as recommended by VA. An additional presumption termed *any of the anxiety states* was added to the statute. As noted in House testimony, ". . . psychosis related to the POW experience frequently appears years after service, and not just immediately after separation. This is understandable in view of the psychological torture and 'brainwashing' to which these POWs were subjected" (U.S. Congress, House of Representatives, Committee on Veterans' Affairs, 1981, p. 6).

Three additional presumptions for POWs were added between 1984 and 1988. The first, in the Veterans' Compensation and Program Improvements Amendments of 1984 (Public Law 98-223. 98th Cong., 2d Sess.) added "dysthymic disorder" to the list of disabilities developing any time after a POW's separation from service for which a presumption of service connection would apply. Senator Alan K. Simpson, chairman of the Senate Committee on Veterans Affairs, termed the inclusion a clarification of the original intent of the Former Prisoner of War Benefits Act of 1981. Speaking on the floor of the Senate during consideration of the measure he said that

> The complexity of anxiety states, anxiety neuroses, posttraumatic stress disorder, and dysthymic disorders and their associated and sometimes interrelated diagnoses inadvertently resulted in a lack of clarity regarding the granting of service connection for depression.
>
> (VA, 1993a, p. 55)

Further explanation was contained in the committee's report accompanying the measure that states that at the time the Senate reached agreement with the House on the 1981 Act:

> [The Senate] was not aware that there would be cases in which former POWS suffering from nonpsychotic depressive disorders would not be diagnosed as suffering from posttraumatic stress disorder and therefore not adjudged under VA guidelines to be service-connected disabled. . . . The committee intends that this addition would correct the inadvertent oversight in the original legislation and establish a presumption for a mental disorder that is linked in scientific literature to the POW experience.
>
> (VA, 1993a, pp. 55-56)

Since the late 1980s, a number of well-designed studies have supported increased psychiatric morbidity among former POWs as well as among other veterans experiencing combat. In 1988,

results from the Vietnam Experience Study (VES) conducted by the Centers for Disease Control and Prevention (CDC) were released. The VES selected a random sample of Army personnel discharged between 1965 and 1971. Those who served a single tour in Vietnam (n = 9,324) were compared to a random sample of Army personnel discharged during the same period and who served a single tour of duty elsewhere (n = 8,989). Veterans who were alive at the time of study completed a telephone interview, in-person psychological examinations, and assessments for reproductive outcomes (CDC, 1988, p. 2702).

The VES found that Vietnam veterans had a 45 percent excess of deaths in the first 5 years after discharge in comparison to non-Vietnam veterans. These deaths were largely due to motor vehicle accidents, suicides, and homicides. After the initial 5-year period, the death rates among the two groups of veterans remained approximately the same. Nevertheless, Vietnam veterans were more likely to meet diagnostic criteria for alcohol abuse or dependence, generalized anxiety disorder, and depression. Among Vietnam veterans, 14.7 percent met criteria for posttraumatic stress disorder (PTSD) previously in life and 2.2 percent met criteria for PTSD during the month prior to the examination (CDC, 1988, p. 2705). Though a constellation of psychiatric symptoms among this Vietnam group was similar to studies previously conducted on World War II POWs, this study was significant in the fact that the veterans enrolled in this study were selected due to their combat theater rather than their POW status.

Several studies published in 1991 examined chronic depression among former POWs. Engdahl et al. (1991) found that long-term chronic depressive symptomatology persisted over 40 years and was elevated among POWs of all theaters when compared to control groups. Age, education, medical symptoms during captivity, and level of social support were found to be related to later levels of adjustment. A second, longitudinal study published the same year by Page et al. (1991) elaborated on previous research to show that not only was depressive symptomatology highly elevated in World War II and Korean War POWs, but it was elevated to the point where these populations closely resembled a clinical population of recovering depressives. Two major conclusions from this longitudinal study were that treatment during captivity is statistically linked with depressive symptoms, and that differences in these symptoms were attributable to captivity-related treatment, even when age at capture and education level were considered.

Conducting a 40-year follow-up of U.S. World War II and Korean War former POWs, Engdahl and Page et al. (1991) measured captivity trauma variables and individual protective variables (i.e., age, education, medical symptoms during captivity, social support) to compare with current depressive symptoms. Although depressive symptoms persisted more than 40 years with the knowledge that PTSD and generalized anxiety disorders are known to occur with elevated frequency in POW populations, the degrees of individual protective variables were related to levels of adjustment. This study made a case for the need to examine former POWs that adjusted well in order to understand both the role of specific protective variables and posttrauma adjustment and resiliency.

Page's (1991) work continued with respect to the validity and reliability of some of the work cited above. Despite the heavy reliance on survey data, a noticeable shortage of reports on the effects of nonresponse bias on the measurement of depression existed. Longitudinal data presented opportunities for different types of nonresponse bias, but these data could also be useful in modeling for bias because of previously collected data. Page found that a predictive model shows nonresponse bias on the reporting of depressive symptoms among former World War II and Korean War POWs to be small.

In 1992, the Institute of Medicine (IOM) produced a report entitled *The Health of Former Prisoners of War*. This longitudinal study focused on morbidity and was initiated in 1986 and built on the earlier work of Cohen and Cooper (1954), Nefzger (1970), and Keehn (1980), which has been previously discussed. Veterans were invited to a medical center to undergo the VA protocol exam, which included a comprehensive physical and psychiatric examination. In addition, a face-to-face psychiatric interview and a battery of psychological tests were administered. A caution was provided at the outset of the report that due to low response rates there could be "no confidence . . . that the group of respondents accurately reflects the composition of all former POWs" (IOM, 1992, p. 4). Nevertheless, the results were presented as descriptive data that constituted the largest national collection of POW examinations ever gathered and analyzed. Some of the findings confirmed earlier studies while other findings were suggestive and served the purpose of generating more definitive research studies. The report urged a "maximum of reasonable caution in (the) interpretation" of the results (IOM, 1992, p. 5). The report brought attention to the high prevalence of a number of medical conditions for POWs as compared to the controls, especially with regard to psychiatric illness. Prevalence rates for over 20 different medical conditions were discussed, with key results including the following:

- Pacific theater POWs had higher prevalence rates of PTSD, ulcer, schizophrenia, and generalized anxiety than European theater and Korean War POWs.
- Visual symptoms were associated with higher prevalence rates of cerebrovascular disease, ulcers, asthma, and PTSD.
- Korean War POWs showed higher prevalence rates for schizophrenia.

(IOM, 1992, pp. 6-11)

The IOM report stated that many of the organ-specific findings were familiar and that the increased prevalence of depressive disorders, PTSD, and generalized anxiety among POWs was not unexpected.

To better understand the characteristics that affect POWs' reintegration into civilian life, Engdahl et al. published a report in 1993 that investigated long-term responses to captivity trauma among former POWs. Engdahl et al. reported that symptoms at 20 years following release were related to those at 40 years following release. Many factors known to affect POWs' long-term adjustment were not included in the study (e.g., combat exposure, postwar social support). This was due in part to their statistical infrequency or skewed nature (i.e., family history of mental illness, marital status at capture, military rank at capture). Trauma response was found to be determined by an interaction of characteristics of the individual and characteristics of the trauma, not primarily one over the other. The authors suggested that trauma response, from an evolutionary standpoint, may be better understood as adaptive due to its persistent nature.

As previously discussed, Congress has delegated to the VA Secretary the general authority to prescribe "all rules and regulations . . . with respect to the nature and extent of proof and evidence and the method of taking and furnishing them in order to establish the right to benefits under such laws" (38 USC § 501[a]). Pursuant to that authority, VA published evidentiary presumptions with respect to establishing PTSD claims in 1993 (VA, 1993b). The regulation initially observes that service connection for PTSD requires "medical evidence establishing a clear diagnosis of the condition, credible supporting evidence that the claimed in-service stressor actually occurred, and a link, establishing by medical evidence, between current symptomatology and the claimed in-service stressor" (VA, 1993b, p. 3). The regulation provided that

> If the claimed stressor is related to combat, service department evidence that the veteran engaged in combat or that the veteran was awarded the Purple Heart, Combat Infantryman Badge, or similar combat citation will be accepted, in the absence of evidence to the contrary, as *conclusive evidence of the claimed in-service stressor*.
>
> (VA, 1993b, pp. 3-4; emphasis added)

In addition, the regulation provided that status as a POW would similarly be regarded as evidence of an in-service stressor.

PTSD continued to gain great attention. Page et al. (1997) examined the literature on PTSD in POWs and compared lifetime PTSD prevalence among POWs and control subjects. After a follow-up period of 40 years, differences in prevalence rates existed between POWs and control subjects for depressive disorders as well as generalized anxiety. All groups of POWs shared nearly the same lifetime and current PTSD rates. Among World War II POWs, however, roughly half of the POWs who once suffered from PTSD were not currently diagnosed with that condition, suggesting the possible presence of chronic, stable PTSD in the other half of the POWs evaluated. However, the authors stated that this may be explained by the symptoms causing less stress on the first group of individuals. The authors suggested that those with higher distress levels should be evaluated for secondary symptoms of PTSD, such as depression. They concluded that

> *Sensitivity toward older war veterans is vital.* An awareness that their PTSD may have gone unnoticed by other health-care professionals for decades should encourage direct clinical inquiries about possible PTSD symptoms. We strongly recommend a structured interview. . . . *PTSD symptoms have been all too common, yet undiagnosed* among older war veterans, especially POWs.
>
> (Page et al., 1997, p. 157; emphasis added)

Work on PTSD continued into the new millennium when World War II and the Korean War POW interviews were examined for two separate index measures at two points in time—1965 and 1990. Results from Gold et al. (2000) supported previous research highlighting the severe psychological consequences of POW status 40-50 years following captivity. Trauma severity during captivity was found to be the best predictor of current PTSD symptomatology.

The Veterans Benefits Act of 2003 (Public Law 108-183. 108th Cong., 1st Sess.) included provisions that removed the 30-day minimum confinement requirement for 5 of the 16 POW presumptive conditions. Included in those 5, for which no minimum confinement was required, were (a) psychosis, (b) any of the anxiety states, and (c) dysthymic disorder (or depressive neurosis). In justifying the change, a Senate committee report on a similar bill observed that POWs were often treated brutally and, even if treated humanely, often suffered extreme mental anguish. Thus, the "30-day minimum requirement for purposes of presumptive service connection may be too restrictive for certain conditions" (U.S. Congress, Senate, Committee on Veterans' Affairs, 2003, p. 10).

Lessons Learned

Presumptive decisions for mental disorders have been established for veterans who are former POWs and for veterans who developed chronic mental problems during or shortly after military service. The subjective nature and self-reporting aspects of mental disorders have made it

more difficult to determine the mental disorders that should be presumptively service connected. Although legislation has been informed by the scientific evidence available at the time (Beebe, 1975; CDC, 1988; Cohen and Cooper, 1954; Engdahl and Page, 1991; Keehn, 1980; Nefgzer, 1970; Page et al., 1997), the scientific evidence has been limited by inconsistency surrounding the disorders that have been included in the research. For example, if the limited and suggestive evidence led to presumptive decisions for PTSD, dysthymic disorders, and any anxiety state among former POWs, then there does not appear to be a clear basis for excluding other mental disorders with equal or stronger evidence of connection to being a POW, such as major depression or substance abuse. The presumptive decisions with regard to these mental disorders demonstrate that these decisions have been influenced not only by the evidence, but also by political and social considerations that apply to these veterans and the specific mental disorders they manifest. The need to develop stronger evidence and consistency with regard to these disorders is great, particularly in light of evidence of high rates of disorders among military personnel currently assigned to Iraq. This case study illustrates the need for a process that can continually carry out research while updating the scientific evidence used in presumptive disability decision making. Improved future studies will be aided by pre- and postdeployment mental health assessments of Service members and more thorough assessment and documentation of exposures while deployed. This information will facilitate a deeper understanding of the relationship between military service and the subsequent development of mental health disorders.

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CASE STUDY 2: MULTIPLE SCLEROSIS PRESUMPTION

This case study examines the 1962 decision to grant presumptive service-connected disability to any veteran with multiple sclerosis (MS) whose disease is diagnosed within 7 years of separation from the military. This case study illustrates the challenges of evaluating scientific evidence and compensating veterans when the etiology of a disease is unknown and the possibility of a service-related cause cannot be excluded with certainty.

Background

MS is a neurological disease characterized by inflammation, destruction, and scarring of myelin cells that protect the neurons in the central nervous system. Symptoms of MS typically present in young adulthood, with a prevalence in the United States of 1 in 1,000 (IOM, 2001, p. 17; Noseworthy et al., 2000). Women have higher rates of both incident and prevalent disease, and studies in the United States and Canada suggest that the female-to-male disease ratio has been increasing over time (Figures I-1 and I-2).

Two features of MS have proven challenging in evaluating the scientific basis for a presumption of service connection. First, the point of onset of MS can be difficult to determine. There are no clinical symptoms unique to MS; rather, a variety of neurological symptoms are possible. These symptoms often occur in distinct episodes that may at least partially resolve, and the nature of the symptoms can vary over time. Diagnosis of MS can be delayed either because an affected individual may not seek medical attention for a neurological symptom that may be resolving or because physicians may not recognize symptoms as suggestive of MS.

Second, the etiology and pathogenesis of MS remain largely unknown. A variety of environmental, genetic, and autoimmune factors have been implicated, and perhaps the most intriguing observation in the epidemiology of MS is the finding that individuals at higher latitudes are at increased risk of disease (IOM, 2001). In the Nurses' Health Study, for example, a graded increase in risk of MS was observed in those in the northern United States compared with the

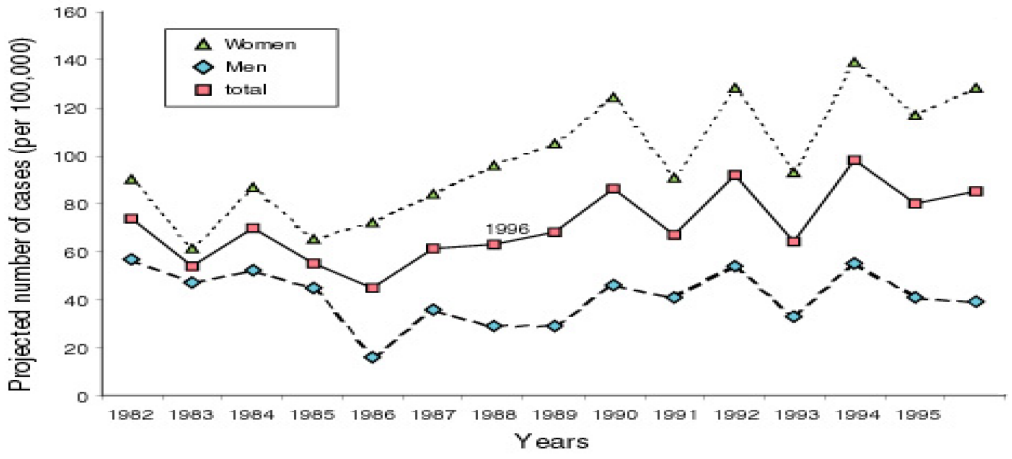

FIGURE I-1 Prevalence of multiple sclerosis in the United States (from the National Health Interview Survey).
SOURCE: Noonan et al., 2002.

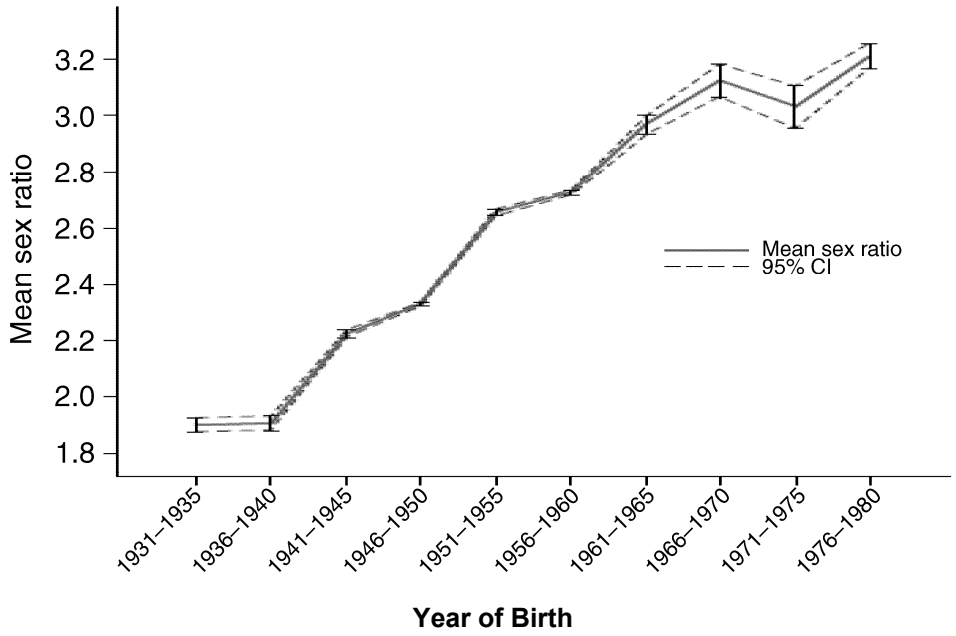

FIGURE I-2 Female-to-male ratio of multiple sclerosis in a Canadian registry.
SOURCE: Orton et al., 2006.

southern United States (Hernán et al., 1999). Individuals migrating from a high-risk to low-risk area appear to adopt the risk of their new home, although the age at migration may influence how this risk is reassigned (IOM, 2001). Why location may be important in the epidemiology of MS

is unknown, and the nature of the environmental exposure associated with higher latitudes that potentially contributes to MS risk is unclear. Triggers or exposures ranging from viral illness to lack of vitamin D related to lower levels of sun exposure have been postulated (IOM, 2001).

The Need for a Presumption

The rationale for the MS presumption is different from that of other presumptions discussed in the case studies and appears to have shifted over time. While most other presumptions serve to fill gaps in evidence for exposure (e.g., the Agent Orange presumptions) or gaps in evidence for association (e.g., cardiovascular disease among amputees), the original basis for this presumption fits in neither of these two categories. This presumption stems from the VA's interest in compensating disease and disability that has its onset *during* military service. A defined list of chronic conditions have long been granted service connection if diagnosed within 1 year of separation from the military. These diseases are insidious in onset and difficult to diagnose. Presumption is granted because the possibility that these conditions were present *during* military service cannot be excluded with certainty. The presumption for MS, therefore, does not fill gaps in evidence for exposure or association, but rather gaps in evidence for the timing of disease onset. This distinction is important, because the scientific evidence needed to inform this presumption is neither the information about exposure during military service nor for association between military service and disease; rather the scientific evidence needed for this presumption is evidence for an insidious disease course that makes onset during military service nearly impossible to exclude.

Over time, Congress created a special exception for MS in comparison to other presumptive health outcomes, extending the presumptive period for diagnosis of MS first from 1 to 2 years following military service (Veterans' Benefits Act of 1957. Public Law 85-56. 85th Cong., 2d Sess.; VA, 1949; Act of October 12, 1951. ch. 499, 65 Stat. 421, as cited in VA, 1993). Subsequently, Congress extended the presumptive period for diagnosis of MS to 3 years (Act of August 25, 1959. Public Law 86-187. 86th Cong., 1st Sess., as cited in VA, 1993) and then finally to 7 years following military service in 1962 (Veterans' Disability Compensation Increase Act of 1962. Public Law 87-645. 87th Cong., 2d Sess., as cited in VA, 1993). The rationale for this exception was based in part on the continued evidence supporting the insidious onset of this disease. However, with this extension the debate in the *Federal Register* also shifted to the inability to exclude a military exposure as the possible etiological cause of MS in veterans. This shift is significant because the scientific evidence necessary to support this type of presumption would include evaluation of evidence for possible exposures during military service and evidence linking military service with MS.

Because the debate surrounding the MS presumption has taken place over many years (since the 1930s) in congressional committees, the subtle but important shift in the rationale for this presumption and its implications for the scientific evidence needed to support it have not been systematically evaluated. As a result, considerable disagreement and uncertainty remain as to whether this presumption is supported by the scientific evidence.

A Brief History of the MS Presumption

A 1933 executive order first granted presumptive service connection to a defined list of chronic diseases if these were diagnosed within 1 year of separation from the military. The rationale for this order was that these conditions were

> of "such an insidious nature" that the disease did not become manifest to a ten-percent degree immediately upon inception but required as much as a year from the date of inception to become manifest.
>
> (VA Solicitor, 46 Op. Sol. 140 [9-15-39] as cited in VA, 1993, p. 17)

The assumption was that these conditions were eligible for direct service connection because of their temporal relation to military service; their insidious nature required this lag period outlined in the presumption. These chronic diseases were all characterized by their insidious onset and not by any direct evidence that military service caused these conditions. Other illnesses covered in this presumption, in addition to MS, include hypertension, diabetes, and atherosclerosis. The MS presumption was debated by Congress in 1948 and codified in 1949. Again, the language of the debate suggested that this presumption was meant to be an extension of direct service connection for a limited number of diseases that, though present during service, were difficult to diagnose during the period of service (Veterans' Chronic and Tropical Diseases Act of 1948. Public Law 80-748. 80th Cong., 2d Sess.; VA, 1949).

An internal VA memorandum acknowledges this logic as the basis for this presumption and comments on the low likelihood that military service actually caused these illnesses. It states that

> The diseases . . . are indeed of chronic type, and their presence within a year after discharge raises a strong probability that part of the course of the disease . . . coincided with the period of military service, but the likelihood that any of their course was influenced by the facts or circumstances of service is extremely remote.
>
> (Internal VA memorandum, as cited in VA, 1993, p. 28)

In 1951, Congress singled out MS from the other chronic illnesses and extended the period of diagnosis from 1 to 2 years following military service. In 1959, Congress again extended this period to 3 years, and in 1962 the period was extended to 7 years following military service. The congressional decision was based in part on scientific testimony from the National Institutes of Health and the National Multiple Sclerosis Society that 7 years "was not an unreasonable period to recognize as the interval between onset and diagnosis" (VA, 1993, p. 33). The VA opposed these multiple extensions, noting that

> Although the exact cause of the disease is unknown, there is nothing in the circumstances of military service in time of war which from a medical and scientific standpoint would warrant a presumption of fact that a manifestation of the disease . . . years after discharge is in any way related to the factor or circumstances of services. In this connection it does not appear that the disease is any more prevalent among the veteran population than the nonveteran population.
>
> (VA statement, as cited in VA, 1993, p. 33)

This debate illustrates the two different lines of reasoning that have entered the discussion regarding the MS presumption. On the one hand, the insidious nature of disease may make a presumption necessary because of the lag required for diagnosis; the scientific evidence necessary is simply that of the length of time on average required for diagnosis. On the other hand, because the etiology of MS is unknown and an exposure that occurs during military service cannot be ruled out as the cause of MS, a presumption may be necessary on this basis as well. Here the scientific basis for association between exposure and outcome becomes relevant.

During the same time in which the presumptive period for the diagnosis of MS was repeatedly extended, this disease was a focus of epidemiologic investigation by scientists at VA and the Medical Follow-Up Agency (MFUA) (Berkowitz and Santangelo, 1999). This research activity was driven largely by neurologists at VA who had become interested in developing treatments for MS (VA Multiple Sclerosis Study Group, 1956, 1957), and leaders of MFUA, who were interested in making use of the extensive medical records on young individuals to learn more about the manifestation of diseases in that population generally (Berkowitz and Santangelo, 1999). The extension of the presumptive period for service connection to 7 years enhanced the ability to conduct these epidemiologic investigations; at one time, two-thirds of the cases of MS estimated to occur among all veterans of World War II were being studied by VA and MFUA investigators (Kurtzke et al., 1979, p. 1233). Studies of veterans with MS yielded insights into the epidemiology of this disease, confirming that MS appears to be a "disease of place" and that environmental exposures in childhood and young adulthood, as yet still unidentified, may likely play a role in the etiology of this disease (Kurtzke and Page, 1997, p. 204). In addition to the important insights into the epidemiology of MS, these studies of veterans notably failed to find any evidence that military service (or particular exposures during military service) placed veterans at a greater risk for MS than the general population (Kurtzke and Page, 1997; Kurtzke et al., 1979, 1985, 1992; Norman et al., 1983; Page et al., 1993, 1995; Wallin et al., 2000).

Lessons Learned

This presumption straddles the line between compensation for disease that manifests during military service and compensation for the future adverse health effects that occurred as a result of specific exposures during military service. Both lines of argument were used to justify or oppose the MS presumption, but the scientific basis for each of these arguments is very different. In the first case, timing is the standard (specifically the possibility of disease onset during military service), and evidence for association between an exposure and outcome is not required. In the second case, evidence from some association between exposure during service and future disease is necessary. Congress did not call for a systematic review of the scientific literature on this topic; such a review might have allowed for more evidentiary discussion of the premise behind this presumption and the type of evidence that might be necessary to support it.

The exception of repeatedly lengthening the presumptive period of diagnosis following military service was justified because MS is difficult to diagnose and because of the possibility that some, as yet still unidentified, environmental exposures may play a role in its etiology. However, these two characteristics are also true of a variety of other chronic conditions for which presumptions have not been established. MS almost certainly received particular attention because of heightened awareness of MS as a result of the numerous high-profile publications on its epidemiology based on the study of veterans.

The epidemiological insight on MS gained from the study of veterans deserves comment. These studies of MS have had far-reaching benefit beyond those realized by the veterans themselves and have formed the basis of much of the understanding of this complicated chronic disease.

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CASE STUDY 3: PRISONERS OF WAR PRESUMPTIONS

This study examines the scientific evidence and governmental policy decisions concerning veterans who were held as POWs. Covering a period of 60 years commencing with the end of World War II, the case study examines the policy considerations that resulted in the creation of various legal presumptions to facilitate former POWs' access to VA health and disability benefits. It focuses particular attention on epidemiologic and other studies examining the residual health effects of the POW experience and their influence on the policy decisions reached.

Background

In most wars a number of combatants are captured and interned as POWs. In our history there have been over 500,000 American POWs. Almost 70 percent of those were captured by both sides during the Civil War (VA, 2005, p. 4).

In the 20th century over 142,000 service personnel were held as POWs, about 17,000 of which died while held prisoner. Ninety-eight percent of these deaths occurred during World War II and the Korean War (VA, 2006). POW deaths during World War II varied greatly depending on the theater of operation. About 40 percent of the nearly 28,000 Pacific theater POWs—most of whom were interned in the Philippines in the early months of 1942—died while in captivity (VA, 2005, p. 5).

In the European/Mediterranean theater about 1 percent of the over 94,000 POWs perished while interned. One in four of the European/Mediterranean theater POWs were captured during the Battle of the Bulge in late December 1944 and January 1945. During the Korean War 2,700, or nearly 38 percent, of slightly more than 7,100 service personnel died while in captivity (VA, 2005, p. 5).

Of the 125,000 POWs returned to U.S. military control in the last century, almost 4,000 were veterans of World War I, none of whom are alive today. The 116,000 World War II veterans released at the end of hostilities constitute the largest cohort (93 percent) of 20th-century POWs with the remainder either veterans of Korea, Vietnam, or later conflicts (VA, 2006).

VA estimates that at the end of 2005 there were just over 29,000 living POWs of whom 91 percent are World War II veterans and 7 percent veterans of the Korean War. Almost 17,000 POWs were receiving VA disability compensation as of August 2006, and 13,000 of them were rated 100 percent disabled (VA, 2006).

World War II and Its Aftermath

Congressional concern about the difficulties that combat veterans might encounter in establishing claims for service-connected disability benefits was manifested in legislation enacted within 2 weeks of the U.S. entry into World War II. That law, the Veterans Determination of Service Connection of Disabilities Act of 1941 (Public Law 77-361. 77th Cong., 1st Sess.), directed the VA Administrator, in considering benefit claims, to give "due consideration" to the "places, types and circumstances" of the claimant's service and statutorily codified VA's liberal evidentiary rules for establishing proof of service connection (VA, 1993, pp. 22-23). The legislative history reflects that it was intended to overcome the possible lack of official records that might occur under wartime conditions.

Consistent with the 1941 legislation, VA, in issuing its 1945 *Schedule for Rating Disabilities* (the Rating Schedule), acknowledged the difficulties that former POWs might have in establishing service-connected disability claims. The rating schedule provided that in considering claims with respect to tropical diseases, dysentery, and other gastrointestinal diseases, "*great weight* must be assigned to tropical service and to *imprisonment or internment* under unsanitary conditions, or food deprivation" (VA, 1993, pp. 43-44; emphasis added). Additional instructions issued in 1946 concerning the Rating Schedule provided that "prisoner of war experience requires *special consideration*" with respect to claims involving malnutrition, intestinal parasites, weakness and fatigability, and neuropsychiatric disorders. Claims examiners were instructed that the "existence of any chronic disease that may be associated with the circumstances of imprisonment should be carefully checked and reported on" (VA, 1993, pp. 43-44; emphasis added).

The 1950s

Growing concern by members of Congress about the well-being of POWs and the privations they experienced, particularly in the Pacific theater, led to the introduction of legislation and hearings in 1948. One measure would have provided that any veteran held prisoner for a continuous period of at least 2 years would have been *conclusively* presumed to be totally disabled for a period of 5 years from his release. In addition, any death occurring during that 5-year period would be presumed service connected in the absence of clear and convincing evidence to the contrary. After the initial 5-year period the presumption of total disability would be rebuttable but again only by clear and convincing evidence (VA, 1993).

VA opposed the legislation on the ground that service connection should not be granted in the absence of a factual showing of disability. Additionally, it detailed the special consideration for POWs contained in its operating procedures. Although the measure was not acted upon by the House Veterans Affairs Committee, concern continued about the mental and physical effects of imprisonment as various members of Congress introduced bills in the early 1950s to require studies of POW mortality and morbidity. The sponsors anticipated that the studies might provide evidence to support a conclusive presumption for service connection for the purposes of VA hospitalization benefits as well as standards that could be employed in evaluations of POW disability claims. Again, VA demurred, noting the special consideration it was giving to POW claims. VA also pointed out that it was already conducting studies related to the POW experience (VA, 1993).

Ultimately, Congress enacted the War Claims Act Amendments of 1954 that incorporated provisions of these bills with respect to studying mortality and morbidity experiences of POWs, while omitting any of the provisions relating to the proposed development of standards for conclusive presumptions (VA, 1993, p. 45).

In September 1954, VA published *A Follow-Up Study of World War II Prisoners of War*, coauthored by Bernard Cohen of the NRC and Maurice Cooper of VA (Cohen and Cooper, 1954). The study, which was initiated prior to the passage of the War Claims Act, was characterized by the authors as an exploratory record follow-up study of POWs released at the end of World War II that "does not purport to be more than an examination of the surface of the problem." Rather, its purpose was to "delineate the broader consequences of imprisonment that manifest themselves in increases in mortality, hospitalization, disability, health status, and work adjustment, to measure the magnitude of these changes and to describe the gross findings" (Cohen and Cooper, 1954).

A key finding of the study was that Pacific theater veterans had a high rate of mortality in the first 2 years following liberation. By contrast, returned European theater POWs did not have a significant difference in mortality compared with control groups. Some 64 percent of Pacific theater POW deaths were attributable to either tuberculosis or accidents. The frequency of tuberculosis deaths was not unexpected given malnutrition and crowded, unsanitary living quarters, but unanswered questions remained as to whether the degree and duration of malnutrition that Pacific theater POWs experienced could be sufficient to "result in obscure irreversible structural and functional changes that might be expected to affect longevity." With respect to excess accidental deaths, the authors recommended more detailed examination in future studies, particularly as to whether there might be a psychological basis involved (Cohen and Cooper, 1954).
The authors concluded that

> [T]he mortality findings and their implications suggest the existence of organic and emotional residuals of imprisonment severe enough to be factors affecting survival, and raise many questions concerning the future survival potential of those still alive *and their long run morbidity and disability expectations*.
>
> (Cohen and Cooper, 1954; emphasis added)

The early morbidity and disability observations were found to be "quite consistent with those of mortality." Pacific prisoners exhibited a wide variety of illness that occurred with frequencies in nearly every major category of disease that were far in excess of those shown by European POWs or control groups. Chronic conditions that were noticeably frequent and persistent were tuberculosis, residuals of malnutrition, psychoneurosis, ophthalmologic changes, gastrointestinal disorders, and cardiovascular conditions. Among European POWs there was not found "a great deal more illness" than control groups although there was a "relative excess in malnutrition, psychoneurosis, and gastrointestinal disorders." The authors suggested that "[s]ome if not all" of these conditions deserved "more intensive investigation" (Cohen and Cooper, 1954).

The authors concluded their report by recommending a "continuation of the follow-up [study] to detect late effects or confirm early findings, and the desirability of more intensive study in certain areas" (Cohen and Cooper, 1954). The 1954 study was followed by a Department of Health, Education, and Welfare (HEW) study, *Effects of Malnutrition and Other Hardships on the Mortality and Morbidity of Former United States POWs and Civilian Internees* (HEW, 1956), issued in 1956 in response to the direction of the War Claims Act Amendments of 1954 (Public Law 83-774. 83rd Cong., 2d Sess, as referenced in VA, 1993). It relied heavily on the NRC/VA study and its findings and conclusions mirrored that report. It recommended, "in conformity with the stated policy of VA," that "[p]articular attention" should be given in evaluation of POW claims for claimed disabilities resulting from "prolonged malnutrition and other conditions shown by the NRC/VA study to exist in high incidence in Pacific POWs" as well as to the difficult question of "complaints which cannot today be evaluated by objective measurements or test" (HEW, 1956).

For the remainder of the decade, there was little activity regarding establishment of statutory presumptions for POWs with the exception of a measure to officially declare all POWs to be disabled and entitled to full retirement pay, which did not receive favorable consideration from Congress (VA, 1993, pp. 45-46).

The general issue of statutory presumptions, however, did receive considerable attention as a result of a 1956 report of the President's Commission on Veteran's Pensions. Established by executive order, the commission—typically referred to as the Bradley Commission after its chairman, General Omar Bradley who headed VA at the conclusion of World War II—addressed statutory presumptions in one of the 70 recommendations it issued in 1956. Specifically, it recommended withdrawing the "presumption of service connection for chronic disease, tropical diseases, psychoses, tuberculosis, and multiple sclerosis as now listed" (President's Commission on Veterans' Pensions, 1956, p. 178). Relying in large part on the result of a survey of physicians, the Bradley Commission asserted that as to those conditions:

> Accepted medical principles can reasonably and accurately establish the onset of a disease and the disability process. Where there is reasonable doubt, the law provides for the doubt to be resolved in favor of the veteran. . . . The physicians surveyed were in general

> agreement that service connection should be determined in accordance with sound medical principles and not by fiat.
>
> (President's Commission on Veterans' Pensions, 1956, p. 178)

Hearings on the Bradley Commission's recommendations by the House Committee on Veterans Affairs in 1956 elicited strong reactions from national veteran service organizations (VSOs). Witnesses from the Disabled American Veterans challenged the assertion that physicians were in agreement about whether certain chronic diseases discovered 1 or 2 years after separation had their inception in service, and it was for this reason that Congress authorized statutory presumptions (VA, 1993).

The American Legion representative testified that the question was "not entirely a medical one" and that the "purpose of a presumption is to free the veteran from carrying an unconscionable burden of proof" in establishing disability compensation entitlement. The witness added that it "is a rebuttable presumption . . . [which] enables the government, if medical knowledge is what the Bradley Commission says that it is, to rebut the presumption." He concluded that until American medicine can "determine with more than a reasonable degree of accuracy" whether or not certain types of diseases had their inception in service, the veteran should be entitled "to a presumption that his disease or disability, within reasonable periods now or to be specified, was the result of his service" (VA, 1993, p. 41).

This position was essentially endorsed by the committee which declined to act on the Bradley Commission recommendation. In hearings the following year, its chairman, Olin "Tiger" Teague from Texas stated that presumptions were enacted "because Congress did not agree with many of the medical findings" of VA physicians and consequently it was the "only way we can force proper administration" (VA, 1993, p. 42). The American Legion's senior medical consultant testified that the Legion would not ask for presumptive service connection "unless the same was justified on reasonable medical grounds." Presumptions were often required, he said, because of inadequately trained VA personnel which resulted in a lack of uniformity in the application of the law (VA, 1993, p. 42).

The 1960s

Legislation seeking to establish presumptions for POWs began to increase in the 1960s. Some measures would have established a presumption of service connection for any disability for which a veteran was seeking service connection if that veteran had been a Pacific theater POW confined for more than 2 years. Other bills would have increased the existing presumptive period for chronic and tropical diseases to 5 years in the case of any veteran who had been a POW. Still other proposals would have created an irrebuttable presumption that all former World War II and Korean War POWs who had been interned for at least 3 years were service-connected disabled to a 50 percent degree. Variants on that proposal would have reduced the minimum period of confinement to 1 year. None of these POW-specific presumptions received favorable consideration from Congress (VA, 1993).

The 1970s

In the late 1960s, a three-phase program of research, *Follow-Up Studies of World War II and Korean War Prisoners*, was undertaken by the NRC with funding from VA. The first phase, *Study Plan and Mortality*, published in 1970, was authored by M. Dean Nefzger who acknowledged difficulties in obtaining generally useful information because

> Prison experience is a manifold of inadequate food, exposure, disease, physical abuse, and emotional torment. These various ingredients appear to be thoroughly mixed and interdependent. Their relative intensities probably vary from time to time, from place to place, and from man to man; and it seems impossible to separate any one component of this complex experience for the total.
>
> (Nefzger, 1970, p. 124)

Although this "limits the scope and specificity of inferences that may be drawn statistically," the author said that follow-up studies might offer the "hope of learning more about the late effects of stress that is recognized as severe even though not well differentiated." They may also "suggest areas for more penetrating study by other methods" (Nefzger, 1970, p. 124).

The report generally confirmed the earlier findings and trends of the 1954 report by Cohen and Cooper. Pacific theater POWs had excess mortality compared to control groups, although that significantly diminished over time. European POWs showed no significant excess mortality. The report did note, however, that mortality experience for a small group of European prisoners hospitalized for malnutrition immediately after release suggested causes similar to Pacific theater POWs (Bard, 1994).

Korean War POWs, who were included in this report, also experienced excess mortality rates throughout a 12-year follow-up when compared to controls. For Korean War veterans, trauma was the most common cause of death whereas Pacific POW deaths were attributed to tuberculosis, accidents, and cirrhosis of the liver (Nefzger, 1970).

On the question of excess mortality due to disease, Nefzger wrote

> There is a great temptation to conclude that the apparent excess of deaths from diseases of the digestive system, including cirrhosis, resulted from malnutrition during imprisonment. That might be the case, but so specific an interpretation is hard to defend. It is possible that such diseases are an indirect consequence of imprisonment if that experience has contributed to a different standard or manner of living since repatriation.
>
> (Nefzger, 1970, p. 137)

Finally, the report concluded that the contrasts between European prisoners generally and those European POWs hospitalized for malnutrition, and the contrast between European and Pacific prisoners, "suggest a positive association of stress in prison with later mortality," although no general conclusion could be drawn from the data (Nefzger, 1970, pp. 137-138).

The first legislation to create statutory presumptions specifically applicable to POWs was enacted in 1970 (Veterans Disability Compensation Increase. 1970. Public Law 91-376. 91st Cong., 2d Sess.). The act had its origins in S. 3348 that, as introduced, would have presumed service connection for any disability suffered by any POW held captive for more than 6 months. VA opposed the measure, reiterating that it gave special consideration to claims by former POWs, and arguing that the mere fact of 180 days confinement by itself did not justify service connection for "any disability the veteran may acquire at any time during the balance of his life," VA also maintained that it would be "discriminatory" to those POWs who may have sustained equal or greater privations but were confined for less than the specified period—a point agreed to by the American Legion (U.S. Congress, Senate, Committee on Finance, 1970, p. 10).

As finally reported to and passed by the full Senate, the bill had been modified to eliminate any minimum confinement period. Instead, the Senate substituted a requirement that the veteran

had to have suffered from "dietary deficiencies, forced labor, or inhuman treatment in violation of the terms of the Geneva Convention of July 27, 1929" (U.S. Congress, Senate, Committee on Finance, 1970, p. 12). If former POWs met these criteria and had any of seven specified nutritional or gastrointestinal diseases, those diseases would be "considered to have been incurred in or aggravated by such service notwithstanding that there is no record of such disease during the period of service" (U.S. Congress, Senate, Committee on Finance, 1970, p. 12).

Under the act, "psychosis" was also to be considered a service-connected disability provided it became manifest within 2 years of separation from service.

In justifying the statutory presumptions, the accompanying report said that due to the conditions of captivity and the "kinds of long-range harm that may have been caused," it was "sometimes difficult for a former prisoner of war to establish some time after completion of military service" that a disability is related to military service (U.S. Congress, Senate, Committee on Finance, 1970, p. 4).

When the Senate-passed measure was considered by the House, the bill was further amended to add back the provision of not less than 6 months of confinement in addition to the Geneva Code violations required by the Senate. No explanation was given as to the rationale for the 6-month requirement. Following Senate concurrence in the amendments, the measure was enacted as Public Law 91-376 on August 12, 1970 (Veterans Disability Compensation Increase. 1970. Public Law 91-376. 91st Cong., 2d Sess.).

From October 1972 through August 1976, VA issued a number of program guides with respect to Public Law 91-376. These guides were characterized as suggestions for the guidance of personnel in the handling of disability of claims filed by former POWs. The program guides instructed that in light of the "frequent paucity of records" in POW claims, "special attention should be given to POW experiences in determining the relationship of the disability to service." The duration and circumstances of imprisonment were to be associated with pertinent medical principles in making determinations (VA, 1980, p. 118).

The burden of proof as to the occurrence of a POW episode was shifted from the claimant to the government. A veteran's statement as to wounds or injury just prior to imprisonment was to be accepted as proof of actual incurrence when residual disability attributable to service was found. The "unusual hardship and isolation from society" resulting from POW life meant that an "extended period of readjustment to ordinary conditions of life is essential." Claims for IU were to receive liberal construction and if the threshold disability percentage for the IU benefit was not met, the claim was to be submitted to the VA Central Office for further consideration. Finally, it was emphasized that presumptions were rebuttable only where there was "affirmative evidence to the contrary" (VA, 1980, p. 119).

In 1975, the second phase of the *Follow-Up Studies of World War II and Korean War Prisoners*, entitled *Morbidity, Disability and Maladjustments*, was issued (Beebe, 1975). Its author, Gilbert W. Beebe, observed at the outset that studies of the long-term effect of catastrophic stress are "difficult to make and the frequently multidimensional character of such stress severely limits inferences about the etiologic role of specific components, such as malnutrition, social isolation, sensory deprivation, physical punishment, compulsory reeducation, and the like." He further noted that recent studies of survivors of World War II German concentration camps provided useful information on a persistent defective state marked by "severe permanent psychiatric residuals and by nonspecific somatic symptoms" (Beebe, 1975, pp. 400-401). The researchers who conducted those studies believed that

> [S]tarvation caused permanent damage that went largely unrecognized in the early years after release and came to be appreciated only as rehabilitation programs proved ineffective for so many of those who had suffered most severely.
>
> (Beebe, 1975, p. 401)

Beebe's findings were that morbidity, some types of maladjustment, and disability were elevated in POWs relative to controls especially for Pacific theater veterans. The "most remarkable and long-lasting differentials" were seen in hospitalization for psychoneurosis and for psychosis (schizophrenia). Data obtained supported a finding that many Pacific theater and Korean War POWs had "permanent psychologic impairments." But he also noted that European theater POWs did not go "unscathed" with respect to psychoneurosis hospitalization (Beebe, 1975, p. 421).

Conditions causing excess morbidity among World War II Pacific theater POWs were nutritional disorders, neurologic problems, gastrointestinal, genitourinary, and bone diseases. Finally, the study also found higher rates of cardiovascular diseases for which atherosclerotic disease was a major contributor which warranted further scrutiny (Beebe, 1975, pp. 421-422).

Following enactment of Public Law 91-376, several bills were introduced that would have added additional chronic diseases to the presumptive list and/or extended the period of time from separation from service that they first be manifested. None were enacted. The Veterans Health Care Amendments of 1979 (Public Law 96-22. 96th Cong., 1st Sess.) did, however, authorize outpatient dental care benefits for all former POWs detained for 6 months or more. Although the law did not base dental benefit entitlement upon an explicit presumption—nor authorize disability compensation benefits—the Senate committee report accompanying the measure stated that many POWs developed dental conditions as a result of prolonged nutritional deprivation suffered while captive. It justified the provision in order "to provide that VA has full authority to meet the dental needs of former prisoners of war resulting from the conditions of their captivity." The requirement that the former POW have been confined for 6 months or more was added because such "nutritional deficiencies result from a prolonged state of deprivation" and it was consistent with the 6-month requirement that was attached to other POW-related diseases (VA, 1993, p. 50).

In the Veterans Disability Compensation and Survivor Benefits Act of 1978 (Public Law 95-479. 95th Cong., 2d Sess.), Congress included provisions requiring VA to carry out a "comprehensive study on the compensation awarded to, and the health care needs of" former POWs. The results of the study were to include such administrative and legislative recommendations as "may be necessary to assure that former prisoners of war receive compensation and health-care benefits for all disabilities which may *reasonably be attributed to their internment*" (VA, 1993, p. 58; emphasis added).

The study had four requirements. First, VA was to analyze the adequacy of repatriation procedures and medical exams and the resultant medical records of POWs. Second, the study was to set forth the "types and severity of disabilities particularly prevalent" among former POWs "in *various* theaters of operations at *various* times" (emphasis added). Third, VA was charged with analyzing procedures used in determining health-care benefits and in adjudicating disability compensation claims, including an "analysis of the current use of statutory and regulatory provisions specifically relating to former prisoners of war." Finally, VA was directed to survey and analyze "all of the medical literature on health-related problems of former prisoners of war" (Veterans Disability Compensation and Survivor Benefits Act of 1978. Public Law 95-479. 95th Cong., 2d Sess.).

The legislative history indicates that the study was prompted by questions about the adequacy of repatriation examinations and by concerns that health conditions that may have appeared minor at the time were becoming progressively more debilitating. It also cited Beebe's 1975 follow-up study for the proposition that POWs had excess morbidity, and many were suffering from what was termed a "POW syndrome" (VA, 1993, p. 51).

The 1980s

At the beginning of the decade, the third phase of the follow-up studies, *Mortality to January 1, 1976*, authored by Robert Keehn, was issued (Keehn, 1980). That study continued to find increased risks of mortality among World War II Pacific theater and Korean War POWs, though the excess diminished over time. For Pacific theater veterans the principal cause for the mortality increase was tuberculosis and trauma, while for former Korean War POWs it was trauma. As to trauma, the report found that for Pacific theater POWs, suicide was responsible for two-thirds and accidents one-third of the excess deaths.

Given a consistent finding of "persistent psychologic impairment" and reported problems of adjustment to civilian life, the report concluded that

> The finding of increased mortality due to trauma, both accidental (including cases of masked suicide) and suicide in former prisoners of war is not surprising. Increased feelings of frustration, anger, and tension lead to impatience and impulsive actions which are likely to contribute to both the risk and severity of accidental and self-inflicted injury.
>
> (Keehn, 1980, p. 209)

Keehn also found excess deaths due to cirrhosis of the liver for all World War II and Korean War POWs appearing in the 10th year of follow-up. The author said that it was unclear if the increased deaths resulted from "poor nutrition as a prisoner, from the variety of diseases (viral, parasitic) experienced during captivity, or from increased alcohol consumption or a combination of these" (Keehn, 1980, p. 210). He added that

> Although the role of diet in the etiology of alcoholic cirrhosis has not been clearly defined, it seems likely that a poor diet during captivity might predispose the liver to alcohol damage.
>
> (Keehn, 1980, p. 210)

Finally, the study did not find excess POW deaths from malignant neoplasms or chronic and degenerative diseases, concluding that there was "no evidence to support the hypothesis that the stresses of captivity have accelerated degenerative changes in former prisoners" (Keehn, 1980, p. 210).

Thereafter, also in 1980, VA delivered its *Study of Former Prisoners of War* (VA, 1980) to Congress as required by Public Law 95-479 (Veterans Disability Compensation and Survivor Benefits Act of 1978. Public Law 95-479. 95th Cong., 2d Sess.). The principal finding which VA described as "essential to the entire study" was that

> [T]he POW experience—characterized by starvation, diet, poor quality or nonexistent medical care, "death marches," executions and torture—has historically been an extremely harsh and brutal experience.
>
> (VA, 1980, p. 161)

Concerning the initial question about the quality of POW repatriation procedures, exams, and resultant medical records, the study found that the prescribed procedures were generally well designed and reflected "state-of-the-art medical knowledge and technique at the time they were designed," which "if followed would have provided former POWs with adequate records" (VA, 1980, p. 71). Examination of VA claims folders, however, found that less than 20 percent of European theater POWs who filed disability claims had evidence of a repatriation examination. For Pacific theater and Korean War veterans, records of repatriation examinations were located in 60 percent and 85 percent of their files, respectively. In those cases where records were located, VA reviewer physicians judged 67 percent of World War II and 85 percent of Korean War POW repatriation exams as "providing a good or adequate basis for evaluating physical or psychiatric conditions." The limitations were that over half of the examinations contained either no medical history or poor history of health status prior to capture. And, significantly, about one-third of the examinations had "inadequate evaluations of the POWs mental status and psychiatric conditions" (VA, 1980, p. 72).

Addressing the question of the types and severity of disabilities particularly prevalent among POWs in various theaters at various times, VA relied heavily on the NRC-funded follow-up reports previously described (Beebe, 1975; Keehn, 1980; Nefzger, 1970), and on VA mortality and morbidity data. The study found that Pacific theater former POWs were the most severely disabled group followed closely by Korean War POWs. Although European POWs had lower rates of disability, those rates still exceeded that of other World War II veterans. Studies were still continuing on Vietnam era veterans and hence unavailable at that time (VA, 1980).

Although the findings provided support for the contention that an Asian internment environment was harsher, the study cautioned that any attempt to apply it to individual cases would "be mistaken as conditions varied from camp to camp, thus resulting in a wide spectrum of disability even within the same theater." The report specifically noted, contrary to popular opinion, that with the exception of some facilities where aviators were confined, most German stalags where American foot soldiers were held "did not abide by even minimum standards for POW treatment set forth in the Geneva Convention" (VA, 1980, p. 31).

The "most remarkable finding" of the study according to VA was that anxiety neurosis was "the most prevalent disability among former POWS from time of repatriation to the present." Anxiety neurosis accounted for 12.7 percent of all service-connected conditions of former POWs, which was three times the rate of all veterans receiving compensation (VA, 1980, p. 95). VA found that

> The significance of this disability relative to veteran controls remains regardless of the length of internment. This is especially apparent among former European theater POWs in which those POWs interned less as well as more than 6 months exhibit significantly higher rates of anxiety neurosis compared to other service-connected World War II veterans.
>
> (VA, 1980, p. 95)

The study also confirmed that "systemic and malnutrition related diseases—malaria, beriberi, pellagra—are prevalent among former POWs, especially those interned in Asia." Among former World War II Pacific theater and Korean War POWs there were also statistically significant service-connected disabilities with respect to eye diseases, respiratory diseases, and gastrointestinal diseases. Pacific theater former POWs also had statistically significant rates for genitourinary, psychoneurological, and cardiovascular diseases (VA, 1980, pp. 95-96).

The study's third requirement was to analyze procedures used to determine eligibility for benefits with a particular emphasis on the statutory and regulatory provisions unique to POWs. VA concluded that

> Former POWs generally have received special consideration in keeping with statutory and procedural provisions in terms of medical evaluations and disability compensation. Limitations in knowledge as to the long-term effects of the stresses and deprivations experienced by prisoners of war is a major obstacle for decision makers.
>
> (VA, 1980, p. 128)

VA also reported that over the years it had changed its approach to the adjudication of POW claims by gradually developing flexibility in such areas as substantiation of claims in the absence of medical records for periods of internment and in the presumption of service incurrence for certain disabilities. This changed approach reflected the "evolution of the law" and the degree of flexibility roughly coincided with "advancements in medical knowledge" concerning the serious effects of imprisonment on health (VA, 1980, p. 121).

To support its assertion that POWs were accorded special consideration, VA compared their compensation rates with that of other veterans. Although less than 10 percent of war veterans were on the disability compensation rolls, 43.6 percent of former POWs were being compensated. Korean War POWs ranked highest with 59 percent followed by 50.6 percent of Pacific theater POWs and 42.2 percent of European theater POWs (VA, 1980, pp. 78-93).

Some 22.2 percent of non-POW veterans on the compensation roles had severe disabilities (rated 50 percent or more disabled) compared to 48.8 percent of Pacific theater, 20.1 percent European theater, and 34.7 percent Korean War POWs. Veterans on the disability compensation rolls who are rated at 60 percent or more are entitled to be paid at the total disability rate if they are determined to be individually unemployable. Of all veterans on the rolls, 5.3 percent were rated unemployable compared to 22 percent of World War II Pacific theater, 5.3 percent European theater, and 8.9 percent Korean War POWs (VA, 1980, pp. 78-93).

On the question of lack of uniformity raised by VSOs in deciding POW claims among regional offices, VA's response was that an inquiry had been initiated by the General Accounting Office (GAO) in 1974-1975. A sample of cases had been selected and examined at four regional offices. GAO found "occasional variances in disability percentages . . . but no differences as to granting service connection" (VA, 1980, p. 127). Following this initial review, VA reported that GAO decided against conducting a formal study.

The literature review of health problems of former POWs, the fourth requirement of the study, included eyewitness accounts of disabilities during captivity, epidemiologic follow-up studies, analysis of concentration camp populations, and discussions of former POW family and social problems. VA said that its review showed that the higher rate of health problems experienced were "related to malnutrition, torture, climatic exposure, and other deprivations of internment." The epidemiologic follow-up studies indicated that "residuals of these and other disabilities have persisted until the present time" (VA, 1980, p. 154).

Particularly noteworthy, according to VA, was that the psychological problems of former POWs, especially those of World War II, "closely resemble[d]" those of concentration camp survivors of the same period. Known as K-Z syndrome—and discussed in Beebe's 1975 report—symptoms included

> General anxiety and nervousness, "startle" reaction, insomnia and nightmares, phobias, psychosomatic complaints, memory lapses, moodiness, inferiority complex, obsession with the past, depression, apathy, and "survivor guilt."
>
> (VA, 1980, p. 154)

The psychological literature on K-Z syndrome and other forms of psychic stress revealed a "significantly higher amount of family and social maladjustment as evidenced by inadequate functioning in father/parent roles, and higher rates of unemployment and disability compensation" (VA, 1980, p. 154).

VA concluded its literature review by observing that many important questions were left unanswered including whether deaths due to trauma and cirrhosis were directly related to the POW experience, and if the arteriosclerosis experienced by former POWs directly related to the stress of internment (VA, 1980).

Two major legislative recommendations were contained in the study submitted to Congress. First, VA recommended that the law be amended to authorize eligibility for VA health care to former POWs for any disease or neuropsychiatric disability. VA observed that NRC/VA studies showed former POWs generally had higher mortality and morbidity rates and that this was reflected in their higher rates of service-connected disabilities. Yet, despite the special consideration given to POW claims, their adjudication was complicated by the frequent absence of medical information at the time of repatriation and by the fact that "medical science cannot, at this time, conclusively determine on an individual basis the origins of some disabilities particularly prevalent among former POWs." Authorizing comprehensive VA inpatient and outpatient medical care for any disease or neuropsychiatric condition "would remove access barriers to VA medical care for those former POWs currently classified in a lower than 50 percent service-connected priority category" (VA, 1980, pp. 163-164).

The second legislative recommendation was to modify the existing statutory presumption of service connection for psychosis. VA proposed to "eliminate the requirement that psychoses suffered by POWs must become manifest within 2 years following service separation before the rebuttable presumption of service connection arises." VA said that its literature review indicated that psychosis related to the POW experience "frequently appears years after service, not just immediately after separation," citing NRC/VA follow-up studies published between 1946 and 1980 in support thereof (VA, 1980, p. 164).

VA also reported that it was undertaking several administrative actions as a result of its study. First, forthcoming guidelines on "posttraumatic stress neurosis" would have "explicit reference to former POWs as well as other combat veterans." (*Posttraumatic stress neurosis* was a term scheduled on October 1, 1980, to become part of VA's official diagnostic classification system to describe such anxiety neurosis.) The guidelines would "specifically be used to diagnose, treat, and rate former POWs with anxiety neurosis or similar neurotic disorders." VA said this change was justified because former POWs had experienced a wide range of psychological problems, and "anxiety neurosis" had been the most prevalent disability of former POWs, according to NRC epidemiologic studies and VA compensation data. VA added that an analysis of anxiety neurosis with length of internment disclosed that it remained a "statistically significant service-connected disability among former POWs *regardless of the amount of time in prison camp*" (VA, 1980, pp. 165-166; emphasis added).

VA also announced that it would adopt a standardized protocol for disability compensation examinations for all former POWs similar to that developed by the military for former Vietnam

POWs. Additional research into POW problems was promised as was the formation of a POW advisory committee (VA, 1980).

Congressional hearings followed the receipt of VA's study of POWs in both 1980 and 1981. The VSOs concurred with the VA recommendations but criticized them for being inadequate to meet the needs of the POWs and "totally unresponsive to the facts presented" in the report. The VSOs recommended expanding the use of presumptions for POW disability compensation claims (VA, 1993, p. 52).

Legislation was reported in June 1981 and enacted into law on August 14 as the Former Prisoner of War Benefits Act of 1981 (Public Law 97-37. 97th Cong., 1st Sess.). The existing presumptive provisions for POWs were amended to expand the definition of those considered to be prisoners of war and to modify the preconditions necessary for any presumption to attach to a former POW's disability claim. First, the requirement that POWs had suffered dietary deficiencies, forced labor, or inhumane treatment in violation of the Geneva conventions was removed. Second, the minimum period of confinement was reduced from 6 months to 30 days. Third, the requirement that psychosis manifests itself within 2 years of separation of service in order to qualify for a service-connection presumption was deleted as recommended by VA. Finally, an additional presumption termed "any of the anxiety states" was added to the statute.

The legislative history reveals that removing Geneva Convention violations was intended to "relieve to a certain extent the burden on the former POW to submit evidence . . . that certain disabilities are service connected" (VA, 1993, p. 54). Reducing confinement time from 6 months to 30 days was justified on the grounds that

> Though dietary deficiencies are clearly a function of time and malnourishment, medical evidence reveals that a person can suffer from malnutrition in less than 6 months.
>
> (VA, 1993, p. 54)

The act (Former Prisoner of War Benefits Act of 1981. Public Law 97-37. 97th Cong., 1st Sess.) adopted the VA recommendation for unlimited access to health care for POWs. It also statutorily established an Advisory Committee on Former Prisoners of War which, among other things, was directed to submit an annual report to the VA Secretary containing an assessment of the needs of former POWs and any administrative or legislative recommendations the committee considered to be appropriate. The VA Secretary, in turn, was required to furnish his comments and intentions concerning these recommendations in an annual report to Congress (VA, 1993).

An additional presumption for mental disorders in POWs was added in the mid-1980s, the Veterans' Compensation and Program Improvements Amendments of 1984 (Public Law 98-223. 98th Cong., 2d Sess.). This legislation added "dysthymic disorder" to the list of disabilities developing anytime after a POW's separation from service for which a presumption of service connection would attach.

Senator Alan K. Simpson, chairman of the Senate Committee on Veterans Affairs, termed the inclusion a clarification of the original intent of the Former Prisoner of War Benefits Act of 1981. Speaking on the floor of the Senate during consideration of the measure he said that

> The complexity of anxiety states, anxiety neuroses, posttraumatic stress disorder, and dysthymic disorders and their associated and sometimes interrelated diagnoses

> inadvertently resulted in a lack of clarity regarding the granting of service connection for depression.
>
> (VA, 1993, p. 55)

Further explanation was contained in the committee's report accompanying the measure which recites that at the time the Senate reached agreement with the House on the 1981 act:

> [The Senate] was not aware that there would be cases in which former POWS suffering from nonpsychotic depressive disorders would not be diagnosed as suffering from post-traumatic stress disorder and therefore not adjudged under VA guidelines to be service-connected disabled. . . . The committee intends that this addition would correct the inadvertent oversight in the original legislation and establish a presumption for a mental disorder which is linked in scientific literature to the POW experience.
>
> (VA, 1993, pp. 55-56)

Two years later, the Veterans Benefits Improvement and Health Care Authorization Act of 1986 (Public Law 99-576. 99th Cong., 2d Sess.) added presumptions for "posttraumatic osteoarthritis" and "[o]rganic residuals of frostbite, if the VA Secretary determines that the veteran was detained or interned in climatic conditions consistent with the occurrence of frostbite." Report language accompanying the legislation said that Congress expected VA "to give great weight to the veteran's description of the circumstances of frostbite injury and to accept that description if it is possible that these circumstances occurred and the veteran suffers from residuals of frostbite" (U.S. Congress, Senate, Committee on Veterans' Affairs, 1986, p. 30).

As for traumatic arthritis, the report observed that there was "disagreement as to the adequacy of medical science to distinguish between arthritis resulting from earlier trauma and arthritis which is the result of other causes or which normally occurs during the aging process" (U.S. Congress, Senate, Committee on Veterans' Affairs, 1986, p. 30). As reported to the Senate floor, the bill simply directed VA to provide a report of the effectiveness of procedures for evaluating such disability claims. During floor consideration, however, the Senate added the specific presumption of posttraumatic osteoarthritis based on unidentified "additional information" received by the committee after it had filed its report.

In a letter to the Chairman of the Senate Committee on Veterans' Affairs, VA administrator Thomas Turnage questioned the need for these presumptions, saying that if a POW had developed either condition it normally would have "manifested itself and required treatment upon repatriation or shortly thereafter." But VA did not oppose the provisions, acknowledging that the presumption could serve as a safety net for those veterans whose repatriation processes were insufficient and for those "veterans who had a tendency to initially put aside traumatic experiences associated with captivity" (U.S. Congress, Senate, Committee on Veterans' Affairs, 1986, pp. 128-129).

Three additional POW presumptions were added with the enactment of the Veterans Benefits and Services Act of 1988 (Public Law 100-322. 100th Cong., 2d Sess.). They were peripheral neuropathy (except where directly related to infectious causes), irritable bowel syndrome, and peptic ulcer disease. Senator Cranston, who sponsored the presumptions, cited a 1986 VA study of former Pacific and European theater POWs as well as a 1985 Australian study which found higher incidence of duodenal ulcers among POWs than controls (VA, 1993, p. 58). The Senate report accompanying the legislation (U.S. Congress, Senate, Committee on Veterans' Affairs, 1987) found that peripheral neuropathy is causally related to exposure to cold tempera-

tures, exhausting physical activity, and vitamin deficiency resulting from extreme malnutrition. The report also found that stress and malnutrition were probable risk factors for irritable bowel syndrome and peptic and duodenal ulcers.

VA again took the position that the conditions proposed to be added would ordinarily have become manifest and required treatment upon repatriation or shortly thereafter entitling the veterans to direct service connection without resort to a presumption. VA also maintained that irritable bowel syndrome was not a good candidate for a presumption because it was "a functional disorder of unknown etiology and pathogenesis" (VA, 1993, p. 59).

Finally, the measure as enacted reduced the minimum confinement time to qualify for dental health-care benefits to 30 days.

The 1990s

Although there were no new POW presumptions during this decade, it was an active period for studies dealing with the health effects of POW internment.

Several studies published in 1991 examined chronic depression among former POWs. The first, by Engdahl et al. (1991), found that long-term chronic depressive symptomatology persisted over 40 years and was elevated among POWs of all theaters when compared to control groups. The authors found that age, education, medical symptoms during captivity, and level of social support were related to later levels of adjustment. A second longitudinal study published the same year by Page et al. (1991) elaborated on previous research to show that not only was depressive symptomatology highly elevated in World War II and Korean War POWs, but it was elevated to the point where these populations closely resembled a clinical population of recovering depressives. Two major conclusions from this longitudinal study were that treatment during captivity is statistically linked with depressive symptoms, and that differences in these symptoms were attributable to captivity-related treatment, even when age at capture and education level were considered.

Other variables were considered as well. Conducting a 40-year follow-up of U.S. World War II and Korean War former POWs, Engdahl and Page (1991) measured captivity trauma variables and individual protective variables (age, education, medical symptoms during captivity, social support) to current depressive symptoms. Although depressive symptoms persisted more than 40 years with the knowledge that PTSD and generalized anxiety disorders are known to occur with elevated frequency in POW populations, the degrees of individual protective variables were related to levels of adjustment. This study made a case for the need to examine former POWs that adjusted well in order to understand both the role of specific protective variables and adjustment and resiliency following trauma.

Page's (1991) work continued with respect to the validity and reliability of some of the work cited above. Despite the heavy reliance on survey data, a noticeable shortage of reports on the effects of nonresponse bias on the measurement of depression existed. Longitudinal data presented opportunities for different types of nonresponse bias, but could also be useful in modeling for bias because of previously collected data. Page found that a predictive model shows nonresponse bias on the reporting of depressive symptoms among former World War II and Korean POWs to be small.

In 1992, the IOM produced a report entitled *The Health of Former Prisoners of War* (IOM, 1992). This longitudinal study, which focused on morbidity, was initiated in 1986 and built on the earlier work of Cohen and Cooper (1954), Nefzger (1970), Beebe (1975), and Keehn (1980). Veterans were invited to a medical center to undergo the VA protocol exam, which included a

comprehensive physical and psychiatric examination. A face-to-face psychiatric interview and a battery of psychological tests were also administered. A caution was provided at the outset of the report that due to low response rates there could be "no confidence . . . that the group of respondents accurately reflects the composition of all former POWs" (IOM, 1992, p. 4). Nevertheless, the study author noted that the results were presented as descriptive data for two reasons. First, the data, which constituted the largest national collection of POW examinations ever gathered and analyzed, contained a number of findings worthy of note. Some of the findings confirmed earlier studies while other findings were suggestive and served the purpose of generating more definitive research studies.

The second reason to publish the data was not a scientific one, but rather a recognition that

> [T]he examination data will have uses beyond the scientific one—for example, in providing material *for discussion of military service-connected disabilities among former POWs*. Despite the fact that sound inferences about the group of all former POWs cannot be drawn from the exam data in this report, *policymakers who must deal with such issues should be able to review this descriptive information*. . . . Not to report the findings of the examinations would surely raise more questions than the report, with its careful documentation of the study's limitations, would raise. The results of this examination study are thus discussed below, and we urge a *maximum of reasonable caution in their interpretation*.
>
> (IOM, 1992, p. 5; emphasis added)

The report brought attention to the high prevalence of a number of medical conditions for POWs as compared to controls, especially with regard to psychiatric illness. Prevalence rates for over 20 different medical conditions were discussed, with key results including the following:

- Percentage of weight loss was associated with higher prevalence of intermittent claudication and arterial vascular disease and *lower* prevalence of osteoarthritis.
- Pacific POWs had higher prevalence of PTSD, ulcer, schizophrenia, and generalized anxiety than European and Korean POWs.
- Vitamin A deficiency and ulcer prevalence was higher for all groups.
- Edema (also significantly associated with higher prevalence of ischemic heart disease and peripheral nerve disease) and vitamin B1 deficiency was higher for all groups.
- Visual symptoms were associated with higher prevalence rates of cerebrovascular disease, ulcers, asthma, and PTSD.
- Neurologic symptoms were associated with beriberi.
- Korean conflict POWs showed higher prevalence rates for schizophrenia.
- Vitamin A deficiency helped to explain the prevalence of asthma and cerebrovascular disease in POWs with visual symptoms.

(IOM, 1992, pp. 6-11)

The report also said that many of the organ-specific findings were familiar and that the appreciably increased prevalence of depressive disorders, PTSD, and generalized anxiety were not unexpected. Similar findings regarding peripheral nerve disease, ulcer, and gastroenteritis were also not surprising (IOM, 1992).

The report did state that the noteworthy association between current peripheral nerve disease and earlier edema "suggests . . . there may be persistent neurologic effects decades after the original nutritional disease may have been successfully treated and acute symptoms have

abated." It added that the increased prevalence of schizophrenia among Korean War theater POWs and an "appreciable correlation with weight loss in this group offers further material for speculation" (IOM, 1992, p. 121).

Perhaps the most striking finding was the association between ischemic heart disease and previous reporting of localized edema. It was observed that there was much interest in heart disease among former POWs, but cautioned that the "*lack of a clear biologic mechanism* linking nutritional deprivation and subsequent *chronic* heart disease" together with the study's low response rate required that one "remain somewhat skeptical of this finding of association" (IOM, 1992, p. 122; emphasis added). Nevertheless, the report stated that

> Localized edema is a noteworthy risk factor for only two current medical conditions in these POW examinations—peripheral nerve disease and ischemic heart disease—both of which are acutely related to thiamin deficiency. . . . The specificity of association between localized edema and the only two medical conditions with well-established acute relationships to thiamin deficiency suggests that the association between earlier nutritional deprivation in prison camp and chronic ischemic heart disease is not an artifact.
>
> (IOM, 1992, p. 122)

To better understand the characteristics that affect POWs' reintegration into civilian life, Engdahl et al. published a report in 1993 that investigated long-term responses to captivity trauma in former POWs. The authors reported that symptoms at 20 years following release were related to those at 40 years following release. Many factors known to affect POWs' long-term adjustment were not included in the study (e.g., combat exposure, postwar social support). This was due in part to their statistical infrequency or skewed nature (i.e., family history of mental illness, marital status at capture, military rank at capture). Trauma response was found to be determined by an interaction of characteristics of the individual and characteristics of the trauma, not primarily one over the other. The authors suggested that trauma response, from an evolutionary standpoint, may be better understood as adaptive due to its persistent nature (Engdahl et al., 1993).

Research on POWs then turned to more specific disease outcomes in an attempt to ascertain if a relationship existed between POW status and increased mortality or morbidity. A 1994 study by Page and Ostfeld examined why a specific marker of malnutrition (lower limb edema related to vitamin B deficiency) in former POWs of World War II and the Korean War was associated with a three-fold increase in subsequent death attributed to ischemic heart disease. No medical basis for the link was found, but the confirmed findings emphasized the need for further research into links between severe malnutrition and subsequent chronic disease, both for former POWs and for other severely malnourished populations (Page and Ostfeld, 1994).

Brass and Page (1996) examined health records of World War II POWs to see if severe or chronic stress increases risk of cerebrovascular disease. Compared to a control group, there appeared to be an association between stroke and being a former POW. There was no difference, however, in the prevalence of hypertension or diabetes. The results suggested that further research was needed to better define the risk factors for stroke and further understand the chronic effects of stress.

PTSD continued to gain great attention. Page et al. (1997) examined the literature on PTSD in POWs and compared lifetime PTSD prevalence among POWs and control subjects. After a follow-up period of 40 years, differences in prevalence rates existed between POWs and control subjects for depressive disorders as well as generalized anxiety. All groups of POWs shared

nearly the same lifetime and current PTSD rates. Among World War II POWs, however, roughly half of the POWs who once suffered from PTSD were not currently diagnosed with that condition, suggesting the possible presence of chronic, stable PTSD in the other half of the POWs evaluated. However, the authors stated that this may be explained by the symptoms causing less stress on the first group of individuals. The authors suggested that those with higher distress levels should be evaluated for secondary symptoms of PTSD, such as depression. They concluded that

> *Sensitivity toward older war veterans is vital.* An awareness that their PTSD may have gone unnoticed by other health-care professionals for decades should encourage direct clinical inquiries about possible PTSD symptoms. We strongly recommend a structured interview. . . . *PTSD symptoms have been all too common, yet undiagnosed* among older war veterans, especially POWs.
>
> (Page et al., 1997, p. 157; emphasis added)

Recent Developments

Work on PTSD continued into the new millennium when World War II and the Korean War POW interviews were examined for two separate index measures at two points in time—1965 and 1990. Results from Gold et al. (2000) supported previous research highlighting the severe psychological consequences of POW status 40-50 years following captivity. Trauma severity during captivity was found to be the best predictor of current PTSD symptomatology.

Other condition-specific research also continued. Page et al. (2000) examined data from 50 years of follow-up for World War II former POWs in Pacific and European theaters to see whether location or POW status could be linked to death attributed to melanoma. Results showed that higher sun exposure in young adulthood (to the extent that POW status related to higher sun exposure) was associated with higher risk of melanoma mortality, with Pacific POWs at highest risk. A 50-year mortality follow-up by Page and Tanner, also in 2000, reported that Pacific theater POWs had twice the rate of death due to Parkinson's disease and roughly one-sixth the rate of death from motoneuron disease compared to the control group. There was no difference, however, in the death rate due to Parkinson's or other motoneuron disease in European theater POWs.

Although the first 30 years after repatriation showed a survival advantage of World War II and Korean War former POWs for heart disease and stroke mortality, examination of death data at 50 years showed a significantly higher risk of heart disease deaths and slightly higher stroke mortality in POWs (aged 75 years and older) when compared to control groups. Page and Brass (2001) suggested that circulatory diseases from serious acute malnutrition and stresses from imprisonment may not appear until after many decades.

A report that attracted much attention was a 2000 study of cirrhosis mortality among former World War II and Korean War POWs by Page and Miller. The authors conducted a 50-year follow-up study of World War II and Korean War former POWs to compare increased cirrhosis mortality found after a previous 30-year follow-up period with that of controls. World War II POWs were found to have a 32 percent higher risk of cirrhosis mortality compared to controls, while Korean conflict POWs had the same risk of cirrhosis mortality as controls. Lifetime prevalence rates for chronic liver disease, jaundice, helminthiasis, and nutritional deficiency were higher in Pacific and Korean POWs. But, the authors observed that

> [T]here were no remarkable differences in levels of self-reported alcohol consumption among our POWs and controls, nor were their self-reported levels of consumption markedly different from those in the general population. The fact that cirrhosis mortality was not apparently associated with alcohol consumption may have implications for American POWs seeking disability compensation for cirrhosis.
>
> (Page and Miller, 2000, p. 783)

The implications suggested by the authors soon became manifest. In April 2001, VA officials had prepared internal estimates of the budget impact of adding cirrhosis of the liver as a presumption of service connection for former POWs. Annual benefit costs were estimated to be $45,828 in 2002 and $624,106 through 2006 for an estimated caseload of "no more than 70 over 5 years" (VA, 2001).

On February 10, 2003, VA issued a proposed rule to add cirrhosis of the liver to the list of diseases for which entitlement to service connection would be presumed for former prisoners of war (VA, 2003). The proposed rule explained that its intended effect was to make it easier for former POWs to obtain compensation for cirrhosis "based on scientific and medical research showing a significantly higher risk of death from cirrhosis in former World War II POWs than in the general population" (VA, 2003, p. 1). Before discussing the rationale for adding cirrhosis of the liver as a presumptive service-connected condition, the notice observed that under 38 CFR § 3.307(d) (Rebuttal of Service Incurrence of Aggravation) such presumptions may be rebutted by "competent evidence," that is, "affirmative evidence that the disease was not incurred in service based on sound medical reasoning and consideration of all evidence of record" (VA, 2003, p. 2).

In support of the presumption, the proposed rule (VA, 2003) cited the Page and Miller (2000) study that found the risk of cirrhosis mortality for Pacific and European theater former POWs was 1.5 times the rate for the control group. It also cited an Australian study that found World War II POW deaths from cirrhosis at twice the rate as expected. Observing that "it appears that alcohol consumption does not provide an explanation for the higher mortality rates identified in POWs," the rule said that "[t]he VA Secretary believes that the research cited above constitutes sound scientific evidence supporting the conclusion that *an association exists* between cirrhosis and POW status" (VA, 2003, p. 3; emphasis added).

Finally, the rule said that inasmuch as World War II POWs "comprise 93 percent" of all living ex-POWs, the "VA Secretary has therefore determined that it is *appropriate* to add cirrhosis of the liver . . . for which VA presumes service connection *in all former POWs* interned or detained for at least 30 days" (VA, 2003, p. 3). The proposed rule received no comments and became final on July 18, 2003.

Later that same year, the Veterans Benefits Act of 2003 (Public Law 108-183. 108th Cong., 1st Sess.) was signed into law. The measure contained two POW-specific provisions. First, it codified VA's administrative decision concerning cirrhosis of the liver. Second, it removed the 30-day minimum confinement requirement for 5 of the 16 POW presumptive conditions. Those 5, for which no minimum confinement was required, were

> (a) Psychosis; (b) Any of the anxiety states; (c) Dysthymic disorder (or depressive neurosis); (d) Organic residuals of frostbite, if the VA Secretary determines that the veteran was detained or interned in climate conditions consistent with the occurrences of frostbite; and (e) Posttraumatic osteoarthritis.

In justifying the change, a Senate committee report on a similar bill observed that POWs were often treated brutally and, even if treated humanely, often suffered extreme mental anguish. Thus, the "30-day minimum internment requirement for purposes of presumptive service connection may be too restrictive for certain conditions" (U.S. Congress, Senate, Committee on Veterans' Affairs, 2003, p. 10). In this connection, it should be noted that there was considerable public attention paid to Service members who were held as POWs for short periods of time shortly following the inception of Operation Iraqi Freedom in March 2003.

Perhaps the most significant development concerning POW presumptions occurred on October 7, 2004, when VA issued an Interim Final Rule entitled *Presumptions of Service Connection for Disease Associated with Service Involving Detention or Internment as a Prisoner of War* (VA, 2004a). The rule established guidelines for establishing presumptions of service connection for diseases associated with service involving detention or internment as a prisoner of war. VA justified the rules as necessary because POW claims present unique medical issues and because factors including the lack of contemporaneous medical records during periods of captivity and the "relatively small body of available medical information" present obstacles to substantiating claims for service-connected benefits based on POW service.

The guidelines were intended to help VA ensure that the claims are "decided fairly, consistently, and based on all available medical information concerning the diseases associated with detention or internment as a prisoner of war" (VA, 2004a, p. 60083). Finally, in utilizing the new guidelines, VA's interim final rule also established presumptions of service connection for atherosclerotic and hypertensive heart disease and for stroke disease arising in former prisoners of war.

The new guidelines found at 38 CFR 1.18 were as follows:

> **§ 1.18—Guidelines for establishing presumptions of service connection for former prisoners of war.**
>
> (a) *Purpose*. The Secretary of Veterans Affairs will establish presumptions of service connection for former prisoners of war when necessary to prevent denials of benefits in significant numbers of meritorious claims.
> (b) *Standard*. The Secretary may establish a presumption of service connection for a disease when the Secretary finds that there is at least limited/suggestive evidence that an increased risk of such disease is associated with service involving detention or internment as a prisoner of war and an association between such detention or internment and the disease is biologically plausible.
> (1) *Definition*. The phrase "limited/suggestive evidence" refers to evidence of a sound scientific or medical nature that is reasonably suggestive of an association between prisoner-of-war experience and the disease, even though the evidence may be limited because matters such as chance, bias, and confounding could not be ruled out with confidence or because the relatively small size of the affected population restricts the data available for study.
> (2) *Examples*. "Limited/suggestive evidence" may be found where one high-quality study detects a statistically significant association between the prisoner-of-war experience and disease, even though other studies may be inconclusive. It also may be satisfied where several smaller studies detect an association that is consistent in magnitude and direction. These examples are not exhaustive.
> (c) *Duration of Detention or Internment*. In establishing a presumption of service connection under paragraph (b) of this section, the Secretary may, based on sound scien-

tific or medical evidence, specify a minimum duration of detention or internment necessary for application of the presumption.

(d) *Association*. The requirement in paragraph (b) of this section that an increased risk of disease be "associated" with prisoner-of-war service may be satisfied by evidence that demonstrates either a statistical association or a causal association.

(e) *Evidence.* In making determinations under paragraph (b) of this section, the Secretary will consider, to the extent feasible:
  (1) Evidence regarding the increased incidence of disease in former prisoners of war;
  (2) Evidence regarding the health effects of circumstances or hardships similar to those experienced by prisoners of war (such as malnutrition, torture, physical abuse, or psychological stress);
  (3) Evidence regarding the duration of exposure to circumstances or hardships experienced by prisoners of war that is associated with particular health effects; and
  (4) Any other sound scientific or medical evidence the Secretary considers relevant.

(f) *Evaluation of studies*. In evaluating any study for the purposes of this section, the Secretary will consider:
  (1) The degree to which the study's findings are statistically significant;
  (2) The degree to which any conclusions drawn from the study data have withstood peer review;
  (3) Whether the methodology used to obtain the data can be replicated;
  (4) The degree to which the data may be affected by chance, bias, or confounding factors; and
  (5) The degree to which the data may be relevant to the experience of prisoners of war in view of similarities or differences in the circumstances of the study population.

(g) *Contracts for Scientific Review and Analysis*. To assist in making determinations under this section, the Secretary may contract with an appropriate expert body to review and summarize the scientific evidence, and assess the strength thereof, concerning the association between detention or internment as a prisoner of war and the occurrence of any disease, or for any other purpose relevant to the Secretary's determinations.

The interim final rule contained an extended discussion and explication of these guidelines. It first noted that statutory and regulatory standards currently existed to guide VA in identifying diseases associated with exposure to herbicide agents, hazards of service in the Gulf War, and ionizing radiation, and that it would be helpful to establish standards to guide VA in identifying diseases associated with service involving detention or internment as a POW. The POW guidelines were characterized as substantially similar to the existing guidelines noted above, with "minor differences necessary to reflect considerations unique to former POWs" (VA, 2004a, p. 60084).

The rule noted that evidentiary presumptions were to serve a number of purposes, including the promotion of efficient resolution of service-connection issues by codifying medical findings and principles that otherwise may not be familiar to VA adjudicators. Presumptions promote "fair and consistent decision making by establishing simple adjudicatory rules" as well as assisting claimants who might face substantial difficulties "due to the complexity of the factual issues, the lack of contemporaneous medical records during service, *or other circumstances*" (VA, 2004a, p. 60084; emphasis added).

Acknowledging that POW experiences have varied with time, place, and other factors, the rule stated that "certain hardships are so prevalent across the spectrum of POW experience as to support the presumption that POWs as a group have incurred similar health risks." Evidentiary

presumptions were also strongly justified by the absence of "contemporaneous personnel and health records to document events, injuries, or diseases during periods of captivity." Moreover, presumptions simplify and expedite the claims adjudication process, a "particularly significant consideration for former POWs, more than 90 percent of whom served in World War II and are now, on average, over 80 years old" (VA, 2004a, p. 60084).

VA acknowledged that determining whether health effects may be associated with POW experience is "not a simple task." The effects of the POW experience have been less extensively studied, because "there generally are not comparable civilian populations, and the number of former POWs available for study is comparatively small." Accordingly, VA announced that it intended to establish presumptions of service connection when the medical evidence reasonably establishes an "*association* between the POW experience and particular diseases" (VA, 2004a, p. 60084; emphasis added).

Perhaps the most significant feature of the new POW guidelines was the explicit decision to establish POW presumptions utilizing the "limited/suggestive evidence of an association" classification. VA said this was essentially the same standard employed by IOM in reports it prepared for VA (IOM, 1994, 1996, 1999, 2000, 2001, 2003, 2005) analyzing the health effects of exposure to herbicide agents. "Limited/suggestive" evidence is one of four classifications employed by IOM in its Agent Orange reports and was a standard that had been utilized by VA in establishing presumptions of service connection. VA characterized the "limited/suggestive" evidence standard as a "useful analytical framework for assessing scientific evidence and determining whether a presumption of service connection may be warranted" (VA, 2004a, p. 60085).

IOM's use of the term "limited/suggestive evidence of an association" was explained as referring to circumstances in which evidence is suggestive of an association but is limited because matters of chance, bias, and confounding cannot be ruled out with confidence (IOM, 1994, 1996, 1999, 2001, 2003, 2005). VA said its definition for POWs "adds that the evidence may be limited because the relatively small size of the affected population may restrict the data available for study." This addition was significant, VA said, given the circumstances of the POW experience and the fact that "the population of surviving former POWs, most of whom served in World War II, is declining rapidly" (VA, 2004a, p. 60085). In the rule,VA added

> Although we intend that any presumptions VA establishes will be based on sound scientific and medical evidence, we believe . . . that fairness to former POWs requires that VA fully evaluate the available data and not accord undue significance to the fact that such data are comparatively limited by the small size of the affected population.
>
> (VA, 2004a, p. 60085)

Finally, the rule stated that

> The requirement that the association be biologically "plausible" does not require proof of a casual relationship . . . it requires only a determination that there is a possible biologic mechanism, consistent with sound scientific evidence, by which the suspected precipitating event (POW experience) could lead to the health outcome. IOM routinely applies the concept of biologic plausibility in its reviews of the literature concerning the health effects of herbicide exposure and hazards of Gulf War Service. . . .
>
> (VA, 2004a, p. 60085)

Having established the guidelines in the October 7, 2004, rule, VA then applied them in establishing new presumptions of service connection for (1) "stroke and its complications," and (2) "atherosclerotic heart disease or hypertensive vascular disease (including hypertensive heart disease) and their complications (including myocardial infarction, congestive heart failure, arrhythmia" (VA, 2004a, p. 60090).

With respect to the first presumption, VA admitted that there were very few studies investigating the possible relationship between POW experience and stroke. It referenced a 1996 Brass and Page study that found a seven-fold increase in the incidence of stroke among the POWs as compared to the control group. VA noted that the strength of those findings was limited by the small size of the study population. It also referenced a 2001 Brass and Page study that found a statistically significant increase in death from stroke among veterans who had experienced visual symptoms, such as night blindness, during their captivity. Because the presence of visual symptoms during captivity may be associated with vitamin A deficiency, this finding was regarded as consistent with the earlier study in suggesting an association between malnutrition during POW captivity and subsequent stroke (VA, 2004a).

On the recommendation of the Expert Panel on Strokes in Former Prisoners of War, VA's Environmental Epidemiology Service conducted a study in 2003 using medical and death data from VA and the Health Care Financing Administration (HCFA) records (Kang and Bullman, 2003; as referenced in VA, 2004a). That study, which had not been published at the time the rule was issued, found that POWs had a significantly higher incidence of PTSD than the controls and further that POWs with PTSD had a higher incidence of stroke than POWs without PTSD. Although the study did not find a significantly increased risk of stroke among POWs as compared to non-POWs, the evidence for an association between PTSD and stroke among POWs was deemed consistent with findings stated in the 1996 Brass and Page study.

Observing that several studies had provided evidence suggesting an association between stress and stroke, the rule reiterated that the VA Secretary would consider evidence concerning the effects of circumstances or hardships similar to those experienced by POWs, including stress, in assessing the evidence for establishing presumptions of service connection.

Accordingly, based on the evidence discussed above, the VA Secretary determined that a presumption of service connection was warranted for stroke among former prisoners of war. The Brass and Page (1996) and Page and Brass (2001) POW studies both found an increased risk of stroke among former POWs. Although there was an absence of other directly corroborating studies, the lack of additional data was due in part to the small size of the POW population available for study and the limited number of studies generally undertaken in this field. Under those circumstances, VA concluded the lack of corroborating data did not imply the absence of an association (VA, 2004a).

Because "VA consider[ed] stress and malnutrition to be among the hardships ordinarily associated with POW experience" and because "evidence suggest[ed] that the risk of stroke increases with the severity of those hardships" the VA Secretary found that

> [T]he available evidence is suggestive of an association between POW experience and stroke because sound scientific studies provide evidence of an association that is consistent in magnitude and direction, even though it is limited in some respects by the small size of the affected population and the correspondingly limited data available for study.
>
> (VA, 2004a, p. 60086)

The VA Secretary further determined that an association between stroke and POW experience was biologically plausible, and for those reasons VA was establishing a presumption of service connection for stroke in former POWs.

Turning to the second presumption that was administratively added in 2004, VA again acknowledged that there were relatively few studies addressing the association between POW experience and heart disease (VA, 2004a). A series of older studies did not find consistent evidence of an association, as summarized in Page and Ostfeld's 1994 study titled *Malnutrition and Subsequent Ischemic Heart Disease in Former Prisoners of War of World War II and the Korean Conflict*.

VA stated that more recent studies had yielded "intriguing findings concerning the association between heart disease and POW experience." The 1994 study by Page and Ostfeld found a statistically significant increase in deaths due to ischemic heart disease among former POWs who experienced edema in their lower limbs during captivity. As previously discussed, the authors theorized that the findings might suggest an association between malnutrition during captivity and subsequent ischemic heart disease. Current VA regulations provided for presumptive service connection of ischemic heart disease in former POWs who experienced localized edema during captivity (VA, 2004a).

The 2001 study by Page and Brass found a trend of increased excess risk of heart disease with advanced age, with a statistically significant increased risk for former POWs aged 75 years or older. The authors suggested that the findings might indicate that the sequelae of serious, acute malnutrition may not appear until after many decades.

The 2003 VA study (Kang and Bullman, 2003; as referenced in VA, 2004a) analyzed records of inpatient and outpatient treatment from VA and HCFA to determine whether POWs had an increased incidence of certain diseases in comparison to the non-POW controls. The study "detected small increases in the incidence of hypertension and myocardial infarction among some, but not all, of the subpopulations examined, and not all of the findings were statistically significant. However, the study did find a statistically significant increased incidence of hypertension and chronic heart disease among World War II veterans with PTSD" (VA, 2004a, p. 60087). The conclusion that PTSD may be associated with cardiovascular disorders was also supported by a 1997 study (Boscarino, 1997) finding that Vietnam veterans diagnosed with PTSD had a significantly increased risk of circulatory disease many years after service.

Based on the evidence discussed above, the VA Secretary determined that a presumption of service connection was warranted for atherosclerotic heart disease and hypertensive vascular disease among former POWs. As in the instance of stroke, the VA Secretary concluded that the evidence suggesting an association between heart disease and specific hardships of POW experience—malnutrition and stress—was significant. Notwithstanding limited data, the VA Secretary concluded that sound scientific studies provided "limited/suggestive" evidence of an association between POW experience and heart disease, and that it was "biologically plausible" (VA, 2004a).

VA conceded that not all of the studies cited investigated the same range of heart diseases, and thus they did not clearly resolve the question of which types of heart disease may be associated with POW experience. For purposes of the presumption, however, all cardiovascular diseases were included by VA that were deemed consistent, in terms of biologic plausibility, with those findings because the diseases were potentially capable of being caused by the stress or malnutrition hardships of POW service. The presumption did not extend to diseases that arise from viral or bacterial causes, because the evidence concerning biologic plausibility did not support a finding that such heart diseases were associated with POW experience (VA, 2004a).

With respect to certain types of atherosclerotic heart disease or hypertensive vascular disease that were covered by these presumptions, VA acknowledged little available evidence upon which to rule in or rule out the possibility that the condition is capable of being caused by the hardships of POW service. In those cases, VA chose "to resolve the doubt in favor of veterans and include the condition within the scope of the presumption," saying that

> Although the necessity of inclusion of some conditions may be uncertain from a *purely scientific perspective*, VA has decided as a policy matter to resolve this issue in favor of veterans because there is *a reasonable basis for doing so*. Presumptions of service connection for former POWs can be rebutted as provided in 38 U.S.C. 1113(a) and 38 CFR 3.307(d). Accordingly, if evidence in a case supports a finding that a particular presumptive condition was not actually caused by a veteran's POW experience, VA may consider the presumption to be rebutted.
>
> (VA, 2004a, p. 60087; emphasis added)

Finally, no minimum confinement time was required for either of the new presumptions:

> Because the evidence indicates that heart disease and stroke potentially may be associated either with malnutrition during prolonged captivity or with stress due to circumstances such as torture or abuse, which may occur during even brief periods of captivity, we do not believe a minimum period of detention or internment is warranted for these presumptions.
>
> (VA, 2004a, p. 60088)

The VA Secretary said that the rule was issued as an interim final rule without providing an opportunity for prior comment because he believed the rule was unlikely to generate any adverse public comment, "inasmuch as it confers a benefit on a deserving class of veterans based on sound scientific evidence." Moreover, it was "impracticable to delay" inasmuch as

> . . . the class of veterans affected by this rule is elderly and rapidly dwindling. Delay in implementing these rules would have a significant adverse effect and frustrate the beneficial purpose of this rule in view of the high mortality rate among the POW population and the fact that the majority of former POWs are at an age where their medical and financial needs are likely to be at their greatest.
>
> (VA, 2004a, p. 60088)

Only one written comment was received, and it primarily sought to have the presumptions further expanded. The interim rule, without changes, became final on June 28, 2005.

Given the significance of VA guidelines for establishing presumptions of service connection for former POWs, the Committee sought material from VA concerning any information that may have been considered by VA in developing the guidelines and the two presumptions that was not referenced or discussed in the *Federal Register* notice. It also sought to ascertain what role, if any, the Advisory Committee on Former Prisoners of War had in the development of the rule. VA chose not to respond and stated in a letter to the Committee chair that statements made in the "context of robust deliberations" might be "misconstrued or misrepresented" and that to do so would "inhibit free discussion in future deliberations" (Dunne, 2006).

VA estimated that the new presumptions would have a first-year cost of $26 million increasing to $33 million in the fourth year and then gradually declining to $21 million in the

tenth year due to increasing POW mortality. The 5- and 10-year cumulative costs were $152.3 and $279.5 million, respectively (VA, 2004b, p. 4).

No additional POW presumptions have been added since 2005 either administratively or statutorily.

Lessons Learned

Americans and their elected representatives have long been concerned with the welfare of those who protected, defended, and sacrificed for their country. The extensive system of veteran benefits and their liberalized rules for qualification is a manifestation of this concern.

This concern is intensified if those veterans seeking assistance are viewed as having been subjected to extraordinary stresses and sacrifices. POWs are such a group. As VA declared in its 1980 study, the POW experience was an "extremely harsh and brutal experience" that was "characterized by starvation diet, poor quality or nonexistent medical care, 'death marches,' executions, and torture" (VA, 1980, p. 4).

In this context, the creation of certain presumptions with respect to disabilities claimed to be connected with a veteran's experience as a POW is a natural reflection of a long-established concern for their welfare. These presumptions simplify adjudication in what otherwise would be difficult cases to obtain evidence and resolve complex issues, thus relieving the burden on both the veteran and VA. Presumptions have been particularly helpful in assessing POW claims where information about individual conditions of internment and complete medical records were frequently unavailable.

Finally, presumptions have enabled greater consistency in decision making, the absence of which generated much discontent by veterans who strongly communicated their concerns to their elected representatives. Indeed, it might reasonably be inferred that the subsequent modification of certain presumptions by reducing or eliminating preconditions for their applicability has been a further policy response to concerns registered by those former POWs who were not previously covered by presumptions.

These policy considerations were obviously important factors that were weighed by Congress as it considered available epidemiologic and other scientific findings derived from various POW studies. These studies (Beebe, 1975; Brass and Page, 1996; Cohen and Cooper, 1954; IOM, 1992; Keehn, 1980; Nefzger, 1970; Page and Brass, 2001; Page et al., 1991, 1997; VA, 1980) dating back to the early 1950s reveal a slow accretion of data and increased medical knowledge, particularly about malnutrition, stress, and the psychological effects of the POW experience.

At the same time, available evidence for certain presumptions sometimes came from only a single study, and the data were often limited by the small size of the affected number of POWs. Consequently, authors of most studies acknowledged the tentative and inconclusive nature of their findings and urged caution at drawing unwarranted inferences. As one study author stated, the mixture and interdependence of various factors of the POW experience and the variation of their relative intensities "from time to time, from place to place, and from man to man," has "limit[ed] the scope and specificity of the inferences that may be drawn statistically" (Nefzger, 1970, p. 124).

Given the suggestive but scientifically uncertain results of many of the studies, it is not surprising that policy makers frequently decided to create service-connected presumptions when faced with the pressing claims of genuinely sick and disabled former POWs. As one author observed of the 1992 study of POWs, the descriptive data obtained had "uses beyond the scien-

tific," specifically in the discussion of military service-connected disabilities. The author added, "[d]espite the fact that sound inferences about the group of all former POWs cannot be drawn from the exam data in this report, policymakers who must deal with such issues should be able to review this descriptive information" (IOM, 1992, p. 5).

It should also be noted that VA in its 2004 guidelines for POW presumptions, while expressing an intent to base its determinations on "sound scientific and medical evidence," has adopted a standard of "limited/suggestive evidence" for former POWs and added the additional caveat that "fairness to former POWs requires VA to fully evaluate the available data and not accord undue significance to the fact that such data are comparatively limited by the small size of the affected population" (VA, 2004a, p. 60085). Given the forgoing, it is apparent that although various POW studies have often provided useful scientific information to Congress and the executive branch, there were other policy-relevant factors that had equal or greater weight in the presumptive decisions established for POWs. Over time, the requirement that a presumptive decision be based on sound scientific and medical evidence has increasingly been overshadowed by these other considerations.

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CASE STUDY 4: AMPUTEES AND CARDIOVASCULAR DISEASE PRESUMPTION

This case study examines the 1979 presumption of service connection for cardiovascular disease (CVD) that develops in veterans with certain types of service-related amputations. By exploring the scientific basis for this decision, as well as the implications of this decision for the VA, this analysis seeks to illustrate the challenges and implications of establishing a service connection for a common chronic condition with multiple contributing causal risk factors.

Background on Cardiovascular Disease

This presumption establishes service connection for CVD in veterans with certain types of lower extremity amputations. The literature on which this presumption is based examines the broad category of CVD, with specific attention to atherosclerotic (or ischemic) heart disease, the most common of the cardiovascular conditions. Two features of CVD in general and atherosclerotic disease in particular are important for evaluating the scientific evidence and events surrounding this presumption. First, CVDs are common in the general population, and their prevalence increases with advancing age (Figure I-3).

The high prevalence of CVD among the general adult population may pose challenges for determining whether, among veterans, CVD can be attributed to military service. The high prevalence may also translate into a large constituency advocating for a presumption, as well as determine the cost implications of such a presumption for VA. Second, there are multiple established risk factors for CVD, particularly atherosclerotic disease, that are common in the general population. Many of these are lifestyle factors, including smoking, obesity, and physical inactivity. Determining the relationship between risk factors that develop during military service and the additional risk factors that may develop after service is challenging, as is estimating the incremental risk of CVD attributable to military service.

The Need for a Presumption

Veterans with amputations resulting from trauma sustained during military service automatically receive compensation for this service-related condition and may also receive compensation for amputation-related complications. The presumption service connecting CVD among veterans with service-connected amputations (38 CFR § 3.310[b], Cardiovascular disease) was created after a comprehensive review of the prior literature and analysis of data from World War II veterans suggested a link might exist between certain types of amputation and CVD. In contrast with many presumptions that exist because of an evidence gap in exposure assessment (e.g., presumptions related to Agent Orange), this presumption was created because of gaps in the evidence linking amputations to CVD.

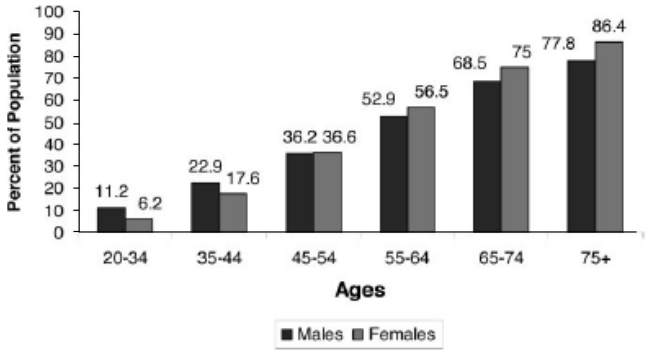

FIGURE I-3 Prevalence of cardiovascular disease by age and sex.
SOURCE: Thom et al., 2006, p. 91.

Scientific and Legislative History of the Presumption for Cardiovascular Disease Among Amputees

The following is a brief review of the scientific and legislative events of relevance to this presumption.

Prior to 1976

In a study conducted by MFUA/NRC, Hrubec and Ryder (1979) reviewed the scientific literature published prior to 1976 on the relationship between amputation and mortality from CVD, the findings of which appeared to be mixed. The evidence for higher cardiovascular mortality rates stemmed primarily from one large Finnish study (Bakalim, 1969) of 4,738 World War II amputees that reported 63.1 percent greater cardiovascular death rates among amputees than among the general population (Hrubec and Ryder, 1979, p. 31). In their review, Hrubec and Ryder noted two major limitations of this study. The first limitation was that mortality among amputees participating in the study was compared with that of the general population, rather than veterans who had also sustained combat-related injuries. The second limitation was that the time period of comparison for the study group included the acute hospitalization for the amputation, a period in which risk of mortality may be higher.

Hrubec and Ryder noted several other studies conducted prior to 1976 that found no increased mortality among amputees. The Advisory Committee on Cardiovascular Disorders and Mortality Rate in Amputees (1954), for example, compared incidence of cardiovascular disorders among 27,000 British amputees from the 1914 war with that of both the general population and veterans with wounds to the lower extremities (not necessarily amputations). They concluded that limb amputation does not appear to "initiate or aggravate cardiovascular disorders to any significant extent" (Hrubec and Ryder, 1979, pp. 30-31).

In an effort to clarify the possible association between amputations and cardiovascular disorders, the Veterans Disability Compensation and Survivor Benefits Act of 1976 (Public Law 94-433. 94th Cong., 2d Sess.) mandated that, in addition to reviewing the existing literature on this topic, "an analysis of statistically valid samples of disability claims of veterans having service-

connected extremity amputation matched by age, sex and war period with nonamputee veterans" be conducted.

The 1979 Medical Follow-Up Agency Report on Service-Connected Traumatic Limb Amputations and Subsequent Mortality from Cardiovascular Diseases

In 1979 Hrubec and Ryder delivered their report conducted by MFUA/NRC as a part of its contract with VA. MFUA had access to summary information from all Army hospitalizations from 1944 and 1945 and used this information to identify three comparison groups based on the type of injury—3,890 Service members with proximal limb amputations (at or above the knee or elbow), 2,918 with distal amputations (loss of part of foot or hand), and 3,890 with disfigurement (disfigurement other than head, face, or skull, and disfiguring scars). The authors compared the observed death rates in each of these three groups to the expected rates based on age and time-specific rates for U.S. males in the general population. Veterans in the three comparison groups were followed from January 1946 to April 1977, and their mortality from a variety of different causes was evaluated.

During more than 30 years of follow-up, 922 proximal amputees died; 714.1 deaths would have been expected based on the general U.S. male death rate (Hrubec and Ryder, 1979, p. 47). Compared with distal amputees and those with disfigurement, proximal amputees had a higher risk of all-cause mortality and mortality related to diabetes and CVD, particularly atherosclerotic (ischemic) heart disease. Mortality from CVD was similar between proximal amputees and the general population during the period immediately following amputation, but increased dramatically among the proximal amputees over later time periods. This greater than expected cardiovascular mortality among the proximal amputees was not affected by their age at amputation. The same pattern of increasing cardiovascular mortality was not observed among those with distal amputations or disfigurement; they continued to have the same or lower than expected death rates. In matched pair comparisons with disfigured veterans, the highest risk of CVD was observed among those with bilateral lower extremity amputations of any degree and unilateral amputations at the knee or above (Hrubec and Ryder, 1979).

Hrubec and Ryder noted that strict time constraints imposed by Congress prevented them from conducting detailed individual analyses to explore the potential mediators of the increased risk of cardiovascular mortality among proximal amputees. Their discussion on this topic included a brief review of the existing literature on other cardiovascular risk factors, and they proposed the following potential explanations for the association: (1) CVD may be a risk factor for amputation, as Service members with CVD at the time of injury may have been more likely to undergo amputation (versus procedures to salvage the limb) because of concerns for peri- and postoperative risk, (2) amputation may itself be a direct risk factor for CVD, and (3) amputation may be a risk factor for other factors (e.g., physiologic factors such as hypertension, as well as lifestyle factors such as inactivity, psychosocial stress, and smoking) known to place individuals at greater risk for CVD.

The authors explored wound infection as a potential mediator and found no increased risk of CVD by the presence of infection at the time of amputation. They also commented that smoking was unlikely to mediate the increased risk since the rates of lung cancer mortality are not higher among proximal amputees (although it is intriguing that increased risk of buccal cavity and pharynx cancer among proximal amputees is noted in this study but not commented on further).

Hrubec and Ryder concluded from their analysis that proximal traumatic amputation of the lower limbs was a risk for subsequent cardiovascular mortality and commented that, based on

their review of the existing risk factor literature, "the most likely factors of importance (for mediating this increased risk) include increased sedentary lifestyle among amputees and increased emotional stress caused by amputation" (Hrubec and Ryder, 1979, p. 43).

The results of this MFUA study led to 38 CFR § 3.310(b) (Cardiovascular disease) granting a service connection "for ischemic heart disease or other cardiovascular disease developing in a veteran who has a service-connected amputation of one lower extremity at or above the knee or service-connected amputations of both lower extremities at or above the ankles."

The Scientific Literature Since the 1979 Presumption

The literature on CVD and amputation since the 1979 Hrubec and Ryder study is limited and has focused on exploring the mechanisms whereby amputation might lead to cardiovascular morbidity and mortality. A small study (Rose et al., 1986) of 31 Vietnam veterans comparing veterans with proximal lower extremity amputations to those with upper extremity amputations noted higher blood pressure, higher body mass index, and impaired glucose metabolism among the lower extremity amputees. Another study (Modan et al., 1998) followed 201 veterans of the Israeli army with proximal amputations for over 24 years and compared their risk factor profile and mortality with 1,832 controls (matched based on age and ethnic origin) from the general population. The authors found an increase in the risk of cardiovascular mortality among traumatic lower limb amputees. Surviving amputees did not have higher rates of obesity, physical inactivity, or hypertension compared with controls from the general population, but were more likely to have hyperinsulinemia and be in a hypercoagulable state. The authors suggested that hypercoagulability and hyperinsulinemia (independent of body mass index or inactivity) may be a consequence of amputation and may be a mechanism leading to higher rates of CVD.

Studies of cardiovascular risk in amputees have had limited ability to explore the mechanism of disease and the nature of the increased cardiovascular risk because (1) baseline data on risk factors and comorbid conditions at the time of amputation are either not available or not analyzed, and (2) longitudinal follow-up studies exploring the interim development of cardiovascular risk factors among amputees who died or developed CVD do not exist.

The presumption of service connection for CVD among amputees has not been reexamined since it was put into place in 1979. No studies have been commissioned to provide any further information regarding association of CVD with amputation in a more contemporary cohort.

Costs to VA Associated with This Presumption

No cost estimates were available for this analysis. However, the long-term cost implications of this legislation are likely to continue to rise as veterans of contemporary conflicts in Iraq and Afghanistan have experienced higher rates of amputations than those of veterans of previous wars (Bilmes, 2007).

Lessons Learned

This case study reveals several important lessons that are relevant when considering strategies for improving the current system of presumptions. These lessons center around the type of evidence necessary to put a presumption in place, specifically what *level of evidence* should be required for a presumption, how the *scientific base of evidence is updated* based on new studies, how to evaluate evidence regarding *exposures, outcomes, and potential mediators*, and what *types of evidence* might make the scientific basis for a presumption more robust.

The scientific basis for this presumption was a single retrospective study of World War II veterans conducted by MFUA (Hrubec and Ryder, 1979). Although this study was large and apparently scientifically sound, confirmation of these findings with additional studies was warranted. Particularly since this presumption was put in place via legislative action (and not the more easily malleable administrative action on the part of VA), the highest standard of scientific evidence should have been employed, including replicating these findings in additional cohorts and exploring potential mechanisms for the observed association.

Understanding the mechanisms whereby an exposure leads to an outcome has important scientific implications for establishing a causal relationship and certainly has clinical relevance. However, understanding the mediators of an association between exposure and outcomes should not have bearing on policy considerations inherent in presumptions. Whether amputation leads to CVD via sedentary lifestyle or derangements in the coagulation cascade are irrelevant from a policy perspective. Both pathways are ultimately initiated by exposure that occurred during military service (i.e., amputation). Only knowledge of exposure (that a veteran was amputated during military service) and the association between exposure and outcome (that amputations lead to higher rates of CVD) are necessary for a valid presumption; knowing which of the multiple, possible pathways might mediate this association is not required.

Cardiovascular mortality rates for men have decreased dramatically over the last 30 years (Figure I-4) because of improved prevention and more aggressive treatment of modifiable risk factors for CVD. Given the decreasing mortality rates because of improved treatment, it is reasonable to question whether the association between amputations and cardiovascular mortality observed in the original MFUA study would be observed among contemporary amputees. Unfortunately, standard procedures are not in place for incorporating new studies of amputations and CVD. The ability to incorporate new evidence is additionally limited because this presumption was issued by Congress and not administratively by VA.

Certain populations of veterans, such as amputees, may be at high risk for complications as a result of military service and in particular need of compensation for these complications. Certain exposures, such as amputations, are particularly challenging to study except in cohort studies of exposed Service members and veterans. Both of these factors argue strongly for ongoing surveillance of high-risk Service member populations by the Department of Defense (DoD) and veteran

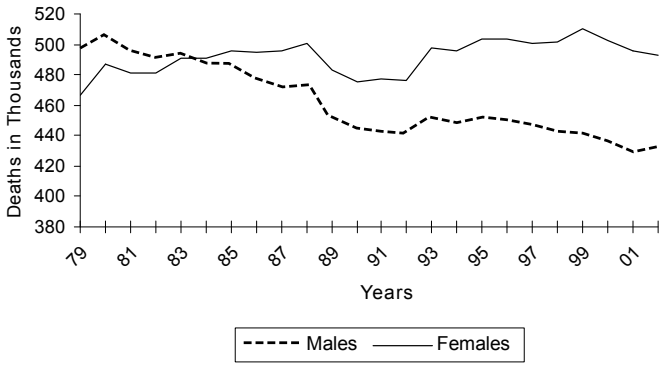

FIGURE I-4 Trends in cardiovascular mortality rates from 1979 to 2003.
SOURCE: Thom et al., 2006, p. 95.

populations by VA. Such ongoing surveillance could have provided important confirmatory evidence to support the basis for this presumption, as well as a natural mechanism to update the scientific evidence with contemporary exposed Service members and veterans.

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CASE STUDY 5: RADIATION PRESUMPTIONS

This case study examines decisions related to radiation made over several decades for various groups of individuals involved in different military efforts. The case study describes the scientific basis and uncertainties for assessing exposure and risk to ionizing radiation.

The Scientific Basis of Risk Assessment for Ionizing Radiation

From the late 1940s to the early 1960s, about 200,000 American servicemen and women—along with civilians and groups from other countries—participated in above-ground tests of nuclear weapons (IOM, 2000, p. 1). U.S. testing was conducted primarily at the Nevada Test Site and the Marshall Islands in the Pacific Ocean. Many of the people at the test sites may have received substantial doses of ionizing radiation, and, as might be expected in any comparable population, many have developed cancer and other chronic diseases over the ensuing years. These "atomic veterans" are understandably concerned that their diseases could be service connected and have been quite vocal in seeking compensation. To provide compensation, it must be determined how likely it is that any particular cancer among the atomic veterans might be service related.

There is no doubt that radiation can cause cancer. Evidence in support of this claim comes from a vast literature of human epidemiologic studies, experimental animal studies, and basic

radiobiology research on cell cultures (ACHRE, 1995; Caldwell et al., 1980, 1983; Dalager et al., 2000; Darby et al., 1988, 1991, 1993; Doll et al., 1998; IOM, 1995, 2000; Johnson et al., 1997; Muirhead and Kendall, 2003; Muirhead et al., 2003, 2004; Pearce et al., 1997; Raman et al., 1987; Robinette et al., 1985; Watanabe et al., 1995). All major national and international advisory committees concerned with radiation risk assessment agree on this point (IARC, 2000; NRC, 2006; UNSCEAR, 2000). There is thus a *prima facie* case for causation for any individual with cancer and a history of radiation exposure. However, the magnitude of the risk and hence the probability of a causal connection in any individual is highly variable, depending upon such factors as the type of cancer, the radiation dose, age at exposure, time interval between exposure and cancer, and individual characteristics that determine response to radiation. Risk estimates are also inherently uncertain, both the estimates of population dose-response relationships and estimates based on an individual's estimated dose and other modifying factors. The rarer the cancer, the more unstable the risk estimates will be, based on epidemiologic data, unless data for rarer sites are combined with other similar cancers (thereby introducing additional uncertainty about the appropriateness of that combination). Thus, it is certainly not the case that every cancer in a radiation-exposed individual is caused by that exposure, and therein lies the difficulty in establishing presumptions of causation or other criteria for compensation.

Although this case study will be focused on cancer, certain other endpoints have been definitely linked to ionizing radiation—notably severe mental retardation in those exposed during pregnancy and cataracts—and evidence for certain other diseases, such as CVD following high doses and nonmalignant tumors, is still evolving (NRC, 2006). There is also the potential for genetic effects that would be transmissible from one generation to the next; although genetic transmission has been demonstrated in animal experiments, there is so far no convincing evidence in humans, and the risk is generally thought to be low (NRC, 2006).

The mechanism by which radiation causes cancer is the physical interaction of a quantum of energy (e.g., an X ray or a particle such as a neutron or alpha particle) with a cell, leading to mutation of its DNA. Although such mutations can take several forms, the most serious come from double-strand breaks. There are several biological pathways for repair of such lesions, but some of these processes are error prone, and if not repaired or repaired incorrectly, a mutation can be fixed into the affected cell and passed on to its daughter cells. Depending upon the specific part of the chromosome affected, a mutation can lead to a chain of subsequent events and the growth of a clone of mutated daughter cells that can ultimately develop into a fully malignant tumor. Thus, radiation most frequently acts as one of the initiating steps in this complex process, although it is also possible that it can promote some of the later steps in an already initiated precancerous lesion. The probability of such an initial mutational event happening thus depends primarily on the probability of a damaging interaction between energy and DNA; the probability of such interaction depends on dose. The resulting cancer risk, however, can be modified by numerous other factors involved in the subsequent stages of malignant transformation or by the sensitivity of the target tissue (NRC, 2006).

The nature of this dose-response relationship and its modification by other factors has been extensively studied, both observationally in humans and in various experimental systems. Although experimental studies can be very useful for exploring the basic mechanisms of radiation carcinogenesis, quantitative risk estimates in humans have been derived from epidemiologic studies that have data on exposure. Numerous radiation-exposed populations have been studied, including the atomic bomb survivors, patients treated with diagnostic and therapeutic radiation, occupationally exposed nuclear workers and uranium miners, and groups exposed environmen-

tally to emissions from nuclear accidents, nuclear weapons production and testing, or other sources. An overall conclusion that can be reached based on this body of evidence is that cancer rates roughly increase linearly with dose, with no evidence of an absolutely "safe" dose (a threshold below which there is no increase in risk). The slope of this dose-response relationship, which varies with cancer type, type of radiation, age, latency, and other factors is basically what determines an individual's risk given their exposure, and hence the probability of causation (PC) if that person develops cancer. Various expert groups such as the NAS (NRC, 2006), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000), and the International Agency for Research on Cancer (IARC, 2000) have compiled the full body of evidence on dose-response relationships and performed extensive joint analyses of the raw data from the major studies in order to develop these risk estimates and evaluate their uncertainties.

Veterans' Studies

Among the sources of human risk estimates uniquely relevant to compensation policy for veterans are direct studies of radiation-exposed military personnel, specifically the atomic veterans. Several hundred thousand such veterans in total, mostly Americans but also substantial numbers of British veterans and other nationalities, have been included in several epidemiologic studies (ACHRE, 1995; Caldwell et al., 1980, 1983; Dalager et al., 2000; Darby et al., 1988, 1991, 1993; IOM, 1995, 2000; Johnson et al., 1997; Muirhead and Kendall, 2003; Muirhead et al., 2003, 2004; Pearce et al., 1997; Raman et al., 1987; Robinette et al., 1985; Watanabe et al., 1995). One of the first of these tests involved about 40,000 participants at the first hydrogen bomb tests at Bikini in 1946 (Operation CROSSROADS), later studied by the MFUA of the IOM (Johnson et al., 1997). A summary of these various studies is provided in the Appendix found at the end of this case study. Unfortunately, results from these studies are somewhat inconsistent, largely because most of these veterans' doses were relatively low, and hence any elevation of cancer risks would be expected to be close to the limits of detection even in large epidemiologic studies.

Uncertainties in doses and the potential for confounding further add to the difficulty of establishing definitive dose-response relationships from such studies. (For example, the majority of participants in the CROSSROADS study had no dose estimates available.) The epidemiologic studies of radiation-exposed veterans are therefore more useful for establishing the plausibility of a population-level causal connection between veterans' radiation exposures and subsequent cancer risks rather than for estimating these risks directly. Indeed, all of the point estimates found in Table I-1 and even most of the upper 95 percent confidence limits are substantially lower than the relative risk of 2, which translates to a 50 percent probability of causation for exposed veterans. Given these uncertainties of the data on veterans, a negative or inconsistent finding cannot be taken as definitive evidence against a causal connection, in the face of the wealth of positive evidence from other epidemiologic studies. But a positive finding could help bolster the evidence from other sources and can suggest specific cancer types that might be plausibly connected to radiation in the absence of compelling evidence against such an association.

For comparison, a graphical presentation of the relative risks from the atomic bomb survivors (Preston et al., 2003) is reproduced in Figure I-5. The specific cancers listed are those with sufficient numbers of cases available to support separate analysis and that show a clear radiation effect. The category "other solid cancers" may be quite heterogeneous in terms of radiosensitivity, but in general, convincing evidence to show that any specific cancer in this group is not radiosensitive would be elusive.

TABLE I-1 Summary of Standardized Mortality Rates (95% Confidence Limits) from U.S. Veterans' Studies of Cancer Conducted by the Institute of Medicine (IOM) in Participants in the CROSSROADS and Five Series of Nuclear Weapons Testing Exercises

Study Population	All Deaths	Cancer Mortality	Leukemia Mortality[a]
CROSSROADS[b]			
All Navy	1.05 (1.02-1.07)	1.01 (0.96-1.07)	1.02 (0.75-1.39)
Boarded target ships	1.06 (1.01-1.10)	1.03 (0.94-1.12)	1.01 (0.61-1.66)
Did not board target ships	1.04 (1.02-1.07)	1.01 (0.95-1.07)	1.02 (0.74-1.42)
Five Series Study[c]			
All participants vs. all non-participants	1.00 (0.98-1.02)	1.02 (0.98-1.06)	1.14 (0.90-1.44)
Land only	0.96 (0.93-0.99)	1.00 (0.95-1.06)	1.49 (1.04-2.13)
Sea only	1.03 (1.00-1.06)	1.04 (0.98-1.10)	0.92 (0.67-1.27)

[a] Excluding chronic lymphocytic leukemia (CLL).
[b] IOM, 1996, p. 65.
[c] IOM, 2002, pp. 63, 71.

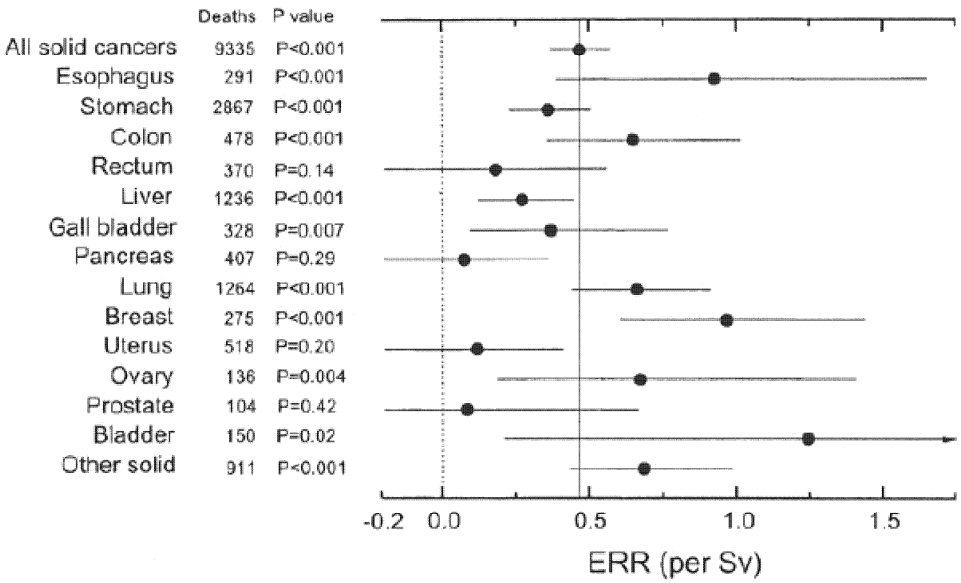

FIGURE I-5 Estimates of excess relative risk per Sv for site-specific cancers among the atomic bomb survivors.
SOURCE: Preston et al., 2003.

The National Institutes of Health Radioepidemiologic Tables and Interactive Radiation Epidemiology Program

Because the risks vary by such factors as dose, type of radiation, age, gender, and latency, it is not particularly useful to settle upon a single summary number for risk. Instead, some algorithm is needed to predict an individual's risk or related PC given the specifics of his or her situa-

tion. In 1985, a provision of the Orphan Drug Act (Orphan Drug Act of 1983. Public Law 97-414. 97th Cong., 2d Sess.) directed the National Institutes of Health (NIH) to assemble a set of "radioepidemiologic tables," which were to provide estimates of the PC for 12 types of cancer as a function of dose, age, gender, latency, and other factors (NIH, 1985, p. 65). Some examples of the calculations provided in the resulting report (NIH, 1985) are illustrated in Table I-2. The report also listed 14 specific cancer sites for which there was either no evidence of radiosensitivity or risk estimates were too uncertain to support PC calculations (NIH, 1985, p. 262). The estimates in the NIH report were derived mainly from risk estimates by earlier expert committees, principally the Biological Effects of Ionizing Radiation (BEIR) III report (NRC, 1980), and the methodology was carefully evaluated by a separate expert committee convened by the NAS (Lagakos and Mosteller, 1986; NRC, 1984). A summary of their conclusions is discussed in Chapter 9 of this report.

The act that created the 1985 radioepidemiologic tables (Orphan Drug Act of 1983. Public Law 97-414. 97th Cong., 2d Sess.) also included a provision calling for the tables to be periodically updated, but more than 15 years passed before this occurred. At that point, a new committee created a computer program, the Interactive Radiation Epidemiology Program (IREP), which could be used by individuals or compensation bodies to compute individualized PC estimates, given the specifics (dose, age, cancer type, etc.) of their experience. In addition to making the calculator accessible interactively on the Internet (https://www.niosh-irep.com/irep%5Fniosh/), an important advance was the inclusion of uncertainty estimates for each PC, based both on uncertainties in the epidemiologic data and the individual's history (see the last two columns of Table I-2 for the previous illustrative examples). The interpretation of these uncertainties will be discussed later in this case study.

History of Radiation Compensation Criteria for Veterans

Congress has enacted three major pieces of legislation addressing compensation standards relating to the exposure of various populations to ionizing radiation from government programs, as reviewed in detail in Chapter 4 and earlier NAS reports (NRC, 2003, 2005). The first of these, the Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984 (Public Law 98-542. 98th Cong., 2d Sess.), did not establish any presumptions, but directed VA to establish a

TABLE I-2 Illustrative Calculations of the Probability of Causation (PC) Provided in the Original Radioepidemiological Tables and the Revised Interactive Radiation Epidemiology Program

Cancer Site	Gender	Age(s) at Exposure	Dose (Gy)	RR	PC	PC (1985)	PC (IREP)	95% CI (IREP)
Breast	Female	25	45	0.1 (X-ray)	1.03	3%	9%	4-26%
Bone	Male	15	20	0.7 (alpha)	15.2	93%	51%	8-92%
Thyroid	Male	17	25	0.3 (X-ray)	12.5	92%	66%	29-90%
Lung	Male (non-smoker)	28	55	0.4 (gamma)	1.23	19%	20%	7-41%
Acute leukemia	Female	20-35	44	0.14 (total)	1.10	9%	16%	4-36%

SOURCE: IREP (https://www.niosh-irep.com/irep%5Fniosh/); NIH, 1985.

system for compensating veterans that eventually formed the basis for nonpresumptive compensation (Claims Based on Exposure to Ionizing Radiation. 2006. 38 CFR § 3.311), requiring evidence of sufficient exposure in the form of a quantitative dose reconstruction. These regulations permit claims for 24 "radiogenic diseases," mainly specific cancers, plus certain cataracts and nonmalignant thyroid disease, as well as "any other cancer" not specifically enumerated.

In response to "concerns about the possible health effects of exposure to radiation" (Podgor, 2007, p. 522), Congress later enacted the Radiation-Exposed Veterans Compensation Act of 1988 (REVCA) (Public Law 100-321. 100th Cong., 2d Sess.) which established presumptions for 13 cancers. Congress later codified these presumptions (Disease Subject to Presumptive Service Connection. 2006. 38 CFR § 3.309) which includes 21 cancer types. The scientific basis for this selection appears to have been based at least in part on a report of the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC, 1988). This report explicitly avoids addressing any policy implications of their conclusions, but mentions a concurrent policy panel that intended to conduct such a review (CIRRPC, 1988, pp. iii-iv); no such report has been located by the Committee, and VA has not responded to queries from this Committee about how the criteria provided in REVCA (Public Law 100-321. 100th Cong., 2d Sess.) were developed. The list first promulgated in REVCA (Public Law 100-321. 100th Cong., 2d Sess.) has been amended several times subsequently in response to developing scientific evidence, but arguably the list did not fully reflect the available scientific evidence at the time. It excluded some clearly radiation-related cancers (e.g., lung, ovarian, and prostate) while including others (e.g., pharynx, small intestine, and bile ducts) with only tenuous scientific evidence to support an association of risk with radiation exposure. Nevertheless, recognizing the general carcinogenic potential of ionizing radiation, some of these rarer cancers, for which site-specific risk has not been convincingly demonstrated, could nevertheless be linked to radiation, as are other more common cancers.

The Radiation Exposure Compensation Act of 1990 (Public Law 101-426. 101st Cong., 2d Sess.) did not directly relate to veterans, but instead focused on two other exposed populations, the Colorado plateau miners and other uranium miners and residents downwind of the Nevada Test Site. The act is relevant to consider here because of how some presumptions that were established for these groups differ from those for veterans. Uranium miners are exposed to radon gas and its radioactive decay products ("radon daughters" or "radon progeny"), which deliver substantial doses to the lung epithelium, leading to lung cancer. The miners could claim compensation only for lung cancer, by criteria that involved their dose and smoking history. Because few if any veterans would have experienced similar types of exposure, this comparison is not particularly relevant here. The downwinders, on the other hand, received qualitatively similar exposures to those of many of the atomic veterans, albeit usually at generally low doses. The Radiation Exposure Compensation Act of 1990 did not require any individualized dose estimates for the downwinders, but rather based presumptions on county of residence and cancer type. As one might expect, the cancers for which these presumptions were established were similar to those of the Radiation-Exposed Veterans Compensation Act of 1988 (Public Law 100-321. 100th Cong., 2d Sess.).

The adjustment for smoking for uranium miners who developed lung cancer deserves further comment. There were relatively few studies of the interaction between smoking and ionizing radiation effects on lung cancer risk, but some of the earlier studies indicated a joint effect that was either approximately additive (or the atomic bomb survivors [Prentice et al., 1983]) or somewhat less than multiplicative (for underground uranium miners [Lubin and Steindorf, 1995]). On this

basis, the relative risk (RR) per unit of radiation would indeed be lower for smokers than for nonsmokers and the corresponding "doubling dose"—the dose required to attain an RR of 2—would be higher. More extensive reanalyses of all the miner data, however, subsequently indicated that a multiplicative model, or one intermediate between additive and multiplicative, was more appropriate (NRC, 1988). Under the multiplicative model, the RR for radiation would be the same for smokers and nonsmokers, and there would be no need to take smoking into account in deciding about compensation, even though the absolute risk is much higher in smokers. The reason for this is that both the background risk and the excess risk due to radiation are raised by the same factor, so the proportion of the risk attributable to radiation is the same. In addition, of course, there is the practical difficulty of establishing a smoking history in the face of an obvious incentive for a claimant to deny it.

Many of the subsequent amendments to these three acts, detailed in the footnotes to Table I-3 under the column heading "Other," were in response to pressure from veterans groups seeking parity with the provisions of the Radiation Exposure Compensation Act of 1990.

Recommendations of the Advisory Committee on Human Radiation Experiments (1995) and the Human Radiation Interagency Working Group

In 1994, President Clinton established the Advisory Committee on Human Radiation Experiments (ACHRE), primarily to consider compensation policy for participants of certain medical experiments on human subjects with ionizing radiation and for people exposed to certain intentional releases of radiation into the environment for research purposes (ACHRE, 1995). However, the advisory committee interpreted its charge to encompass a number of other radiation-exposed groups, including the atomic veterans and the uranium miners. The advisory committee made a number of recommendations regarding compensation policy for these groups, noting the failure to update the radioepidemiological tables and calling for a review of the presumptions for the atomic veterans (ACHRE, 1995, ch. 18). These recommendations were in turn considered by the Radiation Exposure Compensation Act Committee (a committee established by the Human Radiation Interagency Working Group) which concluded that "the latest epidemiologic data suggest that the current exposure criteria do not accurately distinguish among lung cancer cases on a 'more likely than not' basis, and, therefore, do not effectively implement congressional intent" (RECAC, 1996, executive summary). They recommended revised criteria based either on dose or duration of exposure.

Dealing with Uncertainties

Uncertainties arise at both the population and individual level. At the population level, there can be uncertainty about whether a causal relationship between radiation and cancer has been established at all, as discussed in Chapter 9. If there is convincing evidence of a causal relationship, the estimate of risk attributable to exposure will be subject to statistical variation, since these estimates are based on a finite sample. The risk for particular categories of individuals (e.g., categories defined by dose, age, and time since exposure) will inevitably be even more uncertain than the average risk, since such estimates will be based on smaller sample sizes than for the overall risk. Epidemiologic risk estimates can also be distorted by selection bias, uncontrolled confounding, exposure measurement error, or a host of other potential biases. At the individual level, there are additional uncertainties about the specifics of an individual's history (as discussed in Chapters 7 and 9). These might include the estimate of an individual's dose (or

TABLE I-3 Selected Cancers and Diseases for Which Presumptive Service Connection Has Been Established Under Various Acts of Congress or Regulations

Disease	Veterans Dioxin and Radiation Exposure Compensation Standards Act of 1984	Radiation-Exposed Veterans Compensation Act of 1988	Radiation Exposure Compensation Act of 1990	Other	BEIR VII
Leukemia (excluding CLL)	x	x	x		x
Cancer:					
Thyroid	x	x	x		x
Urinary bladder				*f*	x
Kidney				*k*	
Lung	x			*h, j*	x
Bronchiolo-alveolar				*g*	
Bone	x			*h, j*	
Female breast	x	x	x		x
Male breast				*f*	
Pharynx		x	x		
Esophagus		x	x		
Stomach		x	x		x
Colon				*f, h, j*	x
Small intestine		x	x		
Pancreas		x	x		
Bile ducts		x	x		
Gall bladder		x	x		
Skin	x				
Liver	x	x	x		x
Salivary				*f*	
Ovarian				*b, f, h, j*	x
Brain and CNS				*c, f, h, j*	
Rectum				*d*	
Prostate				*e*	x
Uterus					x
Any other cancer				*e*	x
Multiple myeloma		x	x		
Lymphomas (excl. Hodgkin's)		x	x	*d*	
Nonmalignant thyroid nodules				*a*	
Cataracts (posterior subcapsulary)				*a*	
Parathyroid adenoma				*b, k*	
Polycythemia vera	x			*i*	

SOURCES: [a]VA, 1989; [b]VA, 1993; [c]VA, 1994; [d]VA, 1995; [e]VA, 1998; [f]Radiation Exposure Compensation Act Amendments of 2000 (Public Law 106-245. 106th Cong., 2d Sess.); [g]VA, 2000; [h]VA, 2002b; [i]VA, 2002a; [j]Veterans Benefits Improvement Act of 2004 (Public Law 108-454. 108th Cong., 2d Sess.); [k]Claims Based on Exposure to Ionizing Radiation. 2006. 38 CFR § 3.311.

even, in the case of a presumptive causation case, whether the individual met the minimum exposure criterion to qualify for the class at all), as well as other specific criteria (e.g., latency). IREP, described above, makes an attempt to incorporate both types of uncertainty into a "credibility interval" for each PC estimate it computes.

Other Considerations

Costs

The only information on the costs of existing radiation presumptions available to the Committee came from a single memo prepared by the Office of Resource Management concerning the proposal to add bronchiolo-aveolar carcinoma of the lung to the list of presumptions. This document estimated a caseload of 120 veterans and 338 survivors during fiscal year 2000, at a cost of $5.9 million, cumulative cost through 2004 of $33.3 million, with administrative costs of $308,000 (VA, 1999, p. 1).

Sensitivity and Specificity

As there is no unique marker for the cause of any given cancer and because cancers can be caused by any of a number of different factors (separately or acting in combination), any compensation scheme must necessarily lead to both false positives (compensation of cases not caused by radiation) and false negatives (failure to compensate a case that in fact was caused by radiation). Current VA policy is to err on the side of false positives. Thus, the aim of the current policy is to achieve high sensitivity, necessarily at the expense of low specificity. Given the probabilistic nature of radiation carcinogenesis, no compensation policy can hope to be both highly sensitive and highly specific.

Secrecy

Arguably a unique feature of much of the radiation story concerns the national security elements that pervaded the entire Cold War culture in which nuclear weapons testing exercises were conducted. This secrecy element has been addressed in detail in the ACHRE report (1995) and Chapter 11 of this report. Although much of the information about the veterans' participation in nuclear weapons testing has now been declassified, access to records and even in some instances the simple fact of a veteran's participation in particular exercises has undeniably been a barrier to establishing a credible claim in the past.

Lessons Learned

This case study illustrates a situation quite different from many of those in other case study chapters; for radiation, there is an abundant literature of solid science—some relating to dose-response relationships in general populations, some specific to veterans—upon which to base compensation policy. Despite this, there remain numerous uncertainties, particularly with respect to estimation of an individual's exposures and with respect to the risk for specific rare cancers. These uncertainties in large part are responsible for the shift in emphasis from individual PC-based criteria for compensation in the 1984 Act (Veterans' Dioxin and Radiation Exposure Compensation Standards Act of 1984. Public Law 98-542. 98th Cong., 2d Sess.) to the estab-

lishment of presumptions in the 1988 act (Radiation-Exposed Veterans Compensation Act of 1988. Public Law 100-321. 100th Cong., 2d Sess.). This evolution reflects the growing recognition of the difficulty of establishing criteria for individual compensation in the face of such uncertainties and the need for presumptions.

In general, studies of the effects of radiation in veteran populations have been of limited utility, in part because of the relatively small number of excess cancers expected in the available cohorts and, importantly, because of the failure to track individual exposures systematically or accurately. For this reason, these direct observations in the population of greatest relevance should not negate the wealth of more informative data from other populations. Nevertheless, the availability of informative epidemiologic data from other populations has made it possible to construct quantitative models to guide compensation policy for radiation-exposed veterans, which has often not been possible for other exposures. These studies also illustrate the difficulty of dealing with other causal risk factors for cancer, such as smoking. Yet even in that case, this case study has demonstrated that it is possible to develop scientifically based policies using strong epidemiologic evidence about their joint effects.

Ultimately, much of the force behind the movement for compensation for the atomic veterans derived from a sense of outrage that their government deliberately exposed them to radiation with at least some knowledge of risks involved at the time (Podgor, 2007). Furthermore, these risks were often denied by government officials, both at the time of exposure when they were not properly informed and later when diseases were manifest and their attempts at redress were rebuffed. On this basis, the veterans feel their claims for compensation are enhanced by the culpability of the government (ACHRE, 1995).

Appendix: Epidemiologic Studies of Radiation-Exposed Veterans

The first study of cancer in the atomic veterans was published by investigators from the CDC in 1980 (Caldwell et al., 1980, p. 1577), describing nine cases of all types of leukemia among the 3,224 participants of nuclear test explosion “Smoky” conducted in 1957, compared with 3.5 expected, a statistically significant excess. A subsequent report (Caldwell et al., 1983, p. 622) raised the toll to 10 leukemias compared with 4.0 expected, but found no statistically significant excess of any other cancers. The mean dose for the entire cohort was 0.5 cGy (ranging from 0-3.0 cGy for the leukemia cases, with a mean of 1.0 cGy) (Caldwell et al., 1980, p. 1577). The above-ground test conducted at the Nevada Test Site, “Smoky,” produced substantial fallout exposures to Utah downwinders in addition to the onsite military participants. However, the original investigators declared that the measured doses were inadequate to account for all of the observed leukemia excess (Caldwell et al., 1983).

Largely in response to the CDC study, NAS undertook a more extensive epidemiologic study of 46,186 participants in five series of tests at the Nevada Test Site (Robinette et al., 1985, as referenced in IOM, 2000, p. 29). This report confirmed the previous excess of leukemia among Smoky participants, but found no excesses among the other participants or any consistent patterns for other cancers. This study was later found to be flawed by the inclusion of 4,500 individuals who had not participated, the exclusion of 15,000 others who had, and inadequacies in the dosimetry (Gelband, 1992, as referenced in IOM, 2000, p. 29). A separate IOM committee concluded that the film badge dosimetry was unsuitable for epidemiologic purposes and recommended that dose reconstruction methods be used instead to impute dose estimates to study participants (IOM, 1995, p. 14). This formed the basis for a revised report on this cohort, now including 70,000 participants and 65,000 comparable nonparticipants (IOM, 2000, p. 1). This

report found no significant differences between the two groups for overall or site-specific cancer mortality, although a nonsignificant 14 percent increase in leukemia was noted.

A cohort of 40,000 participants at the first hydrogen bomb tests at Bikini in 1946 (Operation CROSSROADS) was compared with a similar cohort of nonparticipants in a study by IOM's MFUA (Johnson et al., 1997). A significant 5 percent increase in all cause mortality ($P < .001$) was seen, but there were no significant excesses for all cancers (1.4 percent) or for leukemia (2 percent). The authors concluded that this pattern did not support a radiation hypothesis.

Another study was conducted on 8,554 Navy participants in a series of 35 tests conducted at the Pacific Proving Grounds in the Marshall Islands in 1958 (Operation HARDTACK) compared with 14,625 Navy veterans who did not participate in any tests (Watanabe et al., 1995, pp. 524-525). Overall, the exposed cohort received an average of 0.4 cGy and experienced a nonsignificant 14 percent increase in total cancer (95% confidence interval [CI], –2 to 33%) and a significant 47 percent increase in digestive cancers (6-104%). Among the 1,064 participants who received over 1 cGy, a significant 42 percent excess (95% CI, 4-96%) of total cancer was seen relative to nonparticipants, but no single site was noteworthy, and there were no significant dose-response trends. In comparison with general population rates, the excess of total cancer was only 12 percent (–1 to 27 percent) and 24 percent for digestive cancers (–4 to 57 percent) (Watanabe et al., 1995, pp. 524-525).

A subsequent analysis (Dalager et al., 2000) expanded the high-dose cohort to include 1,010 participants who received at least 5 cGy (374 Navy participants at the Pacific Proving Grounds, 636 from other services, mainly from the Nevada Test Site). In this group, the overall mortality was increased by 22 percent (RR = 1.22; 95% CI 1.04-1.44%); mortality from all lymphopoietic cancers increased by 272 percent (RR = 3.72; 95% CI 1.28-10.83); and there was a nonsignificant 41 percent increase in respiratory cancers (RR = 1.41; 95% CI 0.91-2.18), but there was no excess of digestive cancers or all other cancers. The comparison of all high-dose participants with Navy-only controls found that the numbers of cancers in the 374 Navy participants was inadequate to establish significant excesses, except for lymphopoietic cancers and all causes combined (Dalager et al., 2000).

In addition to U.S. military participants, veterans from other countries have also been studied, and it is reasonable to expect that their experience would be broadly comparable. A small Canadian study (Raman et al., 1987) of 954 participants and twice as many controls found no differences, but another small cohort of 528 New Zealand participants compared to 1,504 controls (Pearce et al., 1997, p. 139) found a significant 5.6-fold excess mortality from leukemia ($n = 4$) and 3.8-fold excess of deaths from hematologic malignancies ($n = 8$) (Pearce et al., 1997, p. 142).

A much larger study of British participants of nuclear tests conducted in Australia (Darby et al., 1988, p. 335) found higher rates of leukemia and multiple myeloma than in matched controls (28 compared with 6). Compared with national rates, however, it appeared that the excess was driven more by unusually low rates in controls than by high rates in cases. Various updates of the UK studies have been reported (Darby et al., 1991, 1993; Muirhead and Kendall, 2003; Muirhead et al., 2003, 2004), which have generally confirmed the original findings, except for eliminating the excess of multiple myeloma. The most recent publication (Muirhead et al., 2004, p. 227) shows an 83 percent excess (15-193 percent) of all leukemia excluding CLL, rising to a 199 percent excess (26-641 percent) for the period 2 to 25 years after exposure. As before, however, the rate relative to the general population was only slightly elevated in the exposed cohort (RR of 1.06 [$n = 40$] overall or of 1.23 [$n = 18$] 2 to 25 years after exposure), compared with

considerably lower rates in the control cohort (RR of 0.58 [*n* = 23] overall or relative risk of 0.36 [*n* = 6] 2 to 25 years after exposure) (Muirhead et al., 2004, p. 227).

This literature up to 1995 was reviewed by ACHRE (1995, ch. 10), who attempted to put these results in perspective by noting that among the roughly 220,000 U.S. participants, current risk estimates would predict about 100 excess lifetime cancers, a small number in comparison with the 48,000 that would be expected from natural causes, an excess whose magnitude is not only uncertain, but would be virtually undetectable by even the best designed epidemiologic study. They also estimated that among the 1,200 veterans who received more than 5 cGy, about 8 excess cancers would be expected. Nevertheless, the committee was highly critical of the government's culture of secrecy that made it very difficult for veterans to learn about their experiences, their failure to protect participants against any but acute effects from high-dose exposures, and their failure to maintain adequate records about either the individuals' participation or their policy-making process.

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CASE STUDY 6: MUSTARD GAS AND LEWISITE PRESUMPTIONS

This case study examines the 1992 and 1994 decisions by the VA to establish presumptive service connection for health outcomes related to mustard gas and lewisite exposures among World War II veterans. It outlines several issues critical to protecting and treating those in military service: secrecy and classification of exposures, the latency period to adverse health outcome following exposures, lack of medical records, the involvement of "volunteers" in chemical experiments, the classification of scientific evidence and the use of scientific evidence, and the impact of policy considerations in making compensation decisions.

Background

In 1992, VA recognized that some World War II veterans had been exposed to mustard gas during laboratory experiments that involved full-body, field, or chamber tests of protective equipment. A presumption was proposed that covered several diseases associated with exposure to mustard gas. VA justified this presumptive service connection based on several factors: (1) the studies were classified; (2) participants were directed not to discuss their participation in the studies; (3) their medical records were sparse; and (4) no long-term follow-up was conducted or provided for the participants (VA, 1992a). After public comment on this proposed regulation, VA issued a final rule in July 1992 (VA, 1992b). In early 1994, VA revised the presumption

based on a study conducted by the IOM on the health effects of exposure to mustard gas and lewisite and issued a proposed rule (VA, 1994a). The second presumptive service-connection rule was issued in August 1994 and amended the original proposal by (1) adding more diseases to the original list of diseases; (2) adding the compound lewisite to the rule; (3) adding veterans who might have been exposed during World War I and in studies after the end of World War II; and (4) clarifying the extent of exposure. Again the presumptive decision was based on the same factors stated in the original proposed rule (VA, 1994b). In August 2006, the VA Under Secretary for Health issued an information letter intended to inform health-care providers about the diseases resulting from exposure to mustard gas, lewisite, and some 250 different agents used in studies conducted at Edgewood-Aberdeen during the period of 1955 to 1975 (VA, 2006a). However, this letter specifically states that VA does not presumptively recognize any long-term health effects from agents other than mustard agents and lewisite. Any health effects from exposure to the 250 chemical agents used during chemical warfare testing studies are to be addressed on an individual basis (VA, 2006a).

Although chemical warfare has its roots in antiquity, World War I was the beginning of modern day chemical agent usage. The German army released tens of thousands of pounds of chlorine gas in April 1915 near Ypres, Belgium, as an offensive weapon (Joy, 1997). In July 1917 the blistering agent sulfur mustard, called mustard gas, was released for the first time in the same general area (Joy, 1997). This agent caused the most casualties during World War I, but not the most fatalities. Some 400,000 troops were injured by sulfur mustard during World War I (Gilchrist, 1928, as referenced in IOM, 1993, p. 9). This began the trend of concern regarding mustard gas and other chemical agents. Further concern was forthcoming with the December 1943 Bari Harbor, Italy, incident and the initiation and continued laboratory testing begun during World War II (Alexander, 1947; Harris and Paxman, 1982; Reminick, 2001; Tucker, 2006). The alleged use of mustard agents offensively by other countries since World War II has been documented: Egypt against Yemen in the 1960s (Shoham, 1998) and Iraq against Iran in the 1980s (Balali-Mood et al., 2005; IOM, 1993; Sidell et al., 1997; Tucker, 2006).

Although there was no chemical warfare during World War II, the lingering memories of World War I chemical usage by the German army remained foremost in the minds of the U.S. military. Chemical and biological warfare agent use and testing against the Chinese by the notorious Japanese Unit 731, commanded by General Shiro Ishii, spurred the United States to develop protective clothing and respirators, better termed *gas masks* (Harris, 1994). Sulfur mustard use was a major concern (IOM, 1993). Consequently, history reveals that the U.S. government began preparing for chemical agent usage prior to the attack on Pearl Harbor by the Japanese in December 1941. Under President Franklin D. Roosevelt, war-related research units were established and placed under the control of the White House Office of Scientific Research and Development (IOM, 1993). Two groups were established to investigate different aspects of the mustard agents and lewisite. The Committee on Medical Research studied protective ointments and alternative treatments through the NRC's Committee on Treatment of Gas Casualties. The second group, the National Defense Research Committee, studied protective clothing and gas masks through different military units. Both these groups were involved in secret testing programs involving mustard agents and lewisite. Because of a lack of animal models of human injury, researchers in these programs decided in 1942 to use human subjects (IOM 1993). In total these two testing programs involved approximately 60,000 military personnel as human experimental subjects deemed by the government to be "volunteers" (IOM, 1993, pp. vii, 1). Some 4,000 volunteers participated in gas chamber or field exercises (IOM, 1993, p. 1). The gas chamber tests

involved high concentrations of mustard agents or lewisite. The field exercises were conducted over heavily contaminated soils. Exposure concentrations ranged from mild, such as a drop of agent on the arm in patch tests, to severe, repeated gas chamber trials with and without protective clothing. All human experimental subjects were sworn to secrecy regarding their involvement in these tests (IOM, 1993).

However, concerns regarding health consequences of sulfur mustard and lewisite exposures were not entertained by VA until the early 1990s. Concern by VA at this time was brought about by some of the former human subjects as they attempted to obtain medical help for diseases thought to be associated with exposure to mustard gas or lewisite. VA was unable to resolve these cases for two reasons: (1) the absence of records or documentation regarding the individual's participation in exposure testing, and (2) the uncertainty of health effects linked to the two agents of concern, sulfur mustard and lewisite (VA, 1992a,b). On January 15, 1992, VA announced guidelines for the handling and subsequent adjudication of these cases (VA, 1992a). These guidelines included a lessening of normal requirements for documenting an individual's participation in exposure testing and awarding of compensation based upon disease presentation.

VA at this time was proposing to adjudicate compensation claims for disabilities or deaths resulting from the chronic effects of exposure to mustard gas while in service. Supplementary information provided in the proposed rule states that

> Some Naval personnel were experimentally exposed to mustard gas during full-body, field or chamber tests of protective equipment and clothing conducted at the Naval Research Laboratory, located at Edgewood Arsenal, Washington, DC, between 1943 and 1945. Similar testing may have been conducted at other locations during World War II. These World War II tests were classified, participants were instructed not to discuss their involvement, and medical records associated with the tests are generally unavailable. No long-term follow-up examinations were conducted. For these reasons, some participants may not have filed claims with VA for disabilities resulting from mustard gas poisoning, or, if they did file claims, may have experienced difficulty in establishing entitlement to benefits.
>
> VA believes that the special circumstances surrounding these World War II testing programs have placed veterans who participated in them at a disadvantage when attempting to establish entitlement to compensation for disability or death resulting from experimental exposure. The proposed rule specifies that, if exposure occurred under the described circumstances, disabilities or deaths resulting from certain diseases are to be recognized as connected to a veteran's exposure in-service.
>
> A review of the available medical literature by Veterans Health Administration (VHA) personnel indicates that the chronic, long-term effects of acute mustard gas poisoning may include laryngitis, bronchitis, emphysema, asthma, conjunctivitis, keratitis, and corneal opacities. Chronic forms of these conditions which developed subsequent to experimental exposure during World War II will be service-connected.
>
> (VA, 1992a, pp. 1-2)

After public comment regarding the proposed rule, VA published the final rule with an effective date of July 31, 1992 (VA, 1992b). The proposed rule was modified to include World War I veterans who could claim residual disability from sulfur mustard exposure. These individuals would be able to show service medical record entries regarding acute sulfur mustard exposure

and that the long-term chronic effects from exposure have existed continually since the acute exposure episode.

The use of long-term chronic effects of exposure was retained in the final rule by the following VA rationale:

> Veterans who were exposed to mustard gas during experimental tests of protective clothing and equipment during World War II, however, face a potentially insurmountable disadvantage when attempting to establish entitlement to compensation. Those tests were conducted behind a strictly enforced veil of secrecy, medical records associated with the tests are generally unavailable, and no long-term follow-up examinations were conducted. As a result, service medical records for individuals who participated in those tests may not show evidence of the acute effects of mustard gas exposure. Furthermore, it is likely that participants who developed chronic effects of exposure did not previously file compensation claims with VA solely because they had been instructed not to discuss their involvement in the tests. Physicians who may have treated these veterans for chronic effects more than 40 years ago have almost certainly retired from private practice, making it impossible for a veteran to establish that a chronic form of one of the specified disabilities has existed continually since exposure to mustard gas.
>
> (VA, 1992b, p. 2)

The VA indicated in the final rule that it would not have a significant financial impact: (1) the annual effect on the economy would be less than $100 million; (2) there would be no major increase in costs or prices; and (3) it would not "have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets" (VA, 1992b, p. 2). Additionally, VA would contract with the NAS to address questions raised during the public comment period for which they did not have sufficient information to answer and issue a subsequent rule if necessary (VA, 1992b).

IOM Report Entitled *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite*

As a result of public comment to the proposed rule, VA stated in the final rule that they would contract with NAS to conduct a review of the published literature worldwide, medical and scientific, to include languages other than English, covering the long-term health effects of mustard gas exposure. NAS, through IOM, established a committee to address this issue and to publish a report. The committee (Committee to Survey the Health Effects of Mustard Gas and Lewisite) included experts in the disciplines of toxicology, chemistry, epidemiology, psychology, oncology, dermatology, ophthalmology, occupational medicine, and environmental medicine. The task delivered to this committee was to "survey the medical and scientific literature on mustard agents and lewisite, assess the strength of association between exposure to these agents and the development of specific diseases, identify the gaps in the literature, and recommend strategies and approaches to deal with any gaps found" (IOM, 1993, p. vi).

IOM Report General Conclusions

> The lack of follow-up health assessments of the human subjects in the WWII gas chamber and field tests severely diminished the amount and quality of information that could

be applied in the assessment of long-term health consequences of exposure to mustard agents and Lewisite.

The levels of exposure to mustard agents or Lewisite experienced by the human subjects may have been much higher than inferred in the summaries of the gas chamber and field tests.

The committee was additionally dismayed that there were no epidemiological studies done of mustard agent-exposed, U.S. chemical weapons production workers, war gas handlers and trainers, or combat casualties from WWII.

(IOM, 1993, p. 3)

IOM Report Specific Findings

The data found generally fell into three categories of causal relationships: indicated, suggested, or insufficient evidence of a relationship. The committee emphasized that "*no condition evaluated could be removed from consideration as a health consequence of exposure to these agents.* Thus, for many diseases there remains significant doubt" (IOM, 1993, p. 4).

The evidence found indicated a causal relationship between exposure and the following health conditions:

- Respiratory cancers
  —Nasopharyngeal
  —Laryngeal
  —Lung
- Skin cancer
- Pigmentation abnormalities of the skin
- Chronic skin ulceration and scar formation
- Leukemia (typically acute nonlymphocytic type, nitrogen mustard)
- Chronic respiratory diseases (also Lewisite)
  —Asthma
  —Chronic bronchitis
  —Emphysema
  —Chronic obstructive pulmonary disease
  —Chronic laryngitis
- Recurrent corneal ulcerative disease (includes corneal opacities; acute severe injuries to eye from Lewisite will also persist)
- Delayed recurrent keratitis of the eye
- Chronic conjunctivitis
- Bone marrow depression and (resulting) immunosuppression (an acute effect that may result in greater susceptibility to serious infections with secondary permanent damage to vital organ systems)
- Psychological disorders
  —Mood disorders
  —Anxiety disorders (including post-traumatic stress disorder [PTSD])
  —Other traumatic stress disorder responses (These may result from traumatic or stressful features of the exposure experience, not a toxic effect of the agents themselves.)
- Sexual dysfunction (Scrotal and penile scarring may prevent or inhibit normal sexual performance or activity.)

The evidence found suggested a causal relationship between exposure and the following health conditions:

- Leukemia (acute nonlymphocytic type, sulfur mustard)
- Reproductive dysfunction (genotoxicity, mutagenicity, etc.; mustard agents)

There was insufficient evidence found to demonstrate a causal relationship between exposure and the following health conditions:

- Gastrointestinal diseases
- Hematologic diseases
- Neurological diseases
- Reproductive dysfunction (Lewisite)
- Cardiovascular diseases (Except for those that may result from serious infections shortly following exposure—heart disease resulting from rheumatic fever, for example.)

(IOM, 1993, pp. 4-5)

IOM Report Recommendations

The committee recommends that the Department of Veterans Affairs (VA) institute a program to identify each human subject in the WWII testing programs (chamber and field tests, and to the degree possible, patch tests), so that these individuals can be notified of their exposures and the likely health risks associated with those exposures. Further, all subjects so identified, if still living, should be medically evaluated and followed by the VA as to their health status in the future. These individuals should also, if they request it, be treated by the VA for any exposure-related health problems discovered. Morbidity and mortality studies should be performed by the VA, comparing chamber, field, and patch test cohorts to appropriate control groups, in order to resolve some of the remaining questions about the health risks associated with exposure to these agents.

(IOM, 1993, p. 5)

The committee recommends that careful attention be paid by health care providers to the special problems and concerns of the affected veterans and their families. This attention may include the convening of a special task force of experts in stress disorders and risk perception to aid the VA, further than this committee is able, in the establishment of comprehensive guidelines for handling of these cases.

(IOM, 1993, pp. 6-7)

The committee additionally recommends that the Department of Defense (DoD) should use all means at its disposal, including public channels, to identify former chemical warfare production workers (military or civilian) and individuals exposed to mustard agents or Lewisite from gas handling, training, the Bari Harbor disaster, or other circumstances. Records of former military personnel could be turned over to the VA for notification, inclusion in morbidity and mortality studies, and health status evaluation. Records of the civilian personnel should be used by the DoD to advise former workers as to their health risks and options for seeking appropriate compensation for any illnesses that resulted from their exposures.

(IOM, 1993, p. 7)

> The committee recommends that the VA and DoD publicly announce and widely advertise that personnel exposed to mustard agents or Lewisite during their service are released from any oath of secrecy taken at the time. In addition, professional educational materials should be prepared by the VA or DoD, or both, and made available for physicians who may be treating affected individuals. These materials should incorporate the latest information regarding the long-term health effects of exposure to mustard agents and Lewisite.
>
> (IOM, 1993, p. 8)

After review of the IOM report, VA issued a proposed rule on January 24, 1994 (VA, 1994a). The proposed amendment to VA adjudication regulations was based on the NAS study of the long-term health effects of exposure to mustard agents and lewisite. The NAS study, commissioned by VA, indicated that there is a relationship between mustard agent and lewisite exposure and subsequent development of certain medical conditions. The intended effect of the proposed rule was to expand compensation eligibility.

The NAS study (IOM, 1993) substantiated VA's prior determination that a casual relationship existed between mustard gas exposure and the resultant disease development. Further, the original seven diseases associated with this exposure were confirmed. However, the NAS study revealed numerous other medical effects as indicated above. VA accepted the additional medical conditions indicated by the NAS and included them in the proposed rule. A few minor exceptions were noted. Mesothelioma was excluded from the lung cancer grouping because it has only been associated with asbestos exposure. The term *skin cancer* was considered to be too broad a designation, and VA chose to include only squamous cell carcinomas of the skin. Likewise, VA indicated that, in their opinion,

> . . . there is no reason to establish presumptive service connection for "pigmentation abnormalities of the skin" because these abnormalities would be obvious from the time of the exposure to vesicant agents rather than occurring many years after exposure, as in the case of cancer. Also, because the usual places for mustard gas burns are areas of the body which are not visible, i.e., moist areas of the body such as the groin and axilla, rather than exposed areas as in the case of sunburn, most pigmentation abnormalities resulting from these burns would not be considered disabling, unless they interfered with the veteran's ability to function. . . . Since compensation is only payable for a disability resulting from an injury suffered or disease contracted in line of duty or from aggravation of a preexisting injury or disease contracted in line of duty [Basic Entitlement. 2006. 38 USC 1110; Basic Entitlement. 2005. 38 USC 1121; Basic Entitlement. 2005. 38 USC 1131; Deaths Entitling Survivors to Dependency and Indemnity Compensation. 2005. 38 USC 1310.], and since exposure to vesicant agents does not cause a type of pigmentation abnormality which is disabling, we do not propose to include pigmentation abnormalities of the skin in the regulation. However, we propose to include scar formation in the regulation.
>
> (VA, 1994a, p. 3)

Because the NAS study reported that data demonstrated a "suggestive" causal or "insufficient" causal relationship for certain health outcomes, VA stated the following in its proposed rule:

> NAS found that the evidence was "suggestive" of a causal relationship between exposure to mustard gas and reproductive dysfunction (genotoxicity, mutagenicity, etc.) and expo-

> sure to sulfur mustard and leukemia. NAS found insufficient evidence of a causal relationship between exposure to mustard gas and gastrointestinal diseases, hematologic diseases, neurological diseases, cardiovascular diseases, and for reproductive dysfunction as a result of exposure to Lewisite. As NAS itself indicates, further study in these areas is necessary and in our judgment, the scientific and medical evidence on the whole does not support the establishment of presumptions for these conditions.
>
> (VA, 1994a, p. 4)

The NAS report further did not address any condition of exposure other than whole-body exposure conditions. Therefore, VA did not include any veterans who were engaged in patch or drop testing of vesicants in the proposed rule. VA's rationale was that since the NAS report did not address the issue of patch or drop testing, then the only conclusion that can be drawn is that NAS findings regarding specific diseases are linked only to full-body exposure (VA, 1994a).

Lastly, the proposed rule addressed lewisite as well as mustard gas. Lewisite exposure was not included in the final rule issued July 31, 1992:

> The current regulation applies only to those veterans exposed while participating in secret tests of protective equipment during World War II; we propose to expand it to cover any verified full-body exposure during military service, which will allow veterans exposed to mustard gas under battlefield conditions in World War I, those present at the German air raid on the harbor of Bari, Italy, in World War II, and those engaged in manufacturing and handling vesicant agents during their military service to be eligible for consideration under this regulation.
>
> (VA, 1994a, p. 4)

After public comment on the proposed rule, VA issued the final rule on August 18, 1994:

> The regulation published on July 31, 1992, applied only to those veterans who experienced full-body exposure to mustard gas while participating in secret tests of protective equipment during World War II. This amendment expands that regulation to cover any full-body exposure to mustard gas or Lewisite during military service, and it now applies to veterans exposed under battlefield conditions in World War I, those present at the German air raid on the harbor of Bari, Italy, in World War II, those engaged in manufacturing and handling vesicant agents during their military service, etc. By expanding the number of conditions, vesicant agents, and veterans covered, this amendment clearly represents a significant liberalization of the previous criteria.
>
> (VA, 1994b, p. 4)

VA again expressed a concern about the secrecy issue covering the government's work on mustard gas and lewisite:

> It is unquestionably beyond VA's ability to modify historical events by regulation; however, we believe that this regulation is an appropriate government response to these issues. VA recognizes that because the tests were secret and no follow-up examinations were conducted, veterans who took part in them are at a disadvantage when attempting to

> establish entitlement to compensation. This regulation addresses that situation by establishing a regulatory framework which recognizes that specific conditions are likely to result from exposure to vesicant agents and relieves veterans of the burden of submitting evidence to establish those associations in individual claims.
>
> (VA, 1994b, p. 5)

As a result of the issuance of the final rule, 38 CFR § 3.316 (Claims Based on Chronic Effects of Exposure to Mustard Gas. 2006), currently reads as follows:

> (a) Except as provided in paragraph (b) of this section, exposure to the specified vesicant agents during active military service under the circumstances described below together with the subsequent development of any of the indicated conditions is sufficient to establish service-connection for that condition:
>
> (1) Full-body exposure to nitrogen or sulfur mustard during active military service together with the subsequent development of chronic conjunctivitis, keratitis, corneal opacities, scar formation, or the following cancers: Nasopharyngeal; laryngeal; lung (except mesothelioma); or squamous cell carcinoma of the skin.
>
> (2) Full-body exposure to nitrogen or sulfur mustard or Lewisite during active military service together with the subsequent development of a chronic form of laryngitis, bronchitis, emphysema, asthma or chronic obstructive pulmonary disease.
>
> (3) Full-body exposure to nitrogen mustard during active military service together with the subsequent development of acute nonlymphocytic leukemia. (b) Service connection will not be established under this section if the claimed condition is due to the veteran's own willful misconduct (See Sec. 3.301[c]) or there is affirmative evidence that establishes a nonservice-related supervening condition or event as the cause of the claimed condition (See Sec. 3.303).
>
> (Claims Based on Chronic Effects of Exposure to Mustard Gas. 2006. 38 CFR 3.316)

Analysis of Presumptive Decisions

The final rule published in 1992 (VA, 1992b) was too restrictive, both from a standpoint of the personnel covered by the rule and the health effects considered by the rule. VA addressed only World War II veterans who were experimentally exposed to mustard gas during full-body, field, or chamber tests of protective equipment. The seven health effects and the restricted personnel inclusion were based on a VA review process only. The presumptions used were based on the fact that the World War II tests were classified (minimally Secret), the "volunteers" were directed not to discuss their involvement with any of the studies, medical service records were not maintained or were not available because of the secret classification, and consequently no long-term medical examinations were conducted. Because of these stated reasons some of the human volunteers who experienced adverse health effects probably did not file for any VA assistance, and those who did file would have experienced great difficulty in establishing service connection.

The final rule published in August 1994 (VA, 1994b) greatly expanded the scope of effects and the population of workers covered. Based on the NAS report (IOM, 1993), the regulation was amended to cover any verified full-body exposure to mustard gas or lewisite during military service and included veterans from World War I exposed during battlefield conditions. This rule

also significantly increased the number of adverse health effects which would be covered as a result of full-body exposure to mustard gas or lewisite.

The significantly higher number of medical conditions to be covered and the increased number of Service members to be included for disability coverage indicated that VA was sensitive to veterans' attempts to obtain VA assistance. Because of the secrecy classification applied to the veterans who worked on the projects, and subsequently to their medical service records, the usual methods of establishing eligibility were deemed to be too great a burden for the veteran. Consequently, the presumptions used were to the benefit of the veteran. VA was attempting to be extremely sensitive to the needs of the veteran in lieu of the strict classification assignment. A fine line must be addressed for national security measures and the health needs of the personnel assigned to work on these national security measures. As indicated in the IOM report, there is still hesitancy in declassifying many of the study results (IOM, 1993). The IOM committee addressing this issue was not given full cooperation in retrieving documents from these studies while the DoD stated that they were not declassified.

Costs could not be fully addressed in this case study because no financial information was received from VA. In the July 1992 rule (VA, 1992b) VA did indicate that there would be no significant financial impact on the amended regulation for compensation. The cost of the amendment would not have an annual effect on the economy of $100 million or more, it would not cause a major increase in costs or prices, and it would not have significant adverse effects on other economic parameters. The August 1994 amendment (VA, 1994b) also indicated no adversity in economic impact. However, VA has not presented IOM with any dollar values for either amendment period.

In view of the current classification scheme based upon national security concerns, those individuals working in classified studies remain potentially at risk. Only after a few individuals involved in the World War II studies attempted to obtain VA assistance was VA able to implement disability assistance. Failure to declassify study results up to 50 years after exposure puts our veterans at considerable risk of disease manifestation and progression without possible warranted screening and therapy. Although project classification may be necessary for DoD, a method should be developed and implemented to account for medical intervention in such cases. The absence of medical service records, no long-term medical or epidemiologic follow-up, and the enforced requirement for secrecy hampered veterans and VA from providing the necessary assistance to the veteran or the beneficiary. Future projects must include a means to ensure medical care is afforded to the participants if needed. A thorough communication path and cooperative working arrangements need to be explored and developed between DoD and VA to ensure that such a lack of medical attention does not occur in the future. If secrecy is mandatory to the level exhibited by the current mustard gas and lewisite rule, then future study participants will be hindered as much as past participants. This issue was examined in great detail in the report, *Veterans at Risk*, and recommendations were provided (IOM, 1993). The committee found that the secrecy coverage still existed some 50 years after the World War II programs were initiated. Even though some documents were declassified, many of them remained "restricted" and consequently are not releasable to the public. Additionally, not all facilities freely cooperated with IOM in releasing documents. Some did not release documents until the committee work had essentially been completed.

Classification and Secrecy Requirements

The oath of secrecy is still held inviolate by many of the veterans involved in the World War II mustard gas and lewisite studies. These military and civilian workers took an oath to keep all information involving these studies secret, and they have maintained that oath to this day. Even though this oath has prevented possibly thousands of individuals from obtaining necessary medical care, the oath has not been violated. They took a secrecy oath and legally and ethically then maintained their oath. However, the government that they are protecting has not reciprocated in protecting them. The lack of medical records and long-term medical care for past exposures to mustard gas and/or lewisite has not been provided to all military and civilian workers, ostensibly due to the secrecy clause. Classification is mandatory to preserve national security. Consequences of this same classification can be paramount as is evidenced in the mustard gas and lewisite exposure issue. An appropriate resolution between DoD and VA needs to be made to protect both the nation and the nation's governmental workers.

There are three entities involved in the secrecy issue: DoD scientific and military organizations, VA disability/compensation programs, and the individual Service member. At times, DoD must undertake secret studies to obtain results that will be used to provide the best security possible for our country. To provide the maximum protection, these studies may require a classification level. Many of the studies being conducted today are appropriately under this mantle of classification. On the other hand, VA must provide assistance to the veterans who have provided a necessary service to the government and the country. VA cannot provide this assistance if the necessary information is not given to them to ensure that entitled individuals are tracked, medically treated, and compensated appropriately. Furthermore, the exposures and agents must be identified so that health consequences can be linked. The individual workers must be given the ability to seek VA assistance as the need arises. Using the mantle of secrecy to protect the country is a dire hindrance to the veteran in seeking the necessary medical assistance. Policy considerations may be involved in both the roles played by DoD and VA. Both agencies have requirements and responsibilities that must be met.

The IOM report *Veterans at Risk* (1993) provided three recommendations addressing this issue:

> The committee additionally recommends that the Department of Defense (DoD) should use all means at its disposal, including public channels, to identify former chemical warfare production workers (military or civilian) and individuals exposed to mustard agents or Lewisite from gas handling, training, the Bari harbor disaster, or other circumstances. Records of former military personnel could be turned over to the VA for notification, inclusion in morbidity and mortality studies, and health status evaluation. Records of the civilian personnel should be used by the DoD to advise former workers as to their health risks and options for seeking appropriate compensation for any illnesses that resulted from their exposures.
>
> (IOM, 1993, p. 7)

The IOM committee additionally recommended that the secrecy requirement for workers involved in the World War I and World War II mustard gas and lewisite studies be deleted so that the individuals may seek medical assistance without the threat of punishment for violating the secrecy oath:

> The committee recommends that the VA and DoD publicly announce and widely advertise that personnel exposed to mustard agents or Lewisite during their service are released from any oath of secrecy taken at the time. In addition, professional educational materials should be prepared by the DoD or VA, or both, and made available for physicians who may be treating affected individuals. These materials should incorporate the latest information regarding the long-term health effects of exposure to mustard agents and Lewisite.
>
> (IOM, 1993, p. 8)

The VA final rule issued in August 1994 (VA, 1994b) addressed the disease and eligibility issues for veterans. DoD's response to the IOM committee recommendations has not been fully ascertained.

VHA Under Secretary for Health's Information Letters

Since the IOM report was issued in 1993, three information letters have been released by the VHA Under Secretary for Health as well as a veteran health initiative. The Under Secretary for Health's information letter IL 10-2002-016 (VA, 2002) provided information to clinicians who might encounter and treat veterans involved in Project Shipboard Hazard and Defense. While this letter primarily addressed biological agents, there is a section addressing chemical agents as well. Reference is made to reports produced by IOM. The Under Secretary for Health's information letter IL 10-2005-004 (VA, 2005) provided information to clinicians who might treat veterans who had been exposed to mustard or lewisite chemical warfare agents as part of human experimentation conducted by DoD through World War II. Extensive reference is made to the IOM report (1993). This letter indicates that because of the secrecy issue related to these studies, VA health-care providers were not aware of the history of these chemicals being used. Guidance was presented for the health-care providers to consider the diseases covered by the presumptive decision rule and emphasized that medical care should focus on the current health status of the veteran. Further, direction was given, emphasizing that there is no test available to confirm exposure to these compounds that occurred decades ago. The Under Secretary for Health's information letter IL 10-2006-010 (VA, 2006a) again provided information to clinicians on this issue. This letter stated that the Veterans Benefits Administration released notification letters on June 30, 2006, to DoD-identified veterans who were test subjects in military experiments and advised the veteran of benefits they might be entitled to because of their participatory exposures. Again the diseases identified in the final rule for mustard and lewisite agent exposure as causative were discussed and references to websites for additional information were provided. *Chemical Warfare Agent Experiments Among U.S. Service Members* is a report that describes more chemicals evaluated at Edgewood-Aberdeen than the mustard and lewisite agents (VA, 2006b).

In October 2003, a veterans health initiative was released as an independent study course (VA, 2003). The veterans health initiative, titled *Health Effects from Chemical, Biological and Radiological Weapons*, contained a forwarding message from the VA Under Secretary for Health, Robert H. Roswell, M.D., stating "greater general awareness of the specialized health issues facing persons with [Chemical, Biological and Radiological] injuries is needed to assure therapeutically appropriate clinical processes" (VA, 2003, p. ii). Dr. Roswell emphasized that every clinician must complete the study course in order to better serve the health needs of the veteran.

Lessons Learned

A number of concerns are raised by this presumptive decision. Foremost is the issue of secrecy surrounding military and governmental studies involving warfare agents. Classifying warfare studies based on national security is necessary in many cases. However, this classification can lead to concerns about health that might not be resolved for decades. In the case of mustard and lewisite agents national security took precedence over identifying the long-term health consequences of exposure. Volunteers who participated in these studies maintained their secrecy oaths for decades even though health issues arose. When these issues were brought to the attention of VA a second problem arose: the lack of definitive medical records for these individuals. Medical records that did exist did not contain any information relating to potential mustard gas or lewisite exposures. Consequently, health-care providers were unaware of these health-related issues. Long-term medical follow-up therefore was not provided to the study participants. A third area of concern is that this classification precluded health-care providers from being aware that symptoms of mustard gas or lewisite exposure might be exhibited by patients. As a result, the health-care providers did not look for these occupationally related symptoms.

Several Under Secretary for Health information letters have been issued by VA to address this gap. As indicated in the presidential task force 2003 report (President's Task Force to Improve Health Care Delivery for Our Nation's Veterans, 2003) and a recent GAO report (GAO, 2006a), the health of our veterans must be considered for the entire time of an individual's military service. The presidential task force specifically cited the lack of exposure data to a known environmental hazard as a root cause for not being able to determine compensatory issues for our veterans (GAO, 2006a,b). While DoD apparently is addressing the tracking and recording of the Service members' movements to link with exposure data collected, both areas remain concerns for the veteran. Inadequate exposure data are collected, and the ability to vector these data to location and troop movement has limited attribution of disease to exposure agents for individual veterans. Exposure assessment is the key to disability benefits for veterans. A recent report (GAO, 2004) indicates that force health protection and surveillance policy are not as good as they could be, but are improving, especially with more current deployments. The final rule for mustard gas and lewisite (VA, 1994b), based upon the 1993 IOM report, outlined three categories of causal relationships for health consequences of exposure: indicated, suggested, and insufficient evidence of a relationship. VA acknowledged in the final rule that certain health consequences could be linked directly to mustard gas or lewisite exposure and that a second grouping of health consequences had a suggestive linkage based upon the 1993 IOM report. Although the IOM report recommended many diseases that could be associated with exposure to these agents, VA specifically eliminated several of the diseases as not being related to mustard gas or lewisite exposure. Consequently, a precedent was established by VA for causal health consequences associated with specific chemical agents as recommended by IOM. Lastly, this case study indicates an apparent lack of communication and coordination between DoD and VA regarding individual Service members and government workers involved in studies, chemical agents used in these studies, and any actual or potential exposure data for the individuals involved. This lack of coordination was emphatically pointed out in the IOM 1993 report *Veterans at Risk*.

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CASE STUDY 7: GULF WAR PRESUMPTIONS

Introduction

This case study examines the legislative and scientific history for Gulf War presumptions. This analysis illustrates the challenges and implications of establishing service-connected presumptions for health outcomes when exposure data are limited (or unavailable) but environmental agents present in theater may pose potential health concerns. The case study also addresses a syndrome defined by symptoms, rather than a specific illness linked to a specific etiological factor.

Background

Although the duration of combat engagement during the first Gulf War was measured only in days, it also included a protracted aerial campaign of many weeks and ultimately involved nearly 700,000 U.S. troops (IOM, 2006b, p. 11). As a result, while the first Gulf War's time span may have been relatively brief, its scope and scale affected many U.S. military personnel. It also created a long list of health concerns in Gulf War veterans who believed they had been exposed to biological and chemical agents during Gulf War service that might have adversely affected their health. Veterans from the first Gulf War returned home with a constellation of symptoms that were initially termed *Gulf War syndrome*. However, the diversity of symptoms did not cluster into a specific group such that it could be defined as a syndrome and has been modified to the descriptions of "unexplained illnesses" or "undiagnosed illnesses."

The Gulf War presumption process was heavily influenced by the Agent Orange presumption history. The Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) represented the culmination of repeated efforts to create a comprehensive presumption decision-making process. This process proposed an integration of the VA policy response to complaints of veterans being made to Congress and to a scientific evidence review performed by the IOM. In many ways, the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) was the example

for the Gulf War legislation which provided the guidance for a review process examining agents of interest in light of Gulf War illnesses. The history of the government's sluggish response to radiation and herbicide exposure concerns played a role in the establishment of Congress' Gulf War presumptions for undiagnosed illnesses and chronic multisymptom illness. Following Congress' experiences with establishing radiation and Agent Orange legislation in the 1980s and early 1990s, Congress did not want to wait to lend aid to the first Gulf War veterans.

A Review of the Scientific and Legislative Landmarks Related to Gulf War Presumptions

Almost immediately following the first Gulf War, veterans began to complain of numerous adverse health effects that they attributed to service in the Persian Gulf. It became evident that the Persian Gulf veterans' health complaints differed significantly from those voiced by Vietnam veterans. Vietnam veterans ascribed many of their medical woes to one agent—Agent Orange—and claimed that the numerous well-defined illnesses from which they suffered, ranging from skin and liver illnesses to a variety of cancers, could be attributed to exposure to Agent Orange. Persian Gulf War veterans, on the other hand, appeared to be suffering from syndromes and symptoms rather than established illnesses. They were concerned about exposures to a host of toxic environmental agents that were present during the Persian Gulf War. VA claimed that many of the exposures experienced by Persian Gulf War veterans were no different from those experienced by civilians in the United States and for the great majority of veterans, the magnitude of the exposures was small and limited to a short period of time (Brown, 2005).

Congress responded by authorizing VA to provide health-care services on a priority basis (Priority VA Health Care for Persian Gulf Veterans. 1993. Public Law 103-210. 103d Cong., 1st Sess.). An effort to gather data about the nature of the illnesses and symptoms that veterans claimed to have, as well as to conduct research on environmental exposures that occurred during the war was started. In 1994, Congress passed the Veterans' Benefits Improvements Act of 1994 (Public Law 103-446. 103d Cong., 2d Sess., codified as 38 USC § 1117) which authorized VA to compensate veterans for certain chronic disabilities and illnesses that cannot be attributed to any known clinical diagnosis. Originally, these adverse health effects had to manifest within 2 years of service in the Persian Gulf for a veteran to receive compensation. This presumptive interval has, however, been extended a number of times, most recently in December 2006, so that compensation is provided to the veteran if the disability manifests itself by December 31, 2011 (VA, 2006).

In 1998, Congress passed the Persian Gulf War Veterans Act of 1998 (Public Law 105-277, 105th Cong., 2d Sess., codified, in part, as Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf during the Persian Gulf War. 2006. 38 USC § 1118) and the Veterans Programs Enhancement Act of 1998 (Public Law 105-368. 105th Cong., 2d Sess.). These acts, which used the Vietnam War Agent Orange legislation as a starting point, set up procedures for establishing presumptions of service connection for diseases incurred by Gulf War Veterans. As in the Agent Orange legislation, "a positive association" is required between an environmental exposure associated with service in the Persian Gulf War and "the occurrence of a diagnosed or undiagnosed illness in humans or animals" (Presumptions of Service Connection for Illnesses Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 USC § 1118[b][1][B][ii]). In addition, the Gulf War Act stated that an association "shall be considered to be positive . . . if the credible evidence for the association is equal to or outweighs the credible evidence against the association" (Presumptions of Service Connection for Illnesses

Associated with Service in the Persian Gulf During the Persian Gulf War. 2006. 38 USC § 1118 [b][3]). The same scientific review process was established as for Agent Orange; an agreement was made with the NAS to set up a committee that was charged with answering the same three questions previously asked with regard to Agent Orange (Persian Gulf War Veterans Act of 1998. Public Law 105-277. 105th Cong., 2d Sess. § 1603). However, as discussed later in this case study, the charges for the Gulf War committees were not identical and addressed many different potential etiological agents of interest. As with the Agent Orange reports, each IOM committee was to provide a report to VA, and the VA Secretary was to determine whether a presumption should be made for specific health outcomes and then publish the decision(s) in the *Federal Register*. IOM has issued several volumes of Gulf War reports (IOM, 2000, 2003, 2005, 2006b, 2007). VA published a *Federal Register* notice (VA, 2001a) following receipt of IOM's report for Gulf War Volume 1 (IOM, 2000). However, *Federal Register* notices and determination of presumptions for the Gulf War have yet to be published by VA following the receipt of the remaining IOM Gulf War reports.

In 2001, the VA Secretary "determined that there [was] no basis to establish a presumption of service connection for any disease based on service in the Persian Gulf during the Persian Gulf War" (VA, 2001b, p. 35702). This determination was based, in part, on review of the first Gulf War and Health report (IOM, 2000) which reviewed the evidence regarding associations between health outcomes and exposures experienced during the Persian Gulf War, including depleted uranium, pyridostigmine bromide (PB), sarin, and vaccines (anthrax, botulinum toxoid, and multiple vaccines) (IOM, 2000). The VA Secretary determined that "neither the acute and transient symptoms resulting from possible sarin exposure, nor any long-term health consequences associated with possible sarin exposure, warrant a presumption of service-connection" (VA, 2001b, p. 35708). For PB, the VA Secretary concluded that "these acute effects [of PB, as reported in IOM, 2000] were not in the nature of an illness within the contemplation of the governing statute" and that "such effects failed to meet the standards for establishment of presumptive service connection based on exposure to PB" (VA, 2001b, p. 35708). Regarding long-term adverse health effects based on exposure to PB, the VA Secretary determined that "the credible evidence against an association between long-term adverse health effects and PB outweighs the credible evidence for such an association" (VA, 2001b, p. 35708). A similar conclusion was reached for exposure to vaccines and transient acute local and systemic effects. The VA Secretary concluded that "such [acute] effects failed to meet the standards for establishment of presumptive service connection based on anthrax vaccination, botulinum toxoid vaccination or multiple vaccinations" (VA, 2001b, p. 35710).

The Presumption for "Undiagnosed Illnesses" in 1995

The initial presumptive legislation for the Gulf War was in response to numerous symptoms experienced by returning Gulf War veterans. The symptoms were not related to a single or even a few organ systems and were not easily explained by a unifying mechanism, such as being attributed to an infectious cause or the result of drinking tainted water, for example. The legislation arose primarily from the concerns expressed by veterans and without the interaction between VA and IOM that occurred previous to the passage of the Agent Orange legislation.

The list of "signs or symptoms which may be manifestations of undiagnosed illness or medically unexplained chronic multisymptom illness" that were considered as associated with undiagnosed illnesses during the Persian Gulf War and that were ultimately presumptively linked by Congress to service in the Persian Gulf via legislation in 1995 "include, but are not limited to

- Fatigue
- Signs or symptoms involving skin
- Headache
- Muscle pain
- Joint pain
- Neurologic signs or symptoms
- Neuropsychological signs or symptoms
- Signs or symptoms involving the respiratory system (upper or lower)
- Sleep disturbances
- Gastrointestinal signs or symptoms
- Cardiovascular signs or symptoms
- Abnormal weight loss
- Menstrual disorders" (VA, 1995, pp. 6665-6666)

The Presumption of Chronic Multisymptom Illness in 2001

In 2001, chronic multisymptom illness was added by Congress to the unexplained illness provision for presumption of disability acquired during Gulf War service (Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.). Several additional health outcomes were included under this grouping. The list of symptom complexes that were considered as associated with chronic multisymptom illness included: chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. Although some of these symptoms overlap with the list included in the undiagnosed illness provision, these symptoms were not specifically designated under one or the other grouping but may exist under either. This new terminology added confusion to an already nonspecific nomenclature for the symptoms or conditions qualifying for presumptive coverage of Gulf War veterans.

Additional Legislative Actions for Gulf War Veterans

Between the time of the initial Gulf War presumption legislation of 1995 (VA, 1995) and the addition of the chronic multisymptom illness provision in 2001 (Veterans Education and Benefits Expansion Act of 2001. Public Law 107-103. 107th Cong., 1st Sess.), there were several other legislative actions to address Gulf War veterans' needs. These legislative actions did not enlarge the domain of diseases or symptoms being considered as presumptively linked to Gulf War service, but rather addressed administrative aspects of the existing legislation, such as the timeframe of the presumptive period. Extension of the presumptive time period has occurred several times. Originally, it was required that a disease manifest itself within 2 years following military service. At the close of 2001, the presumptive time period was extended to 5 years following military service (VA, 2001a). In December 2006, the presumptive time period was again extended so that compensation would be provided if the disability manifested by December 31, 2011 (VA, 2006). VA stated in this *Federal Register* notice that "this amendment is necessary to extend the presumptive period for qualifying chronic disabilities resulting from undiagnosed illnesses that must become manifest to a compensable degree in order that entitlement for compensation be established. The intended effect of this amendment is to provide consistency in VA adjudication policy and preserve certain rights afforded to Persian Gulf War veterans and ensure fairness for current and future Persian Gulf War veterans" (VA, 2006, p. 75670). VA also stated in this *Federal*

Register notice that it had extended the presumptive period for undiagnosed illnesses from December 31, 2001, to December 31, 2006, "based upon ongoing research that would require review by the Secretary" (VA, 2006, p. 75670).

Exposures of Concern

A number of candidate toxicants were mentioned as potential causes for undiagnosed illnesses in the initial legislation of 1994-1995 (Veterans' Benefits Improvements Act of 1994. Public Law 103-446. 103d Cong., 2d Sess. § 102, codified as 38 USC § 1117). Congress found that U.S. troops in the Gulf War were exposed to "fumes and smoke from military operations, oil well fires, diesel exhaust, paints, pesticides, depleted uranium, infectious agents, investigational drugs and vaccines, and indigenous diseases, and were also given multiple immunizations" (Veterans' Benefits Improvements Act of 1994. Public Law 103-446. 103d Cong., 2d Sess. § 102). However, these nominated toxicants were not well linked to specific types of symptoms nor was a retrospective exposure assessment performed to estimate exposure intensities or likelihood of exposure potential. Instead several descriptive scenarios were suggested as plausibly leading to opportunities for exposure, at least to some Service members.

In the Persian Gulf War Veterans Act of 1998 (Public Law 105-277. 105th Cong., 2d Sess. § 1602), diseases related to a presumed exposure to "a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine" were added to the description of illnesses presumed to be service connected. This change in the legislative focus moved the presumption from one based upon an outcome (i.e., unexplained illnesses) to one based on an exposure agent (e.g., depleted uranium or PB). This important change resulted in adding potential adverse health outcomes to the presumptions list that might be linked to the action or toxicity of the now "presumed" agent of exposure.

This change in focus was likely influenced by maturation of hypotheses regarding environmental exposures in the Persian Gulf that had only been alluded to in the first presumptive legislation of 1995 (VA, 1995). In addition, the Presidential Advisory Committee on Gulf War Veterans' Illnesses commissioned by President Clinton issued their report in December of 1996 regarding the nature and risk factors for Gulf War illness. While not specifically focused on presumptions of service connection, the report did raise inadequately characterized environmental exposures and poor troop tracking as areas in need of improvement to avoid future postconflict health concerns (Presidential Advisory Committee on Gulf War Veterans' Illnesses, 1996). The controversies about such hazards had motivated VA to commission reports by IOM on possible health effects associated with exposures during the Persian Gulf War (IOM, 1999, 2000, 2003, 2005, 2006b, 2007).

IOM Gulf War Reports

IOM reports were initially requested by VA that focused on the group of toxicants that had emerged as possible candidates for causing unexplained illnesses (IOM, 2000, 2003, 2005). Review of the first grouping of toxicants began in late 1998, and a report was published in 2000 (IOM, 2000). This first report reviewed depleted uranium (a modestly radioactive heavy metal used in projectiles and armament), PB (a chemical antidote for cholinergic "nerve" agent weapons), sarin (a chemical nerve agent with cholinergic properties), and vaccines, including that for anthrax (IOM, 2000).

A second Gulf War report by IOM was completed in 2003 that reviewed insecticides and solvents used by U.S. troops during the Gulf War. The committee was charged by VA "to assess the scientific evidence regarding long-term health effects associated with exposure to specific agents that were potentially present during the Gulf War" (IOM, 2003, p. 2).

The third major Gulf War review by IOM included fuels, combustion products, and propellants as its focus (IOM, 2005). Although driven by a toxicological literature review, it appears that this study was also commissioned by VA to think more broadly about exposures and to inform VA about illnesses (among veterans) that might not be fully appreciated. This committee was to look not only at specific hazards that may have been encountered in the Persian Gulf, but also asked to comment on "the increased risk of illness among people exposed to the putative agents during service in the Persian Gulf" (IOM, 2005, p. 2). This committee's report was issued in 2005 and was also hoped to offer some prevention strategies for troops deployed to Iraq for the current conflict.

A fourth Gulf War review by IOM, which was commissioned by VA, did not focus on toxicants but rather was directed at determining what peer-reviewed medical literature, taken together, can tell us about the health status of Gulf War veterans (IOM, 2006b). In this instance, VA was interested in an integrated review and asked for the committee's insight about deployment-related illnesses that might not be fully appreciated. Their report was issued in 2006.

A fifth Gulf War review by IOM was commissioned by VA in 2004 to examine the infectious agent exposures that may have contributed to illness in the deployed Gulf War cohort. The report of the committee was issued in 2007 (IOM, 2007) and identified nine pathogenic agents endemic to the Gulf War theater and capable of causing illnesses with long-term adverse health effects. These agents were listed regardless of whether or not their related illnesses were acutely diagnosed in Gulf War troops. Further refinement of this list would require that the likelihood of infection with a candidate agent during deployment be equal to or greater than the likelihood of infection when not deployed.

Interspersed among these major review activities by IOM were several smaller projects commissioned by VA that addressed more limited topics, such as updated literature reviews for sarin (IOM, 2004) or a review for a specific disease or complaint (IOM, 2006a,c). Two additional studies are in progress—one dealing with PTSD and one with deployment-related stress. Work continues at IOM to provide VA with the most up-to-date research and published studies related to the Gulf War.

A summary of the statements of task as well as the conclusions from each of the IOM Gulf War reports can be found in Appendix H.

The VA Response to IOM Gulf War Reports

Typically, VA responds to IOM reports with policy decisions that it publishes in the *Federal Register*. To date, only one *Federal Register* notice (VA, 2001a) has been published by VA following receipt of an IOM Gulf War report (IOM, 2000). *Federal Register* notices have not yet been published in response to IOM Gulf War reports, volumes 2-5 (IOM, 2003, 2005, 2006b, 2007). To date, presumptions have not been granted by VA for Persian Gulf veterans pursuant to 38 USC § 1118 (Compensation for Service-Connected Disability or Death. 2006. 38 USC § 1118), although the machinery for establishing presumptions is in place. In February 2006, the VA Secretary wrote to leaders of the House and Senate Veterans' Affairs Committees advising them that the evidence currently available did not warrant the establishment of Persian Gulf presumptions, and that VA would publish notices of its decision in the *Federal Register* "explaining

the basis for that determination" (Nicholson, 2006a,b,c,d). As of the writing of this report, no statement appears in the *Federal Register*, although such statements are required to be filed within 60 days of the receipt of an IOM report (Persian Gulf War Veterans Act of 1998. Public Law 105-277, 105th Cong., 2d Sess. § 1602). Although the presumptive service-connection mechanism has not been a major pathway for service connection of Persian Gulf veterans, it has been reported that a comparatively large percentage of Persian Gulf veterans have been able to collect compensation through the direct service-connection route (as stated by Pamperin, 2006).

As of now, the Persian Gulf statutes would govern any presumptions dealing with current service in Iraq or any other area in the Persian Gulf. (As defined in 38 USC § 101, the term "Persian Gulf War" means " the period beginning on August 2, 1990, and ending on the date thereafter prescribed by Presidential proclamation or by law" [Definitions. 2006. 38 USC § 101(33)]).

Cost Implications of Gulf War Presumptions

No cost estimates were made available by VA or published in the *Federal Register* for this analysis. However, the long-term cost implications of Gulf War legislation are likely to continue to rise as veterans of contemporary conflicts in the Persian Gulf continue to return from Iraq and Afghanistan. During the Committee's first open session meeting, Mr. Tom Pamperin, a VA representative, stated that 3,259 veterans had been presumptively service-connected for undiagnosed illnesses and that these individuals had typically been rated at 10 percent (Pamperin, 2006). Mr. Pamperin stated that most of the Gulf War veterans who have secured service connection did so via the direct service-connection route (as stated during Pamperin, 2006). In VA's *Federal Register* notice that extended the presumptive period for compensation of Gulf War veterans to 2011, VA stated that "VA continues to receive claims for qualifying chronic disabilities. In 2005 for example, VA received 2,241 new claims with diagnostic codes that would be affected by this final rule, and we continue to receive such claims during 2006" (VA, 2006, p. 75671).

Lessons Learned

This case study offers several lessons that are relevant when considering strategies for improving the current presumptive disability decision-making process. These lessons relate to the role of Congress in issuing Gulf War legislation and establishing presumptions, VA in responding to the receipt of IOM reports, and IOM in evaluating and presenting the body of evidence relating to potential Gulf War exposures. In addition, the case study makes clear that closer coordination and collaboration between the DoD and VA are needed with regard to health monitoring and tracking of military personnel and veterans as well as exposure assessment efforts.

The principal participants in the current framework of the presumptive disability decision-making process include veterans and VSOs, VA, Congress, and IOM. Although each of these entities is motivated to assure the well-being of the veteran, there is also a need to balance the granting of benefits against resource constraints. Comparative fairness needs to be maintained by Congress and VA in its handling of each group of veterans. The current presumptive framework for Gulf War illnesses appears to have been strongly driven by time pressures on Congress and VA to respond to the concerns of Gulf War veterans, and to do so more rapidly than took place with radiation and Agent Orange. When a presumption of service connection for a disease or health condition is legislated by Congress (e.g., unexplained illnesses) rather than through the accrual and evaluation of scientific evidence, there is the potential to diminish the credibility of a presumptive decision-making process that is evidence based. A misperception then may arise that the decision was evidence based, even though it was actually driven by other considerations.

Congress

In the politically charged and time-pressured context of responding to Gulf War veterans in the 1990s, it was clear that Congress believed that action needed to be taken quickly. However, the response was not grounded in specific diagnostic tests or in a validated pattern of symptoms that could be linked to exposures in the Gulf War. Rather, a presumption was made for the entity, undiagnosed illnesses, that was based largely around features of numerous individual cases. The affected veterans, many previously robust in their health, experienced inexplicable symptomatology and deterioration of health. Thus, a decision was made by Congress to endorse the veteran's self-reported symptom complaints as sufficient evidence for documenting the occurrence of a Gulf War service-connected illness.

In establishing undiagnosed illnesses and chronic multisymptom illness, Congress defined medical conditions and health outcomes for the presumptive disability decision-making process for the first time.

There seems to have been little application of exposure assessment in determining eligibility for a service-connected Gulf War condition. This approach to handling affected veterans was largely authored outside of VA by Congress and then handed to VA to administer. The decision to not consider exposure history in determining eligibility for a presumption is similar to the exposure presumption made for Agent Orange, meaning if a Service member set foot in the Vietnam theater they were considered "exposed," and thus any illnesses linked to that exposure can be presumed to be service connected. In the example of the Gulf War, Congress directed VA to apply an approach with high sensitivity (i.e., toward including all possible claims, but thereby risking a high false positive rate).

Congress used two legislative approaches for veterans of the Gulf War in the absence of exposure data or a unifying case definition of Gulf War illness. The 1995 decision (VA, 1995) to term a list of conditions as presumptive signs or symptoms clustered under the rubric of undiagnosed illnesses permitted medical care and other benefits to be provided to affected veterans by VA. The second approach departed from the initial symptom-based presumption model and in the 1998 Act (Persian Gulf War Veterans Act of 1998. Public Law 105-277. 105th Cong., 2d Sess. § 1602) mandated any additional conditions or symptoms as presumptive that could be linked to "a biological, chemical, or other toxic agent, environmental or wartime hazard, or preventive medicine or vaccine." This decision added to the menu of potential illnesses that could be considered presumptively linked to service in the Gulf that had not yet been so deemed.

VA

The Gulf War example makes clear the critical need for improved collaboration and cooperation between DoD and VA with respect to health monitoring and tracking of military personnel and veterans as well as improved exposure assessment efforts. Attempts at retrospective reconstruction of troop exposures during military service have identified the gaps in exposure information available to inform decisions about veterans' health. Indeed, lack of these data has been noted by many IOM committees and by stakeholders grappling with service-connected disability determinations (IOM, 2000, 2003, 2005). There are many barriers, both historical and contemporary, to eliminating such information gaps through research and data collection. Certainly, the most obvious is the potential conflict of mission in collecting exposure data during wartime deployments. On the other hand, since the Gulf War began and perhaps taking into consideration the Agent Orange experience, there has been increased understanding of the need for exposure

assessment as an element of force health protection and readiness (DoD, 1997, 2006). The Committee fully understands that exposure assessment and troop tracking are challenging in a fixed environment; the Committee also recognizes the considerable efforts that both DoD and VA will need to make to improve exposure assessment and troop tracking during the chaotic and immediately hazardous environment of a wartime deployment. Nevertheless, talented professionals with technical knowledge, trained in scientific disciplines including engineering, toxicology, industrial hygiene, and epidemiology, regularly perform such assessments in other complex work environments and can be more fully engaged in troop exposure assessment. Indeed, substantial effort is needed before deployment to anticipate and evaluate potential hazards and the fielding of monitoring equipment and control measures that will be needed. The plans of DoD to develop and link health and environmental surveillance data will be an important element in attaining a longitudinal database for such information on every Service member. Applied research in the areas of large surveillance database development and real-time exposure assessment for candidate toxicants is to be encouraged. The commitment of DoD and VA to work more closely in harmonizing the medical records of all Service members to allow a truly seamless transition from DoD to VA health care and follow-up is strongly endorsed by the Committee and should be well resourced by the leadership of both DoD and VA.

VA has now received several IOM reports; however, *Federal Register* notices have not been published to explain how VA has evaluated the IOM reports and if VA will or will not establish presumptive connections as a result of the IOM reports.

VA continues to extend the presumptive time period for undiagnosed illnesses, and will likely continue to do so because of the current conflict in Iraq.

VA had an apparently limited role in the initial approach to Gulf War presumptions; its role primarily consisted of implementing a policy assigned by Congress in the absence of scientific evidence, a contrast to VA's actions in subsequent Gulf War-related presumptive decision-making actions. In latter examples, VA has asked IOM to examine adverse health effects rather than the existing "undiagnosed illness" or "chronic diseases" provisions established by Congress with relation to Gulf War service. These reviews have been the basis for subsequent decision-making by VA, which has not yet established any presumptions for the Gulf War.

The Committee was provided with an example of how VA was considering exposure potential to Gulf War veterans in a presentation made by a VA official. The VA official discussed VA's consideration of an IOM review regarding leukemia and its links to benzene exposure. VA took the position that leukemia developing in a Gulf War veteran was not presumptively service connected. VA explained to the Committee that because benzene is widely encountered in the environment generally, such a presumption of exposure occurring exclusively or primarily in the Persian Gulf could not be made. VA also pointed out that the individual exposure opportunity of the veteran during military service, which could be examined for service-connected benefits on a case-by-case basis, was a reasonable remedy for the veteran for whom exposure during Gulf War service and leukemia development were linked. This would occur via direct service-connection methods.

IOM

The Committee agrees with the inclusion of a category for evidence sufficient to infer causality, "Sufficient Evidence of a Causal Relationship," in IOM evaluations for the Gulf War and Health series.

The lack of exposure information for Gulf War veterans was emphasized in the Gulf War and Health series by IOM (2000, 2003, 2005). The inclusion of a specific substance, such as benzene, on a list of candidate toxicants that a veteran may have encountered in the Persian Gulf was based on one of the following qualitative assessments—a listing of solvents potentially used or obtained locally or known constituents of a product used—and not necessarily on actual supply lists or industrial hygiene measurements. Indeed, for just this reason, the vast majority of evidence considered in the IOM Gulf War reports does not come from studies of veterans but of other exposed cohorts described in the published scientific literature (IOM, 2000, 2003, 2005). This lack of exposure and health information from studies on veterans points to the need for exposure estimation and surveillance for health risks.

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CASE STUDY 8: AGENT ORANGE AND PROSTATE CANCER PRESUMPTION

This case study examines the 1996 decision by the VA to establish presumptive service connection for prostate cancer based on herbicide exposure among Vietnam veterans. VA's presumption followed IOM's Agent Orange committee's report which assigned a classification of "limited/suggestive evidence" for the association of exposure to Agent Orange and prostate cancer. This case study explores aspects of the development of a presumption for Vietnam veterans. It illustrates the challenges and implications of establishing a service connection for a common chronic condition when exposure data are unavailable and evidence of association is limited.

Background Information on Prostate Cancer

Prostate cancer is among the most common cancers in men. In fact, it is the second highest cause of cancer deaths in U.S. males. Overall prostate cancer age-adjusted death rates for all U.S. males are reasonably stable (27.9/100,000 in 2004) (see http://seer.cancer.gov/csr/1975_2004/results_merged/topic_mor_trends.pdf). There is a marked difference between Caucasians and African Americans—the 2004 death rate for African Americans is more than twice that of Caucasians (62.3 vs. 25.6 per 100,000). Prostate cancer is primarily a disease of older males; the comparable Surveillance, Epidemiology, and End Results data for annual death rates from prostate cancer for men over age 65 is 188.7 per 100,000 while the rate for men younger than 65 is 1.8 per 100,000 (see http://seer.cancer.gov/csr/1975_2004/results_merged/topic_annualrates.pdf). The steep increase in age incidence has led the medical community to the conclusion that if a man lives long enough, he will develop prostate cancer. The prevalence of prostate cancer in the United States is increasing, possibly reflecting earlier diagnosis and better treatment modalities.

The Need for a Presumption

The history of the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.), establishing a presumption of service connection for diseases associated with herbicide exposure during the Vietnam conflict, as well as the procedure of adding additional diseases to this presumption, has been reviewed elsewhere in this report (see Chapter 2, Chapter 4, and Appendix D). The need for an exposure presumption for Agent Orange-associated diseases is based in part on the difficulty of establishing with certainty the degree of exposure to herbicides among Vietnam veterans (IOM, 1994). The Agent Orange Act eliminates the need for an individual Vietnam veteran to provide evidence of herbicide exposure; exposure is presumed for all Vietnam veterans.

Although the need for a presumption is based primarily on the difficulty of establishing exposure, presumptions also address gaps in the evidence for association. An examination of the

exact charge to IOM for determining the diseases that are linked to herbicides is instructive. For each disease, IOM has been asked to determine, to the extent that available data permit meaningful determinations,

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. the increased risk of the disease among those exposed to herbicides during Vietnam service; and
3. whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

Each of the IOM reports that examined herbicides and prostate cancer risk (IOM, 1994, 1996, 1999, 2001, 2003, 2005) focused almost exclusively on addressing the task described in charge 1, and each report included additional discussions of the more limited data to address charge 3. Each of the IOM reports address charge 2 but acknowledge the difficulty of providing risk estimates because of the lack of exposure data. IOM (2005) notes that

> Although there are data to suggest an association between exposure to the chemicals of interest and prostate cancer, the lack of exposure information on Vietnam veterans precludes quantification of any possible increase in their risk.
>
> (IOM, 2005, p. 282)

The presumption of service connection for prostate cancer in Vietnam veterans therefore serves more than just to address the *gap in evidence of exposure.* As the lack of exposure data makes quantification of the magnitude of the association between military service and prostate cancer difficult, this presumption also implicitly serves to address *a gap in the evidence for association* between herbicides and prostate cancer among Vietnam veterans.

Development of the Prostate Cancer Presumption

As a result of Public Law 102-4 (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess.), IOM signed an agreement with VA to review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and diseases or conditions that may be associated with this exposure. The first report was issued in 1994 (IOM, 1994) and has been updated on a biennial basis since that time. This section reviews the scientific evidence contained in the IOM reports and the legislative events that resulted from the conclusions of these reports. It is not meant to be a comprehensive analysis of the entire body of scientific literature on this topic, but rather to highlight those events and data that inform the conclusions in the reports and changes in legislation.

Each of the IOM Agent Orange committees' reviews of prostate cancer has categorized the evidence between Agent Orange and prostate cancer as "limited/suggestive evidence of an association." The IOM Agent Orange committees' definition of the category "limited/suggestive evidence of an association" includes an example that "at least one high-quality study shows a positive association, but the results of other studies are inconsistent" (IOM, 1994, 1996, 1999, 2001, 2003, 2005). Each of the IOM Agent Orange committees reviewing prostate cancer found at least one study of agricultural workers exposed to herbicides, in particular phenoxy herbicides, that

had statistically significant findings and was deemed to be of high quality. Each IOM report also cites other studies with some supporting evidence of an association between Agent Orange and prostate cancer, although the results of some of the studies are not statistically significant (IOM, 1994, 1996, 1999, 2001, 2003, 2005). The 1994 IOM report states that

> One large well-done study in farmers showed an increased risk, and subanalyses in this study indicate that the increased risk is specifically associated with herbicide exposure (OR = 2.2, confidence interval [CI] 1.3-3.8; Morrison et al., 1993).
>
> (IOM, 1994, p. 519)

The IOM Agent Orange committees have tended to rely largely on epidemiologic findings for the evidentiary classifications. For example, the Conclusions section of the 2003 report states that

> **Strength of Evidence from Epidemiologic Studies**
> On the basis of its evaluation of the epidemiologic evidence reviewed in this and previous *Veterans and Agent Orange* reports, the committee finds that there is limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest (2,4-D, 2,4,5-T or its contaminant TCDD, picloram, or cacodylic acid) and prostate cancer. Although the associations are not large, a number of studies provide evidence suggestive of a small increase in morbidity or mortality from prostate cancer. The evidence regarding association is drawn from occupational studies in which subjects were exposed to a variety of pesticides, herbicides, and herbicide components and from studies of Vietnam veterans.
>
> (IOM, 2003, p. 323)

The Extent of Association Reported by the IOM Agent Orange Committees and the Presumptive Decision for Prostate Cancer by VA

The Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) specifies two categories of diseases that may be presumptively service connected. For one group of specified diseases, a presumption is to be given "unless there is affirmative evidence to establish that the veteran was not exposed to any such agent during that service" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess. § 2[a][3]). The act then specifies a second group: "each additional disease (if any) that the VA Secretary determines in regulations prescribed under this section warrants a presumption of service connection by reason of having *positive association with exposure to an herbicide agent*" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess. § 2[a][1][B]; emphasis added). Prostate cancer falls into the second group. The language in the act defines a positive association as one in which "the credible evidence of the association is equal to or outweighs the credible evidence against the association" (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess., § 2[b][3]). Each of the IOM Agent Orange committees was charged with determining

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. the increased risk of the disease among those exposed to herbicides during Vietnam service; and

3. whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

In 2007, the Committee has no way to assess how the congressional language ("equal to or outweighs") and the three points of the charge to the IOM Agent Orange committees were viewed by VA and the IOM Agent Orange committees. We could not specifically determine how these points were considered by the 1994 IOM Agent Orange committee, and the subsequent committees, in their deliberations and their design of the evidence categories chosen by the 1994 committee. We could also not judge the rationale for VA's translation of the Agent Orange committee's category of "limited/suggestive" and its evaluation of biological plausibility in response to charge 3 into a 1996 presumptive decision for prostate cancer based upon the congressional language of "equal to or outweighs."

In 1994, after review of the first IOM Agent Orange report (IOM, 1994), the VA Secretary determined that "the credible evidence against an association between prostate cancer and herbicide exposure outweighs the credible evidence for such an association, and he has determined that a positive association does not exist" (VA, 1994, p. 342). At this time, no presumption of service connection based on exposure to herbicides used in the Republic of Vietnam during the Vietnam era was issued for prostate cancer. Two years later, after the release of the second IOM Agent Orange report (IOM, 1996), the VA Secretary determined that, although prostate cancer remained in the "limited/suggestive" category of evidence, there was "a positive association between herbicide exposure and prostate cancer" (VA, 1996c, p. 41369). VA's determination was based, in part, on the review of several new occupational studies and veteran studies as reported in the 1996 IOM report (IOM, 1996) and presumptive service connection for prostate cancer was established (VA, 1996d).

Biological Plausibility

The relationship between prostate cancer and endocrine hormones has long been posited, as having the "endocrine-disruptive" effects of dioxins. This hormonal hypothesis implies toxicological mechanisms that might contribute to understanding the plausibility of a causal association. The lack of integration with epidemiological evidence of animal toxicology and dose issues related to biological plausibility to make an overall conclusion regarding the causal evidence for effect distinguishes the IOM approach from those of other national and international agencies considering the causal relationship between dioxins and cancer.

It is usual in assessing the evidence of a causal relationship between an environmental agent and cancer to evaluate its biological plausibility. For example, issues related to potential mechanisms of carcinogenesis are prominently discussed in reviews of possible adverse health consequences of dioxins by the International Agency for Research on Cancer (IARC, 1997), the National Toxicology Program (NTP, 2006), the Agency for Toxic Substances and Disease Registry (ATSDR, 1998), the U.S. Environmental Protection Agency (EPA, 2003), and the NAS (NRC, 2006a). The integration of basic mechanistic considerations, experimentation in laboratory animals, and findings in exposed humans are central to the weight-of-evidence approaches used by these organizations in considering the potential consequences of environmental agents. National Academy committees using this holistic process include those responsible for the various BEIR reports (NRC, 1972, 1979, 1980, 1988, 1990, 1998, 1999b, 2006b) and such documents as *Arsenic in Drinking Water* (NRC, 1999a).

As previously stated, the congressional language of "[w]hether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease" directs the review of the issue of biological plausibility for each disease evaluated (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess. § 3[d][C]). The first IOM Agent Orange committee noted the paucity of data on chlorophenoxy herbicides and most of its emphasis was on dioxin in its discussions of biological plausibility. The first IOM Agent Orange committee summarized their review of the carcinogenicity data as follows:

> TCDD has been shown to have a wide range of effects in laboratory animals on growth regulation, hormone systems, and other factors associated with the regulation of activities in normal cells. In addition, TCDD has been shown to cause cancer in laboratory animals at a variety of sites. If TCDD has similar effects on cell regulation in humans, it is plausible that it could have an effect on human cancer incidence.
>
> (IOM, 1994, pp. 521-522)

This conclusion that TCDD is a plausible carcinogen was subsequently supported by IARC (IARC, 1997). It should be noted that the epidemiologic data used by the IOM Agent Orange committees to categorize prostate cancer as "limited/suggestive" was due to the evaluation of a study of agricultural workers using phenoxy herbicides contaminated with dioxins. It could be hypothesized that phenoxy herbicides, irrespective of contamination with dioxins, may cause prostate cancer. This hypothesis might explain why studies of industrial workers and the Seveso population which have been heavily exposed to dioxins, but not phenoxy herbicides, have not shown evidence that exposure to dioxins is causally related to prostate cancer. If this hypothesis were correct, then the paragraph quoted above from the 1994 report as well as below from the 1996 report would not provide a biological basis for this association.

The second IOM Agent Orange committee provided more in-depth information about dioxins, in general, as well as a rationale for not considering specific cancers as requested by Congress (IOM, 1996). Based on its review of an extensive toxicological database, the committee stated

> Given these data, which establish biological plausibility for cancer in general but not for all specific sites, the committee chose not to summarize biologic plausibility for each cancer reviewed in this chapter. Toxicological data are provided only for a small number of cancer types that have specific, relevant experimental data.
>
> (IOM, 1996, p. 176)

The most recent IOM Agent Orange committee provided a much more detailed review of the toxicological mechanisms underlying the effects of dioxins, including a brief discussion of potential mechanisms related to prostate cancer (IOM, 2005). However, the Committee could not determine how this information was generally considered when classifying the extent of an association between Agent Orange and prostate cancer—which was still based upon review of individual epidemiologic studies (IOM, 2005).

Dose Issues

A common epidemiologic approach to exploring whether there is a causal relationship between chemicals and a specific cancer has been to focus on cohorts with particularly high levels of exposure, usually in an occupational setting. There are a number of such cohorts that have

been heavily exposed to dioxins and related compounds. As a corollary, biological markers of effect (when available) can serve as useful indicators of high levels of exposure. For dioxins and related compounds, chloracne is a common health outcome in those most heavily exposed and has been used as an exposure surrogate.

Consideration of comparative doses among published studies does not appear to have played a major role in the deliberations of the IOM Agent Orange committees. For example, the findings of the studies were not arranged by likelihood of high-dose exposures, such as in IARC reviews. The IOM Agent Orange committees give consideration to dose issues within a cohort. For example, evidence in a study shows that a higher risk for prostate cancer is observed in those who estimated to have the largest number of acres sprayed with pesticides.

Congruency of the IOM Process with That of IARC and Other Organizations

The process used by the IOM Agent Orange committees in developing the categorization of the strength of scientific evidence appears to have been adapted from the IARC process. The overall approach differs in that the IOM Agent Orange committees developed findings separately for epidemiological evidence (using criteria adapted from IARC) and biological plausibility based on toxicological and mechanistic studies but do not integrate these, like IARC and other organizations, to make an overall evaluation regarding causality. During the time period in which the IOM Agent Orange committees have conducted their biennial reviews, IARC has also reviewed the evidence concerning dioxins and cancer, as have other organizations including NTP, EPA, and ATSDR. IARC's 1997 review focused extensively on the experimental literature and an understanding of dose issues (IARC, 1997). Further, the findings in these areas were determinative of the IARC classification of TCDD as a Group 1 carcinogen which is defined as "[t]he agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans" (see http://www.inchem.org/documents/iarc/monoeval/eval.html).

In reaching the determination that TCDD should be classified as a Group 1 carcinogen, IARC particularly relied on mechanistic data and on findings in heavily exposed workgroups. IARC found limited evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. This normally would lead to categorizing a compound as a Group 2 carcinogen rather than a Group 1 carcinogen. However, the IARC document explained that

> In making the overall evaluation, the Working Group took into consideration the following supporting evidence: (i) 2,3,7,8-TCDD is a multisite carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor; (ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals; (iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.
>
> (IARC, 1997, pp. 8-9)

The approach used by IARC, as well as its focus on dose, lead to cautionary language in considering the epidemiologic evidence:

> Overall, the strongest evidence for the carcinogenicity of 2,3,7,8-TCDD is for all cancers combined, rather than for any specific site. The relative risk for all cancers combined in

> the most highly exposed and longer-latency subcohorts is 1.4. While this relative risk does not appear likely to be explained by confounding, this possibility cannot be excluded. There are few examples of agents which cause an increase in cancers at many sites; examples are smoking and ionizing radiation in the atomic bombing survivors (for which, however, there are clearly elevated risks for certain specific cancer sites). This lack of precedent for a multisite carcinogen without particular sites predominating means that the epidemiologic findings must be treated with caution; on the other hand, the lack of precedent cannot preclude the possibility that in fact 2,3,7,8-TCDD, at high doses does act as a multisite carcinogen. It should be borne in mind that the general population is exposed to levels far lower than those experienced by the industrial populations.
>
> (IARC, 1997, p. 4)

Emphasis on the toxicological database and on dose-response issues is also common to other agencies (e.g., NTP, ATSDR, EPA) reviewing the evidence of adverse health consequences resulting from exposure to dioxins or Agent Orange. The focus by IARC on mechanistic considerations and on cohorts with high levels of exposure as determinative of a cause-and-effect relationship has also been carried through in subsequent reviews. Steenland et al. reviewed the evidence that had accumulated since the 1997 IARC report and summarized additional analyses of the four industrial cohorts whose high-level TCDD exposures had been the focus of the IARC review (Steenland et al., 2004). Steenland et al. also reviewed additional findings in the Seveso cohort and discussed recent toxicological findings supportive of the potential for TCDD carcinogenesis. In the section on new studies they described the Ranch Hand studies of Air Force personnel involved in herbicide spraying, including the increased incidence of malignant melanoma. The authors stated the following regarding elevated prostate cancer findings in these studies:

> Akhtar et al. (2004) also found excesses of prostate cancer incidence, but these occurred in both exposed and nonexposed Air Force personnel and may have been due to increased cancer surveillance in both groups; both are subject to intense medical follow-up.
>
> (Steenland et al., 2004, pp. 1266-1267)

Cost Implications of the Presumption for Prostate Cancer

There are limited data regarding the costs to VA associated with the prostate cancer presumption. The commentary on 38 CFR Part 3 includes a brief discussion of the cost of this prostate cancer presumption. It states that

> The 6-year benefit cost for prostate cancer based on herbicide exposure is $65.3 million, with an administrative cost of $959,000. Additionally, the medical care cost over 6 years is $38 million. Prostate cancer is a male genitourinary cancer that shows marked increased prevalence with age. Accordingly, costs beyond the 6-year period would likely be substantially higher.
>
> (VA, 1996c, p. 41370)

VA provided the Committee two summary cost estimate documents relating to prostate cancer (VA, 1996a,b). These documents, entitled *Cost Estimate for Regulation on Claims Based on Exposure to Herbicides* (dated June 10, 1996, and November 6, 1996) summarize the anticipated benefit (i.e., veterans and survivors) and administrative costs for the prostate cancer presumption. Both documents state the "methodology was developed in collaboration with the Office of Man-

agement and Budget (OMB)." Caseload was projected by applying DoD mortality rates in military retirees to the estimated number of gross separations of veterans who had service in the Vietnam theater from 1965 through 1981. Age-specific incident and mortality rates for prostate cancer, as found in the Cancer Statistics Review of 1973-1986, were applied to the base population. On June 10, 1996, the total benefit costs estimated for years 1997-2001 were $56.4 million while the administrative costs were estimated at $787,000. On November 6, 1996, the total benefit costs estimated for years 1997-2002 were $65.3 million. The Committee was not provided recent cost estimates with regard to the prostate cancer presumption nor could the Committee confirm the actual costs following the 1996 estimates through year 2002. Taking into account the number of surviving Vietnam veterans who will soon enter into the age range for which there is a steep increase in age-related incidence of prostate cancer, it can be anticipated that a marked rise of prostate cancer in the Vietnam veteran population is virtually certain.

Lessons Learned

This case study offers several lessons that are relevant when considering strategies for improving the current system of presumptions. These lessons relate to the role of Congress in issuing the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.), VA in its use of scientific evidence and issuance of a presumption related to prostate cancer, and IOM in its evaluation and presentation of the body of evidence on the relationship between Agent Orange and prostate cancer.

Congress

In describing the type of relationship between dioxin and health outcomes necessary for a presumption, Congress used the language both of "association" as well as "causation" in the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) (see Chapter 4). Association appears to be the standard set for VA:

> An association between the occurrence of a disease in humans and exposure to an herbicide agent shall be considered to be positive for the purposes of this section if the credible evidence for the association is equal to or outweighs the credible evidence against the association.
>
> (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess. § 2[b][3])

However, the congressional language regarding "Scientific Determinations Concerning Diseases" includes evidence related to causation (Public Law 102-4):

> 1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
> 2. the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
> 3. whether there exists a plausible biological mechanism or other evidence of a *causal relationship* between herbicide exposure and disease.
>
> (Agent Orange Act of 1991. Public Law 102-4. 102d Cong., 1st Sess. § 3[d]; emphasis added)

This inconsistency around "causation" and "association" in the congressional language may have allowed differing interpretations of whether sufficient scientific evidence exists for establishing a presumption. The difficulties that result from this lack of clarity in the Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess.) may have been problematic for prostate cancer for which some evidence for association is present from epidemiological data, but limited by chance, bias, or confounding while the current toxicological evidence for causation (particularly evidence from animal studies and on plausible biological mechanisms) differs from that of the epidemiologic data and was not integrated to make an overall conclusion regarding causality.

In addition to the more general confusion between "association" and "causation" in the Agent Orange Act described above, the second charge set for IOM by this act—evaluating evidence for the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era—is particularly difficult to address. Nearly all of the Agent Orange reports issued by IOM (1994, 1996, 1999, 2001, 2003, 2005) comment on the challenge of addressing this second charge noting that the lack of exposure data on Vietnam veterans made the task difficult to fulfill. The intent of Congress in this second charge is unclear, particularly as the lack of exposure data for Vietnam veterans was well known at the time of the Agent Orange Act.

VA

Overall, VA's process for using the IOM reports to inform presumptive decisions is not transparent. The prostate cancer presumption was based on a "limited/suggestive" classification of the levels of evidence, rather than the highest standard of "sufficient" evidence of an association. This decision was most likely influenced by a variety of considerations (i.e., political, economic, and administrative factors) and not just by the scientific evidence. The interplay of these multiple factors and their relative weighting by VA are not easily characterized because of lack of transparency in the VA process for using scientific evidence to arrive at the final decision of issuing a presumption. This attempt at a balanced critique of the various parties in the Agent Orange and prostate cancer presumption is limited by the nonspecific information provided by VA on this subject, in particular the use of the "limited/suggestive" classification of an association.

VA's cost projections for the prostate cancer presumption are likely underestimates and did not consider the very large cohort of aging Vietnam veterans past year 2002. Taking into account the number of surviving Vietnam veterans who will soon enter into the age range for which there is a steep increase in age-related incidence of prostate cancer, it can be anticipated that a marked rise of prostate cancer in the Vietnam veteran population is virtually certain.

IOM

There were some questions regarding the responsiveness of the IOM process (via VA) to congressional intent. The Agent Orange Act of 1991 (Public Law 102-4. 102d Cong., 1st Sess. § 2[b][3]) states that a positive association is one for which "the credible evidence of the association is equal to or outweighs the credible evidence against the association." This statement is not necessarily equivalent to the category of "limited/suggestive" evidence for association used by IOM Agent Orange committees. The IOM "limited/suggestive" category covers a potential range of epidemiologic evidence from relatively weak to strongly suggestive. In the instance of Agent Orange and prostate cancer, VA established a presumption based on the IOM's 1996 classification of "limited/suggestive" evidence of an association. The evidence at the time was relatively

limited, but it did include one study showing a statistically significant excess and a number of other studies showing positive, but weak and nonsignificant associations.

Biological Plausibility The IOM Agent Orange committees did not appear to have an explicit and formal methodological protocol for synthesizing evidence and updating the classification of evidence based on new studies. The IOM Agent Orange committees appear to have developed a process which differs somewhat from that used by other Academies' committees and national and international organizations in their review of the level of evidence between an environmental agent and adverse consequences. In reviewing evidence on Agent Orange, the 2005 review considered biological and toxicological evidence when evaluating the biological plausibility of the association between prostate cancer and exposure to Agent Orange but did not integrate these other lines of evidence with epidemiologic findings to develop an overall evaluation. In seeking to classify the strength of evidence with regard to *association* only, prior IOM committees have relied almost entirely on epidemiologic findings in classifying the strength of evidence.

Approach to Dose-Response The criterion for reaching "limited/suggestive" evidence for association of Agent Orange used by the IOM committees is that the "(e)vidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent" (IOM, 2005, p. 8). The Agent Orange committees' evaluations for prostate cancer considered the totality of epidemiologic evidence, but did not take into account the very much higher exposures in certain exposed worker groups and in the population exposed during the Seveso incident. Several studies were of worker groups and measures of exposure to either the chlorophenoxy compounds or dioxin but were not available to enable comparisons across studies. Dose-response relationships could be considered for a few studies; for example, the RR "of prostate cancer in the Ranch Hands study correlated with putative exposure to Agent Orange (high 6.04 versus low 2.17 versus background 1.5*; P* = 0.01)" (IOM, 2005, p. 282). The lack of accurate estimates of exposure from the military experience has limited the study of the association between prostate cancer and exposure to Agent Orange in veterans.

The IOM reports did not attempt to address the fraction of prostate cancer risk that might be attributed to military service. It nonetheless notes that "(p)rostatic cancer is a common condition in older men, so it is likely that multiple factors are responsible and unlikely that herbicide exposure is a major cause" (IOM, 2005, p. 282) An explicit evaluation of attributable fraction might have been useful to policy makers considering this presumption by placing the scientific evidence on the link between Agent Orange exposure and prostate cancer in context of overall prostate cancer risks, although determining the magnitude of this attributable fraction would remain difficult in the absence of accurate exposure data.

General

The Agent Orange and prostate case study illustrates the challenge—both for scientists and policy makers—of evaluating evidence for an association between exposure and subsequent disease when accurate exposure data are lacking. This challenge is particularly striking for a disease like prostate cancer where multiple factors often contribute to the onset of disease, and the other known risk factors (e.g., race, age, family history of the disease, and a diet high in fats) are common in the general population. In this context, the contribution of exposures incurred during

prior military service to overall disease risk is likely to be small as acknowledged in the IOM reports. In the absence of accurate exposure data, determining whether this small increased risk of disease is present and further quantifying the magnitude of this risk is difficult.

Faced with this challenge of identifying a possible small increased risk of disease without accurate exposure data, it appears that policy makers have adopted an approach in the prostate cancer presumption that minimizes the possibility of denying service connection to a veteran whose prostate cancer may have been caused by Agent Orange (maximizing sensitivity). The implicit assumption in the prostate cancer presumption is that if any possibility exists, no matter how small, that a veteran may have been exposed to any amount of Agent Orange (presumption of exposure), and any possibility exists, no matter how small, that Agent Orange may have contributed even the smallest incremental increased risk of prostate cancer (presumption of association), service connection should be granted.

High-quality data for a cohort of veterans are essential for improving this process; ideally such data would include more accurate assessments of exposure during service, evaluation of other risk factors that may have been present during service or have developed after service before the onset of disease, and longitudinal assessments for evaluation of diseases that may have long latency periods. The prostate cancer case study highlights the potential value of such an ongoing cohort study and the missed opportunities when such studies are not continued.

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CASE STUDY 9: AGENT ORANGE AND TYPE 2 DIABETES PRESUMPTION

This case study examines the 2001 decision by the VA to establish presumptive service connection for type 2 diabetes based on herbicide exposure among Vietnam veterans. By exploring the scientific and legislative history of this decision, as well as the consequences of this decision for VA, this analysis seeks to illustrate the challenges and implications of establishing a service connection for a common chronic condition when exposure data are unavailable and evidence for association with the putative causal agent is limited.

Type 2 Diabetes

This presumption establishes service connection for type 2 diabetes developing in veterans of the Vietnam era. Several clinical and epidemiological features of type 2 diabetes are noted as they inform some of the challenges in the epidemiologic investigations of type 2 diabetes, particularly with regard to characterizing the effect of Agent Orange. First, type 2 diabetes is common in the general population, and its prevalence increases with advancing age (Figure I-6). This high background prevalence may pose challenges for determining additional risk attributable to military service in many studies. The high prevalence of type 2 diabetes may also translate into a

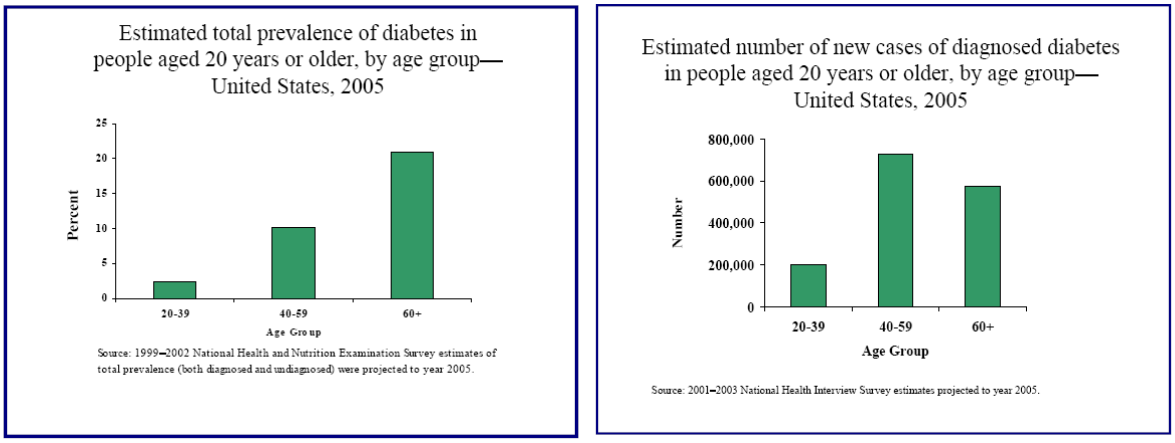

FIGURE I-6 Prevalence and incidence of type 2 diabetes in the United States.
SOURCE: CDC, 2005, pp. 4, 6.

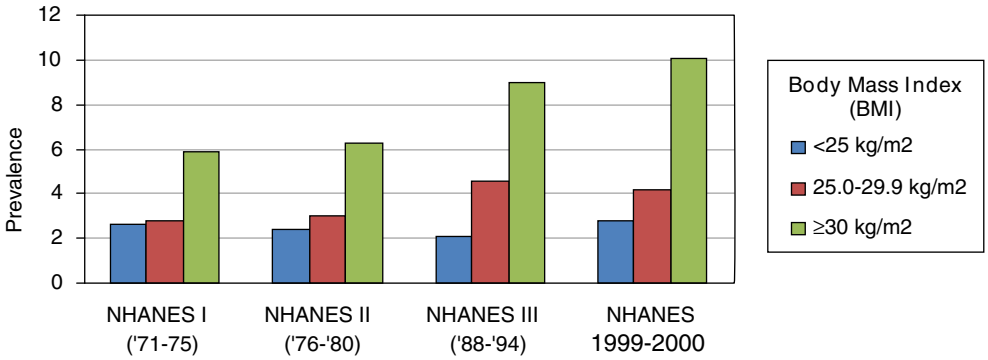

FIGURE I-7 Age- and sex-adjusted trends in type 2 diabetes prevalence.
SOURCE: Adapted, with permission, from Gregg et al., 2005, p. 1871.

larger constituency advocating for this presumption and affect the financial implications of a decision.

Second, there are multiple established risk factors for type 2 diabetes that are common in the general population. These contributors to type 2 diabetes risk include family history and lifestyle factors such as obesity and physical inactivity (Figure I-7). Because these risk factors are common, estimating the incremental risk of type 2 diabetes attributable to herbicide exposure among Vietnam veterans is challenging.

The known link between obesity and type 2 diabetes has particularly important implications for evaluating the observational studies exploring the risk of type 2 diabetes associated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) levels. Adipose tissue is a primary site of distribution for TCDD, and percentage of body fat appears to correlate with serum TCDD levels (IOM, 1994). Increasing body fat may also decrease the rate of TCDD elimination (IOM, 1994). The relationship between body fat and TCDD pharmacokinetics suggests that body mass index and other measures of body fat are important covariates that must be considered in observational studies of dioxins and risk for type 2 diabetes.

Third, type 2 diabetes is a disorder of carbohydrate metabolism that is characterized by hyperglycemia. Many individuals with type 2 diabetes initially exhibit few or no symptoms, making the exact onset of this disease difficult to establish. The diagnostic criteria for type 2 diabetes are based primarily on blood glucose levels, and the level of hyperglycemia that is diagnostic of type 2 diabetes has been adjusted downward over time. The current criteria are fasting blood glucose ≥126 mg/dL or a random blood glucose ≥200 mg/dL in the presence of symptoms (often polyuria or polydipsia) (ADA, 2007). The World Health Organization and American Diabetes Association definitions recognize a state of impaired glucose tolerance (fasting blood glucose of 100-125 mg/dL) that is not diagnostic of type 2 diabetes, but places individuals at high risk for subsequent development of this disease (ADA, 1997, 2003, 2007; Alberti and Zimmet, 1998). These changing definitions of type 2 diabetes make comparisons of studies across time potentially difficult. In addition, many studies evaluate both type 2 diabetes and blood glucose levels as outcomes; although hyperglycemia not meeting diagnostic criteria for type 2 diabetes may signal an important increased risk of type 2 diabetes, the significance of small increases in mean glucose concentrations within the range of normal glucose levels (<100 mg/dL) (ADA, 2007) may be less clear.

Finally, type 2 diabetes is an extraordinarily morbid condition that affects virtually every organ system. Heart disease and stroke account for nearly 65 percent of deaths among individuals with type 2 diabetes (CDC, 2005, p. 6). Type 2 diabetes is also associated with significantly higher rates of nontraumatic amputations, kidney disease, neuropathies, and blindness (CDC, 2005). There are two important implications of this high rate of morbidity associated with type 2 diabetes. First, mortality studies of this disease are limited because complications of type 2 diabetes (i.e., heart disease) are often listed as the underlying cause of death, resulting in an underestimate of type 2 diabetes-related mortality from use of death certificate diagnoses. Second, the multiple complications of type 2 diabetes could have significant consequences for the true costs associated with a service connection for this common and highly morbid chronic condition.

The Need for a Presumption

The history of the Agent Orange Act of 1991 (Public Law.102-4. 102nd Cong., 1st Sess.) establishing a presumption of service connection for diseases associated with herbicide exposure during the Vietnam conflict as well as the procedure of adding additional diseases to this presumption has been reviewed elsewhere in this report (see Chapter 2, Chapter 4, Appendix D). The need for a presumption for Agent Orange-associated diseases generally is based in part on the difficulty of establishing with certainty the degree of exposure to herbicides among Vietnam veterans (IOM, 1994). The Agent Orange Act eliminates the need for an individual Vietnam veteran to provide evidence of herbicide exposure; exposure is presumed for all Vietnam veterans.

Although the need for a presumption is based primarily on the difficulty of establishing exposure, presumptions also address gaps in the evidence for association. An examination of the exact charge to the IOM for determining the diseases that are linked to herbicides is instructive. For each disease, IOM has been asked to determine, to the extent that available data permit meaningful determinations,

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;
2. the increased risk of the disease among those exposed to herbicides during Vietnam service; and

3. whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

Each of the IOM reports that examined herbicides and type 2 diabetes risk (IOM, 1994, 1996, 1999, 2000, 2001, 2003, 2005) has focused almost exclusively on addressing the task described in charge 1 and have included additional discussions of the more limited data to address charge 3. Each of the IOM reports address charge 2 but acknowledge the difficulty of providing risk estimates because of the lack of exposure data:

> Although there are data to suggest an association between exposure to the chemicals of interest and type 2 diabetes, the lack of exposure information on Vietnam veterans precludes quantification of any possible increase in their risk.
>
> (IOM, 2005, p. 446)

Some committees additionally note, in response to charge 2, that the epidemiological evidence on known risk factors for type 2 diabetes would suggest that the contribution of exposures during military to overall diabetes risk is likely to be small:

> Available data allow for the possibility of an increased risk of type 2 diabetes in Vietnam veterans. It must be noted, however, that studies indicate that the increased risk, if any, posed by herbicide or TCDD exposure appears to be small. The known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk posed by wartime exposure to herbicides.
>
> (IOM, 2003, p. 492)

The presumption of service connection for type 2 diabetes in Vietnam veterans therefore serves more than just to address *the gap in evidence of exposure.* As the lack of exposure data makes quantification of the magnitude of the association between military service and diabetes difficult, this presumption also implicitly serves to address *a gap in the evidence for association* between herbicides and type 2 diabetes among Vietnam veterans.

A Review of the Scientific and Legislative Landmarks Leading to the Agent Orange and Type 2 Diabetes Presumption by VA

As a result of Public Law 102-4 (Agent Orange Act of 1991. Public Law 102-4. 102nd Cong., 1st Sess.), the NAS signed an agreement with VA to review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and diseases or conditions that may be associated with this exposure. The first report from NAS was issued in 1994 (IOM, 1994) and has been updated on a biennial basis since that time. Additionally, a special report on Agent Orange and type 2 diabetes was published in 2000 (IOM, 2000). This section reviews the scientific evidence contained in the IOM Agent Orange reports of 1994-2005 and the legislative events that resulted from the conclusions of these reports. It is not meant to be a comprehensive analysis of the entire body of scientific literature on this topic, but rather to highlight those events and data that inform the conclusions in the reports and changes in legislation.

1994-1999

The earliest publication reviewed by IOM that suggested a link between the herbicides and type 2 diabetes was a report of the 10-year follow-up of 55 workers who had become acutely ill after exposure to TCDD. Eight percent of these workers developed type 2 diabetes immediately following exposure; after 10 years, 11 of the 55 had developed type 2 diabetes (Pazderova-Vejlupkova et al., 1981, pp. 6, 7). Several small epidemiologic and occupational studies that followed the report of these cases failed to show a statistically significant association between exposure to these compounds and type 2 diabetes risk or type 2 diabetes mortality (Bertazzi et al., 1998; Cook et al., 1987, as referenced in IOM, 1999; Henneberger et al., 1989, as referenced in IOM, 1999; Moses et al., 1984, as referenced in IOM, 1999; May, 1982, as referenced in IOM, 1999; von Benner et al., 1994, as referenced in IOM, 1996; Zober et al., 1994, as referenced in IOM, 1996).

The National Institute for Occupational Safety and Health (NIOSH) studied 281 workers at dioxin plants in New Jersey and Missouri and compared them with 260 unexposed workers. Sweeney et al. found that increasing concentrations of TCDD were associated with a slight, but statistically significant increased risk of type 2 diabetes [odds ratio (OR) 1.1, $P < .003$] and elevated fasting glucose ($\geq$ 140 mg/dL) ($P < .001$) (Sweeney et al., 1996, p. 245; Sweeney et al., 1997, as referenced in IOM, 2000, pp. 16, 54). An earlier study of this cohort found that exposed workers had a type 2 diabetes prevalence of 9.2 percent compared with 5.8 percent among unexposed workers, a difference that did not reach statistical significance (Sweeney et al., 1992, as referenced in IOM, 1999, p. 500). The authors of these studies concluded that more analyses were necessary to eliminate the possibility of confounding from other established risk factors for type 2 diabetes, including age and weight, and the IOM Agent Orange 1998 update (IOM, 1999) called for a more detailed analysis of this cohort.

A study of Air Force veterans involved in herbicide spraying—the Air Force Health Study (AFHS)—suggested that serum concentration of TCDD was associated with glucose intolerance or type 2 diabetes in a dose-dependent manner. In this 1997 study (Henriksen et al., 1997, pp. 253-256), 989 Air Force veterans involved in Agent Orange spraying (Operation Ranch Hand) were categorized based on their TCDD levels; initial TCDD levels at the time of wartime exposure were estimated based on their current serum TCDD. In addition to comparing disease outcomes between veterans involved in Agent Orange spraying in different categories of TCDD levels, these subjects were also compared with 1,276 Air Force veterans that were not involved in spraying. Those with the highest level of TCDD had a significantly increased risk of elevated blood glucose (RR 1.4, 95% CI 1.1-1.8) and type 2 diabetes (RR 1.5, 95% CI 1.2-2.0) and a decreased time to onset of disease after adjusting for age and body mass index, compared to those with the lowest level of TCDD. Veterans involved in Agent Orange spraying with intermediate levels of TCDD exhibited an intermediate risk for these outcomes. This study was commended in the IOM Agent Orange 1998 update (IOM, 1999), but two concerns were also noted. First, there were no differences in type 2 diabetes rates overall between veterans involved in Agent Orange spraying and the designated comparison group that was not involved in spraying, despite significant differences in their serum TCDD levels (median 12.2 ppt versus 4.0 ppt [Henriksen et al., 1997]) (IOM, 1999, p. 499). Second, the dose-dependent association with TCDD concentration was also observed within the comparison group that was not involved with spraying (IOM, 1999, p. 500). Taken together these additional observations are concerning for residual confounding by a third factor such as weight or body fat that may be related to both TCDD levels

and type 2 diabetes. The IOM Agent Orange 1998 Update (IOM, 1999) called for a more detailed analysis of the AFHS.

One omission from the otherwise comprehensive review of scientific literature in the IOM reports of this period is an analysis of the Vietnam Experience Study of the CDC. CDC used a random sample of military records to identify a cohort of U.S. enlisted men who had served a single tour in Vietnam between 1965 and 1971 and a comparison cohort of U.S. Army enlisted men who had served elsewhere during this period. TCDD levels were not assessed in this study; rather Vietnam service was used as a proxy for exposure to herbicides. A total of 7,924 Vietnam and 7,364 Vietnam-era veterans completed telephone health surveys in 1985 and 1986 (CDC, 1989b, p. 1). Vietnam veterans did not have an increased risk of self-reported type 2 diabetes compared with the Vietnam-era veterans (adjusted OR = 1.2, $P > 0.05$) (CDC, 1989b, pp. 109, 114). A random subsample of these individuals (2,490 Vietnam veterans and 1,972 Vietnam-era veterans) underwent complete physical examinations in 1985 and 1986 (CDC, 1989a). The crude geometric mean of fasting serum glucose was slightly higher for Vietnam veterans (93.4 mg/dL) than for Vietnam-era veterans (92.4 mg/dL), a difference that was found to be significant even after adjustment for a variety of factors including age, race, military specialty, body mass index, and medications known to affect glucose metabolism (CDC, 1989c, p. 174). Despite this difference in mean glucose levels, there was no significant difference between the two groups in the number of veterans with abnormal blood glucose levels (> 140 mg/dL in this study) (CDC, 1989c, pp. 172, 175).

Although the Vietnam Experience Study is directly relevant to the IOM charge of determining whether herbicide exposure during the Vietnam era resulted in an increased risk of type 2 diabetes among Vietnam veterans, the IOM reports do not comment on the type 2 diabetes results found in the Vietnam Experience Study. The finding of no association between military service in Vietnam and type 2 diabetes in this study is not included in the summary analyses presented in the various tables of these reports. As participants in the Vietnam Experience Study were not followed beyond this assessment in the 1980s, it is impossible to determine whether the very small but significant increases in blood glucose concentration observed in this younger cohort might have been an indicator of subsequent type 2 diabetes risk.

In reviewing the studies of this period, the IOM Agent Orange reports of 1994, 1996, and 1998 (IOM, 1994, 1996, 1999) all concluded that there was inadequate or insufficient evidence to determine whether an association existed between herbicide exposure and type 2 diabetes. No presumption of service connection for type 2 diabetes among Vietnam veterans exists for this time period.

1999-2001

In 1999 VA asked IOM to convene a special committee to conduct a focused review of the scientific evidence regarding the association between Agent Orange and type 2 diabetes in advance of the regularly scheduled biennial IOM reports (IOM, 2000). VA's reason for convening this special committee out of the scheduled sequence of IOM reports on Agent Orange is outlined in the *Federal Register* (VA, 2001a) and reviewed here.

In 1999, NIOSH published a further analysis of exposed and unexposed workers in the New Jersey and Missouri dioxin plants (Calvert et al., 1999). The authors of this study summarize their findings in this way:

> Overall, the prevalence of diabetes mellitus was not significantly different between the workers and referents. Also, there was not a significant positive trend between prevalence of diabetes and increasing serum TCDD concentration. However, diabetes was found in six of 10 workers with current serum TCDD concentrations >1500 pg/g lipid.
>
> (Calvert et al., 1999, p. 270)

In the *Federal Register* outlining the rationale for the special diabetes report, the NIOSH study is summarized in the following way:

> . . . a report that detects an association, though not a strong association, between type 2 diabetes and dioxin exposure. The study does suggest a dose response relationship because of excess cases of type 2 diabetes found in workers having the highest serum-lipid levels of dioxin.
>
> (VA, 2001a, p. 2378)

The VA Secretary viewed this study as potentially important enough to warrant a full review of the scientific literature on Agent Orange and type 2 diabetes and commissioned a special report (IOM, 2000) on this topic from IOM. As with the prior Agent Orange committees, the charge of the Agent Orange and type 2 diabetes committee was to review evidence from epidemiologic studies, evidence for increased risk among Vietnam veterans, and evidence for biologic plausibility; the majority of this report focused on the epidemiologic evidence (as was the case with prior and subsequent reports). In their summary, the Agent Orange and type 2 diabetes committee (IOM, 2000) commented on two trends that they noted in the literature on this topic published since the IOM Agent Orange 1998 Update (IOM, 1999).

The report stated "*[p]ositive associations* are reported in many mortality studies, which may underestimate the incidence of diabetes" (IOM, 2000, pp. 2, 36). This statement was based on the data from four mortality studies that had not been reviewed in previous IOM reports:

- A 1998 report of the 5-year follow-up of individuals living near a 1976 industrial accident site involving dioxin (Pesatori et al., 1998). Individuals were grouped into three categories based on their distance from the site of the accident and compared with an unexposed reference group. Women with substantial exposure (41,391 person-years of follow-up) had significantly higher rates of type 2 diabetes mortality (RR 1.9, 95% CI 1.1-3.2); the same effect was observed among men with substantial exposure (42,219 person-years of follow-up), although the results did not reach significance (RR 1.3, 95% CI 0.6-2.9) (Pesatori et al., 1998, pp. 127-128). Only age and calendar period were included as covariates in this study.
- A study of 5,172 workers exposed to TCDD at 12 U.S. plants did not find an increase in the standardized mortality ratio (SMR) for type 2 diabetes as the primary cause of death (SMR 1.18, 95% CI 0.77-1.73) or type 2 diabetes as the primary or secondary cause of death (SMR 1.08, 0.87-1.33) (Steenland et al., 1999, p. 782). In fact, analysis of this cohort categorized by septiles of TCDD exposure revealed a statistically significant *inverse* trend between cumulative exposure and type 2 diabetes risk (those with the highest exposure had the lowest type 2 diabetes risk; $p = 0.02$), though the trend was not statistically significant when the logarithm of cumulative exposure was considered ($p = 0.12$) (Steenland et al., 1999). An analysis of the 608 individuals who developed chloracne after the exposure (a condition

that may indicate high exposure) failed to reveal an increased risk of type 2 diabetes (Steenland et al., 1999, p. 781). These studies accounted for age and calendar year.

- A 1998 study that combined data from multiple exposed cohorts internationally (including the U.S. cohort analyzed in the study by Steenland et al. referenced above) found that exposure was associated with an RR of type 2 diabetes of 2.25 (0.53-9.50), although these results did not reach the level of statistical significance (Vena et al., 1998, p. 649). Age, gender, country, employment status, and calendar period were included as covariates in this analysis.

The results of these studies are mixed with a nonsignificant trend toward association between exposure and type 2 diabetes observed in some studies and a significant inverse association between TCDD and type 2 diabetes noted in another study. Additionally, the relevance of the committee's concern that mortality studies may underestimate the risk of type 2 diabetes is not entirely clear. The report (IOM, 2000, pp. 2, 36), as quoted extensively in the *Federal Register* (VA, 2001a, p. 2378), notes that (1) type 2 diabetes is not typically fatal, (2) complications of type 2 diabetes are more likely to be listed as a cause of death rather than type 2 diabetes itself, and (3) contributory factors (such as type 2 diabetes) are not routinely listed on death certificates. Although these features are likely all true and would be expected to underestimate type 2 diabetes-associated mortality generally, there is no reason to suspect that this underreporting of type 2 diabetes as a cause of death should differ based on exposure status. The strength of association between dioxin exposure and type 2 diabetes, therefore, would likely be unaffected by overall underreporting of type 2 diabetes on death certificates. However, the IOM report (IOM, 2000) and its summary by VA in the *Federal Register* (VA, 2001a) appear to suggest that the associations observed in these mortality studies be given additional weight because the type 2 diabetes mortality is underestimated.

The report stated "*[p]ositive associations* are reported in most of the morbidity studies identified by the committee" (IOM, 2000, pp. 3, 37). Studies of three cohorts are described to support this statement:

- A survey of male Australian veterans of Vietnam found a statistically significant excess of self-reported type 2 diabetes (2,391 reported cases; 1,780 expected cases with an expected range of 1,558-2,003 (CDVA, 1998, as referenced in IOM, 2000, pp. 32, 37).
- A further analysis of the NIOSH cohort (the impetus for convening the special Agent Orange type 2 diabetes committee) of 281 workers (exposed to TCDD in chemical plants more than 15 years prior) and 260 controls (from the same residential neighborhood as the exposed individuals and matched on age, race, and sex) found no significantly increased risk of type 2 diabetes among exposed individuals compared with reference individuals (OR 1.49, 95% CI 0.77-2.91) (Calvert et al., 1999, pp. 270-271, 273). Additionally, there was no trend observed between increasing TCDD concentration and type 2 diabetes risk. However, when individuals with type 2 diabetes were excluded from the analysis, individuals in the highest TCDD group had significantly higher glucose concentrations than the unexposed group (geometric mean 5.45 mmol/L [1.02] vs. 5.21 mmol/L [1.01]).

These analyses were all adjusted for age, gender, race, body mass index, and medications that affect glucose metabolism.

- The AFHS again provided important, though perhaps conflicting, evidence related to TCDD and type 2 diabetes. Updated analysis of veterans of Operation Ranch Hand estimated TCDD concentration at the time of exposure based on the elimination kinetics observed in a sample of Ranch Hand veterans with multiple TCDD measures over time. Among Ranch Hand veterans, both measured TCDD concentrations from the start of the study (1987) and estimated time-of-exposure TCDD concentrations were associated with the risk of diabetes. Those Ranch Hand veterans with the highest estimated time-of-exposure TCDD concentration also had higher rates of diabetes compared with the unexposed comparison cohort that had not been involved in Agent Orange spraying, although overall diabetes rates did not differ between Ranch Hand veterans and the unexposed comparison cohort (AFHS, 2000). Among the comparison cohort that had not been involved in Agent Orange spraying, a significant dose-dependent relationship between TCDD concentration and type 2 diabetes prevalence was also observed, with an RR of 1.71 (95% CI 1.00-2.91) for the highest quartile concentration compared with the lowest (Longnecker and Michalek, 2000, p. 46). Veterans in this comparison cohort had very low serum TCDD concentrations, within the range of background exposure typically seen in the United States (≤10 ng/kg lipid) (Longnecker and Michalek, 2000, p. 45). The committee noted that the observations from AFHS, including a graded risk of diabetes associated with very low levels of TCDD, continued to leave open the possibility that residual confounding related to body fat or correlated factors such as triglyceride concentration may interfere with accurate evaluation of the relationship between TCDD and type 2 diabetes (IOM, 2000).

Because of the trends that the committee found in the newly published mortality and morbidity literature, the IOM report on type 2 diabetes concluded that evidence for the association between herbicides and type 2 diabetes had reached the level of limited/suggestive—that is, evidence is suggestive of an association between herbicides and the outcome, but limited because chance, bias, and confounding could not be ruled out with confidence (IOM, 2000).

This "limited/suggestive" finding of the IOM report was submitted to the VA Secretary. In accordance with Title 38 USC 1116(b)(1) (Compensation for Service-Connected Disability or Death. 2006. 38 USC § 1116[b][1]), the VA Secretary was required to review this report and determine whether a presumption was warranted. The VA Secretary determined that evidence of a "positive association" between Agent Orange and type 2 diabetes existed, noting that an association is considered "positive" if the credible evidence for the association is equal to or outweighs the credible evidence against the association. Additional information regarding how data from the IOM report and the IOM summary finding of "limited/suggestive" figured into VA's recommendation is unavailable. The VA Secretary's determination of a positive association between herbicide and type 2 diabetes resulted in the May 8, 2001, 38 CFR Part 3 (VA, 2001b) finding of presumptive service connection for type 2 diabetes based on herbicide exposure during Vietnam.

In the *Federal Register* commentary, the increasing rates of type 2 diabetes associated with the obesity prevalence was noted, and the suggestion was made that more studies be undertaken that control for the background high rates of obesity before the type 2 diabetes presumption be considered. In response to these comments, the VA Secretary noted that IOM "adequately took

into consideration the recognized relationship between obesity and type 2 diabetes" (VA, 2001b, p. 23167). This statement appears to conflict with the IOM reports, as the 2000 IOM type 2 diabetes report stated that "the known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides" (IOM, 2000, pp. 3, 37). In the *Federal Register* commentary, the VA Secretary also notes that the time requirements imposed by section 1116(c)(2) limited the capacity of VA to wait for additional studies on this topic (VA, 2001b).

> Title 38 USC 1116(c)(1) (Compensation for Service-Connected Disability or Death. 2006. 38 USC § 1116[c][1]) requires that the Secretary, not later than 60 days after the date on which he receives a report from NAS, determine whether a presumption of service connection is warranted for each disease covered by the report, and if the Secretary determines that a presumption is warranted, issue proposed regulations within 60 days thereafter. . . . We believe that NAS adequately took into consideration the recognized relationship between obesity and type 2 diabetes, and the existence of additional studies concerning this risk factor does not warrant ignoring the time requirements of section 1116(c)(2).
>
> (VA, 2001b, p. 23167)

2002-2004

IOM reports over this time period (IOM, 2003, 2005) continued to find limited/suggestive evidence for the association between herbicides and type 2 diabetes. One important study of this period includes an attempt to pool the data on participants from the NIOSH study with those from AFHS (Steenland et al., 2001). To match the criteria in AFHS, the cut-off values defining type 2 diabetes in the NIOSH study were adjusted downward (from > 140 mg/dL to > 126 mg/dL) and 55 individuals included in the NIOSH study were excluded from the joint analysis. As a result of these changes, the OR for the NIOSH data was reduced from 1.49 to 1.22 and the dose-dependent association was no longer observed (OR = 0.84, 95% CI 0.4-1.8 for the highest TCDD concentration compared with the lowest). The significant association between serum concentration of TCDD and type 2 diabetes observed in the AFHS cohort was unchanged. Another study explored one possible mechanism for residual confounding in the AFHS studies and found that the significant association between TCDD concentration and type 2 diabetes risk noted in AFHS was not attributable to a third factor that both caused type 2 diabetes and slowed elimination of TCDD (Michalek et al., 2003). The 2002 and 2004 reports again rated the evidence for an association between herbicides and type 2 diabetes as "limited/suggestive."

Cost Implications of the Presumption for Type 2 Diabetes

There are limited data regarding the costs to VA associated with the type 2 diabetes presumption. The commentary on 38 CFR Part 3 (VA, 2001b, p. 23168) includes a brief discussion of the cost of this type 2 diabetes presumption. Cost projections were estimated by applying a type 2 diabetes prevalence rate of 9 percent to the 2.3 million estimated living Vietnam veterans (VA, 2000). National survey data suggest that 9 percent may be an underestimate, particularly as the population of Vietnam veterans ages and national trends continue to demonstrate increasing rates of incident type 2 diabetes across all age groups (Figure I-8).

The discussion in 38 CFR Part 3 also estimates the average monthly award for type 2 diabetes or its ancillary conditions at $462 (for original claims) (VA, 2001b, p. 23168). Although the

bases for this estimate are not described, the multiple possible complications associated with type 2 diabetes suggests that this average payment would likely increase over time for a given veteran with type 2 diabetes. Estimated administrative costs for type 2 diabetes from 2001 through 2005 were $62 million with estimated benefit costs of $3.3 billion during that same time period. VA estimated that there would be 20,399 new type 2 diabetes awards in the first year and 179,000 over the next 5 years. The estimates did not include retroactive payments (McLenachen, 2005). Today, the most frequent service-connected disability for which Vietnam veterans are receiving compensation is type 2 diabetes (VBA, 2006). "At the end of fiscal year 2006, nearly 248,000 veterans were service connected for diabetes. More than 215,000 of these awards were based upon herbicide exposure in Vietnam. As veterans with diabetes reach and move past the 10-year point since initial diagnosis, additional secondary conditions tend to manifest. VA has started to see increasingly complex medical cases resulting in neuropathies, vision problems, cardiovascular problems, and other issues directly related to diabetes" (VA, 2007, pp. 6B-13).

Lessons Learned

This case study offers several lessons that are relevant when considering strategies for improving the current system of presumptions. These lessons relate to the role of Congress in issuing the Agent Orange Act of 1991 (Public Law 102-4. 102nd Cong., 1st Sess.), VA in their use of scientific evidence to both convene the special IOM committee on type 2 diabetes (IOM, 2000) and eventually issue a presumption related to type 2 diabetes, and IOM in its evaluation and presentation of the body of evidence for the relationship between Agent Orange and type 2 diabetes.

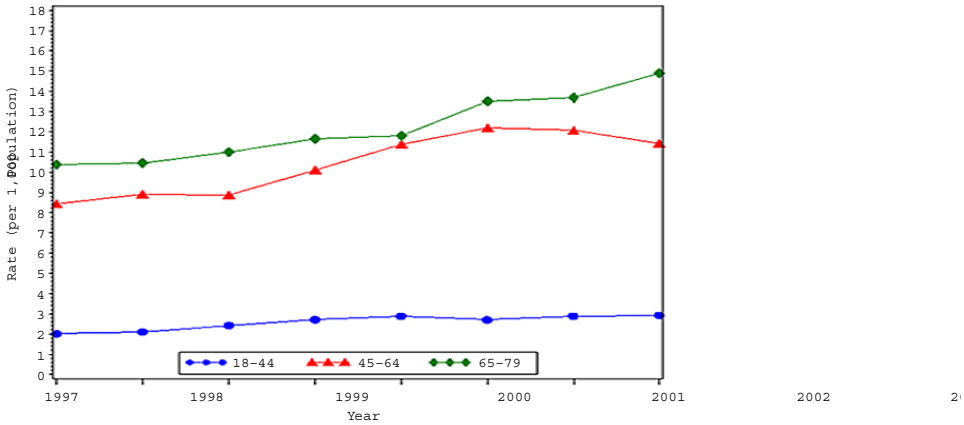

FIGURE I-8 Annual incidence of diagnosed type 2 diabetes per 1,000 population aged 18-79 years, by age, United States, 1997-2004.
SOURCE: See http://www.cdc.gov/diabetes/statistics/incidence/fig3.htm.

Congress

In describing the type of relationship between dioxin and health outcomes necessary for a presumption, Congress used the language both of "association" as well as "causation" in the Agent Orange Act of 1991 (Public Law 102-4. 102nd Cong., 1st Sess., Sec. 2[b][3]) (see Chapter 4). *Association* appears to be the standard set for VA:

> An association between the occurrence of a disease in humans and exposure to an herbicide agent shall be considered to be positive for the purposes of this section if the credible evidence for the association is equal to or outweighs the credible evidence against the association.
>
> (Agent Orange Act of 1991. Public Law 102-4. 102nd Cong., 1st Sess.)

However, the congressional language regarding "Scientific Determinations Concerning Diseases" includes evidence related to causation (Agent Orange Act of 1991. Public Law 102-4. 102nd Cong., 1st Sess., Sec. 3[d]):

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiologic methods used to detect the association;
2. the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and
3. whether there exists a plausible biological mechanism or other evidence of a *causal relationship* between herbicide exposure and disease. (emphasis added)

This inconsistency in the congressional language may have allowed considerable differences in interpretation of whether scientific evidence exists for the basis for a presumption. The difficulties that result from this lack of clarity in the Agent Orange Act of 1991 (Public Law 102-4. 102nd Cong., 1st Sess.) may have been particularly problematic for type 2 diabetes for which some evidence for association is present, but limited by chance, bias, or confounding.

In addition to the more general confusion between "association" and "causation" in the Agent Orange Act described above, the second standard set for IOM by this act—evaluating evidence for the increased risk of disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era—is particularly vague. Nearly all of the Agent Orange reports issued by IOM (1994, 1996, 1999, 2000, 2001, 2003, 2005) comment on the challenge of addressing this second charge, noting that the lack of exposure data on Vietnam veterans made the task difficult to fulfill. The intent of Congress in this second charge is unclear, particularly as the lack of exposure data for Vietnam veterans was well known at the time of the Agent Orange Act.

VA

In justifying its decision to convene a special IOM panel to evaluate the evidence related to Agent Orange and type 2 diabetes, VA may have overstated the findings of the report that prompted this action. Based on the *Federal Register*, VA summarized the report by NIOSH on occupational exposure to dioxin as

> . . . a report that detects an association, though not a strong association, between type 2 diabetes and dioxin exposure. The study does suggest a dose-response relationship because of excess cases of type 2 diabetes found in workers having the highest serum-lipid levels of dioxin.
>
> (VA, 2001a, p. 2378)

By contrast, the authors of the NIOSH report summarized their findings in this way:

> Overall, the prevalence of diabetes mellitus was not significantly different between the workers and referents. Also, there was not a significant positive trend between prevalence of diabetes and increasing serum TCDD concentration. However, diabetes was found in six of 10 (60%) workers with current serum TCDD concentrations > 1500 pg/g lipid.
>
> (Calvert et al., 1999, p. 270)

Because this study was the primary justification for the special IOM committee, an understanding of VA's interpretation of the study results is essential. No additional information regarding how new studies come to the attention of VA or the criteria for evaluating new studies and using these to inform the charge to IOM were made available to the Committee.

In the debate regarding this presumption, VA dismissed the link between national increases in type 2 diabetes rates related to obesity and the calls for more studies that control for the background high rates of obesity, noting that the IOM "adequately took into consideration the relationship between obesity and type 2 diabetes" (VA, 2001b, p. 23167). This statement appears to conflict with the IOM reports, as the IOM type 2 diabetes report stated that "the known predictors of diabetes risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides" (IOM, 2000, pp. 3, 37). VA noted that the requirement of timely action on the part of VA imposed by the Agent Orange Act prevented consideration of additional studies; although action is required within 60 days of the finding of a "positive association" on the part of the VA Secretary, it is notable that this VA finding was based on the lesser "limited/suggestive" categorization of evidence in the IOM report.

VA's cost projections for the type 2 diabetes presumption were likely underestimates. VA failed to consider the likely rise in type 2 diabetes prevalence in the aging veteran population and national trends suggesting increasing rates of type 2 diabetes in all age groups. Furthermore, as type 2 diabetes has many known complications that are also highly morbid, it is likely that the average percentage of service-connected disability for veterans with type 2 diabetes will continue to increase over time.

Overall, the Committee found that VA's process for using IOM reports to inform presumptive decisions has not been transparent. The diabetes presumption signaled an important trend on the part of VA to assign presumption on the basis of "limited/suggestive" classification of the levels of evidence. This decision could have been influenced by a variety of considerations beyond scientific ones, such as political, economic, and administrative factors. The interplay of these multiple factors and their relative weighting by VA are not easily characterized because of the lack of transparency in the VA process for using scientific evidence to arrive at the final decision of issuing a presumption.

This attempt by the Committee to carry out at a balanced critique of the various parties in the Agent Orange and type 2 diabetes presumption is limited by the availability of information from VA on this subject.

IOM

All of the IOM committees reviewing the type 2 diabetes evidence did not consider the results of the Vietnam Experience Study. This CDC study is one of the few large studies comparing the health of Vietnam veterans to other veterans of the same age who did not serve in Vietnam. The Vietnam-enlisted veterans surveyed in the Vietnam Experience Study did not have an increased risk of self-reported type 2 diabetes compared with other Vietnam-era veterans. In the subsample of participants that underwent blood test evaluation, Vietnam veterans also did not show higher rates of abnormal blood glucose concentrations compared with their Vietnam-era counterparts, although the geometric mean of their fasting serum glucose was slightly (and significantly) higher.

The IOM committee did not appear to have an explicit and formal methodological protocol for synthesizing evidence and for updating the classification of evidence based on new studies. The IOM type 2 diabetes committee "upgraded" their assessment of the existing literature from "inadequate/insufficient" (studies of insufficient quality, consistency, or statistical power to permit conclusion) to "limited/suggestive" (studies limited because chance, bias, and confounding could not be ruled out with confidence; for example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent). The committee's conclusion was not reached because of a single high-quality study that provided evidence of a conclusive association between Agent Orange and type 2 diabetes. Rather, the reclassification resulted from the committee's view of the cumulative weight of the evidence from several smaller studies, each limited in varying ways so that overall chance, bias, and confounding could not be ruled out with confidence and some studies differed in the direction of the association found (i.e., positive or negative).

The IOM report emphasized a particular feature of outcome ascertainment in type 2 diabetes research that may have led to overinterpretation of the conclusions of their report. The IOM committee concluded that "[p]ositive associations are reported in many mortality studies, *which may underestimate the incidence of diabetes*" (IOM, 2000, pp. 2, 36; emphasis added). The committee correctly pointed out that death certificates routinely underestimate death rates attributable to type 2 diabetes. Because type 2 diabetes is not typically fatal, complications of type 2 diabetes are more likely to be listed as a cause of death rather than type 2 diabetes itself, and contributory factors (such as type 2 diabetes) are not routinely listed on death certificates. However, these features would only be expected to underestimate type 2 diabetes mortality generally and should not lead to differential outcome ascertainment based on exposure status. Although the strength of association between dioxin exposure and type 2 diabetes would likely be unaffected by overall underreporting of type 2 diabetes on death certificates, the VA summary of the IOM findings appeared to suggest that the associations observed in these mortality studies be given additional weight because the type 2 diabetes mortality associated with dioxin exposure is underestimated.

Although determining the extent of type 2 diabetes risk that might be attributable to military service was not explicitly part of their charge, several of the committee reports address this issue and implicitly suggest that this fraction is likely to be small:

> It must be noted, however, that these studies indicate that the increased risk, if any, posed by herbicide or TCDD exposure appears to be small. The known predictors of diabetes

> risk—family history, physical inactivity, and obesity—continue to greatly outweigh any suggested increased risk from wartime exposure to herbicides.
>
> (IOM, 2000, pp. 3, 37)

A more explicit evaluation of attributable fraction might have been useful to policy makers considering this presumption by placing the scientific evidence on the link between TCDD and diabetes in context of overall diabetes risks, although determining the magnitude of this attributable fraction would remain difficult in the absence of accurate exposure data.

General

The Agent Orange and type 2 diabetes case study illustrates the challenge—both for scientists and policy makers—of evaluating evidence for an association between exposure and subsequent disease when accurate exposure data are lacking. This challenge is particularly striking for a disease like diabetes where multiple factors often contribute to the onset of disease, and the other known risk factors (e.g., genetics, obesity) are common in the general population. In this context, the contribution of exposures incurred during prior military service to overall disease risk is likely to be small as acknowledged in the IOM reports. In the absence of accurate exposure data, determining whether this small increased risk of disease is present and further quantifying the magnitude of this risk is difficult.

Faced with this challenge of identifying a possible small increased risk of disease without accurate exposure data, it appears that policy makers have adopted an approach in the diabetes presumption that minimizes the possibility of denying service connection to a veteran whose type 2 diabetes may have been caused by Agent Orange (maximizing sensitivity). The implicit assumption in the type 2 diabetes presumption is if any possibility exists, no matter how small, that a veteran may have been exposed to any amount of Agent Orange (presumption of exposure), and any possibility exists, no matter how small, that Agent Orange may have contributed even the smallest incremental increased risk of type 2 diabetes (presumption of association), service connection should be granted.

High-quality data for a cohort of veterans are essential for improving this process. Ideally such data would include (1) more accurate assessments of exposure during service; (2) evaluation of other risk factors that may have been present during service or have developed after service before the onset of disease; and (3) longitudinal assessments for evaluation of diseases that may have long latency periods. The type 2 diabetes case study highlights the potential value of such an ongoing cohort study and the missed opportunities when such studies are not continued. The VES was the largest study of a representative group of Vietnam veterans exploring whether Vietnam service was associated with a variety of disease outcomes. Although this study did not include an assessment of exposures, the variety of measurements included after military service did provide some ability to address multiple other risk factors that might confound the association observed between military service and type 2 diabetes. Extension of the VES as a cohort study might have provided an opportunity to determine whether the observed increase in mean glucose levels signaled future type 2 diabetes risk, whether this risk was independent of other risk factors present among Vietnam veterans, and what fraction of type 2 diabetes risk is attributable to military service.

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CASE STUDY 10: SPINA BIFIDA PROGRAM

This case study examines the 1996 and 2003 decisions to grant monetary compensation and health benefits to children of Vietnam and Korean War veterans with spina bifida, respectively. These decisions were based on scientific evidence for an association between Agent Orange and this developmental abnormality. This case study illustrates the issues surrounding compensation for reproductive health effects related to exposures incurred during military service. As spina bifida is a condition that affects the children of veterans, it is not a presumptive decision for veterans; however, the children of Vietnam and Korean War veterans are covered by a VA program.

Reproductive Effects of Military Service

Two categories of reproductive effects for exposures to toxic agents have been considered by the IOM committees charged with evaluating the evidence for adverse health effects associated with Agent Orange. The first category relates to the reproductive health of the exposed men and women and includes conditions that affect fertility and impaired ability to conceive and/or to bear live children. The second category relates to developmental effects in the offspring of exposed individuals, including birth defects, growth retardation, and childhood cancers. Exposure to certain toxic agents has long been accepted as leading to developmental abnormalities in the offspring of women. However, the role of paternal exposures in the etiology of developmental outcomes has been more challenging to understand. The Agent Orange reports review the biological plausibility for paternal exposure leading to developmental abnormalities and generally find evidence from both animal and human studies to support the potential for male-mediated developmental toxicity (IOM, 1994, 1996).

The Need for a Spina Bifida Program

The preceding case studies examine presumptions which serve to fill important evidentiary gaps (either gaps for exposure or gaps for association). The program related to spina bifida departs from this pattern in important ways. Strictly speaking, the program for spina bifida is not based on a presumption; however, the program operates in a similar manner as those based on presumptions in the type of evidence that a veteran (and their offspring) is required to produce to claim compensation. The reason for the program for spina bifida is that the existing compensation structure within the Department of Veterans Affairs (VA) does not provide a mechanism for compensating an individual other than the veteran; that is, children with developmental consequences of toxic exposures incurred by the veteran cannot be compensated by existing VA mechanisms for presumptions. This program creates a specific exception, allowing for compensation for one type of developmental effect (i.e., spina bifida) in specific populations (i.e., children of Vietnam and Korea veterans). Therefore, this program exists to fill a gap in legal authority and policy rather than a gap in evidence.

It is important to note that this narrowly tailored program for spina bifida does not address the more general ongoing policy concern that VA is not able to compensate the adverse health

consequences to offspring of veterans due to exposures they may have incurred during military service. Through the presumptive process, VA can only compensate a veteran.

A Brief History of the Spina Bifida Program

Reproductive health effects were evaluated by the first IOM Agent Orange committee (IOM, 1994). The Committee concluded that male exposure to toxins could plausibly be linked to adverse developmental consequences in their offspring, stating that

> The animal and human data indicate that the exposure of the male to various toxic agents may increase the risk of the full spectrum of adverse developmental endpoints from fetal loss to cancer.
>
> (IOM, 1994, p. 595)

However, the committee found the evidence in support of an association between Agent Orange and a range of birth defects to be "inadequate/insufficient" (IOM, 1994, p. 6). In VA's *Federal Register* response to the consideration of developmental toxicities associated with Agent Orange exposure, VA noted that there was no mechanism within the existing VA compensation structure to award benefits to any party other than the veteran; providing compensation to children of veterans with developmental effects attributable to Agent Orange exposure would require additional legislative action (VA, 1994, p. 346).

In the 1996 Agent Orange report (IOM, 1996), the committee included a specific evaluation of the evidence for the association between Agent Orange and spina bifida as "limited/suggestive." This classification of the strength of evidence was based on the review of three studies in Vietnam veterans that, although limited in their ability to completely control the effects of bias, were deemed by the committee to be of high quality and demonstrate a consistent pattern of results (IOM, 1996). The three studies are summarized as follows.

The CDC VES surveyed Vietnam and non-Vietnam veterans and found that Vietnam veterans were more likely to report central nervous system defects in their offspring than non-Vietnam veterans (OR 2.3; 95% CI 1.2-4.5) (CDC, 1989, p. 23). A substudy that attempted to validate these findings with birth records failed to confirm the results, but the substudy was limited by differential participation between Vietnam and non-Vietnam veterans and by the difficulty in validating negative responses (CDC, 1988).

The CDC Birth Defects Study was a case-control study utilizing a population-based birth defects registry in the Atlanta, Georgia area (Erickson et al., 1984a,b). Service in Vietnam was not associated with risk of spina bifida among the offspring of veterans; however, when an exposure opportunity index was used (based on interviews that evaluated which types of activities the veteran engaged in during military service), those veterans with the highest estimated level of exposure to Agent Orange had the highest risk of having children with spina bifida (OR 2.7; 95% CI 1.2-6.2) (Erickson et al., 1984a,b, as referenced in IOM, 1996, p. 9). This study was limited by the low response rates among both cases and controls and the lag between the birth of the offspring and exposure assessment.

The Ranch Hand study of Air Force personnel involved in herbicide spraying found excess cases of neural tube defects among offspring of the Ranch Hands, with two cases of spina bifida occurring among those with the highest level of exposure, and one case of spina bifida and one of anencephaly occurring among the low-exposure group. No cases of neural tube defects were observed in the nonexposed group ($P = .04$) (IOM, 1996, p. 9; Wolfe et al., 1995).

In 1996, VA noted the findings in the IOM report and again stated that providing compensation to anyone other than the veteran would require enabling legislation by Congress (VA, 1996). Public Law 104-204 (Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriation Act, 1997. 104th Cong., 2d Sess.) was passed in 1996 and authorized benefits for children born to Vietnam veterans with spina bifida. Additional legislation in 2000 established benefits for "children of women Vietnam veterans with certain birth defects" (Veterans Benefits and Healthcare Improvement Act of 2000. Public Law 106-419 § 401. 106th Cong., 2d Sess.). This law provided benefits to children of female veterans that covered a broad range of defects potentially attributable to maternal exposure during Vietnam service; however, the law excluded defects that were the result of familial predisposition or of injury suffered at birth. In 2003, these benefits were extended to children of veterans of the Korean War (Veterans Benefits Act of 2003. Public Law 108-103. 108th Cong., 2d Sess.).

Lessons Learned

With the exceptions of the legislative actions to establish the spina bifida program as well as the program for the children of female Vietnam veterans, there continues to be no overall mechanism for compensating the offspring of veterans for health consequences attributable to maternal and paternal exposures incurred during military service. Toxic exposures that occur during military service have the potential to cause adverse developmental effects, and each of the IOM Agent Orange reports (IOM, 1994, 1996, 1999, 2001, 2003, 2005) has described biologically plausible mechanisms for these effects in the offspring of both exposed female and male veterans. Given VA's interest in compensating veterans for adverse health effects incurred as a result of military service and the possibility that such effects may extend to the health of veterans' offspring, the absence of a clear and consistent mechanism and policy on compensating potentially affected offspring is notable. The need for a clear policy statement will continue to grow as VA considers the health effects of military service in the large population of reproductive-aged female and male veterans, especially with the growing number of women who serve in the military.

Although the public laws providing compensation for particular categories of offspring with birth defects may have been expedient for these affected individuals, the approach of addressing the more general policy gap described above with these VA programs runs counter to principles of consistency and equity that should inform the approach for presumptions. Any new adverse reproductive consequences of Agent Orange exposure identified in the IOM reports would again require legislative action for these specific effects in order for compensation to be granted to the offspring of veterans; the administrative route that has applied to all other Agent Orange presumptions is not available for reproductive consequences of exposure at present.

It is worthy of note that the evidence standard for establishing the program for spina bifida was "limited/suggestive evidence of an association" not the more rigorous "sufficient" classification. The challenges in using this lower evidence classification as the basis for VA's presumptions have been described in case studies related to Agent Orange and prostate cancer and type 2 diabetes.

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Appendix J

Causation and Statistical Causal Methods

In this appendix we provide more detail about the meaning of general causal claims, and how the qualitative aspects of causal claims can be precisely modeled. Substantial progress has been made on this front in the last two decades (see Pearl, 2000; Spirtes et al., 2000).

INDIVIDUAL- VERSUS POPULATION-LEVEL CAUSAL CLAIMS

First, consider the difference between individual- and population-level causal claims. In legal contexts, the goal is often to establish whether one particular event was the cause of another particular event. For example, if a child who lives near a chemical factory contracts a rare cancer, a court might seek to establish whether or not a chemical spill adjacent to the child's property was the "cause" of his or her particular cancer. By saying that the chemical spill *caused* the disease, we mean that the cancer would not have occurred had the spill not happened ("but for exposure" in legal terms). This is an individual-level causal claim. For cases in which a particular veteran seeks to service connect a particular disease or disability he or she has contracted after separation from the service is, if causation is the standard, an instance of establishing an individual-level causal claim.

In epidemiologic or scientific contexts, however, the goal is often to establish whether, in a *population* of individuals, generic sorts of exposures result in a change in the *frequency* or *average severity* of a disease. For example, an epidemiologist might ask whether the frequency of abnormal births among American women who were exposed to polychlorinated biphenyls (PCBs) during pregnancy is higher than the frequency among those who were not. If so, then epidemiologists might assert that exposure to PCBs during pregnancy is capable of *causing* birth defects. The causal claim about the population does not entail that every fetus whose mother is exposed to PCBs during pregnancy will develop birth defects, and it does not entail that every birth defect would not have happened but for PCB exposure. On the population level, causal claims typically involve how the *probability distribution* of the disease changes in response to exposure. When either Congress or the Department of Veterans Affairs seeks to presumptively service-connect a particular health condition or disability to a particular population of veterans, establishing a population-level causal claim is required.

CAUSATION AND COUNTERFACTUALS

Beginning in the 1970s, Rubin (1974) and many after him developed a formal theory of causal inference based on counterfactuals, which play an essential role in both individual- and population-level causal claims. On the individual level, for example, we might observe that a particular person was exposed to a chemical and later contracted a disease. The question we would like to answer is *counterfactual*: What *would* have happened had the same individual *not* been exposed to the chemical? Likewise, for other individuals who were not exposed, we might like to know what would have happened had they been exposed.

On the population level the questions are similar. We observe that a population of individuals, such as Gulf War veterans, were exposed to a variety of conditions and substances in their tour of duty in the Mideast and then exhibited a certain frequency of illness years later. The population question we would like to answer is counterfactual: What *would* the frequency of illnesses have been had the same population *not* been exposed to the conditions and substances they were exposed to in the Gulf War?

In Rubin's framework, analyzing randomized clinical trials that involve assigning one group to treatment and another to control is a counterfactual missing data problem. For all the people in the treatment group, we are missing data on their response *had they been assigned* to the control group, and symmetrically for the control group.

INTERVENTION

Underneath these counterfactuals, however, is a subtle but crucial assumption about *how* the world should be imagined to have been different. Recall that "exposure to excessive radiation *caused* Mary to get leukemia" means that "had Mary not been exposed to excessive radiation she would not have gotten leukemia." This makes sense if we envision a world identical to the one Mary did experience, but change it minimally by intervening to prevent her from being exposed to excessive radiation.

Consider a slightly different example, however. Suppose John smoked 30 roll-your-own cigarettes a day from age 25 to 50, had intensely tar-stained fingers during this period, and got lung cancer at the age of 51.

Sticking with common sense, we will assume that smoking caused John to have both tar-stained fingers and lung cancer, but that having tar-stained fingers has no causal influence on getting lung cancer (Figure J-1). By the counterfactual theory, the following ought then to be true: "Had John *not* had tar-stained fingers, he would have gotten lung cancer anyway." To make sense of this counterfactual, we might envision a world in which John still smoked, but either smoked packaged cigarettes that produced no finger stains or washed his hands with tar-

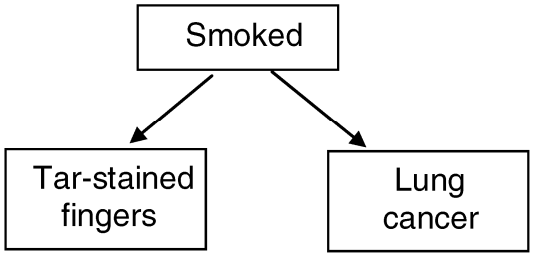

FIGURE J-1 Causal structure for smoking, tar-stained fingers, and lung cancer.

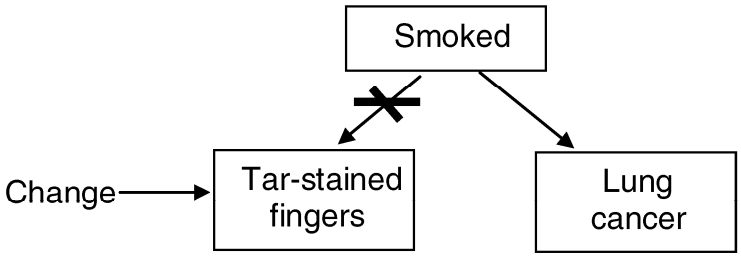

FIGURE J-2 Hypothetical intervention on finger tar stains.

solvent soap every night. Some might object and say: "What I think of when I hear 'Had John *not* had tar-stained fingers' is a situation in which he *didn't* smoke—and in that case he *wouldn't* have gotten lung cancer!" Again, to make sense of the counterfactual: "Had John *not* had tar-stained fingers, he would have gotten lung cancer anyway," we must imagine a world in which we directly change *only* whether John had tar-stained fingers and leave the rest of the story intact (Figure J-2).

Further, in such a world our hypothetical intervention destroys any influence smoking might have had on whether John had tar-stained fingers in the real world. If it didn't, we could not make sense of the hypothetical.

These points apply directly to the same population claims we used above to illustrate presumptive service connection. When we ask the question, "What *would* the frequency of illnesses have been among Gulf War veterans had they *not* been exposed to the conditions and substances they were exposed to in the Gulf War?" we don't mean to imagine a world in which these veterans never signed up for the armed forces because they were medically unfit for duty. Instead, we mean to imagine a world in which *everything* about them was the *same*, but they were prevented from being exposed to the conditions and substances they were exposed to in the Gulf War. This is the counterfactual that bears on presumptive service connection.

So a theory of causation must model hypothetical interventions that are tightly targeted, and, most importantly, describe how the world *would react* to any sort of ideal, hypothetical intervention or treatment we can imagine. Further, the theory ought to make the connection with statistical evidence clear. Over the last two decades, epidemiologists,[1] computer scientists,[2] philosophers,[3] and statisticians[4] have developed a theory of statistical causal inference that incorporates the virtues of Rubin's counterfactual account but also models interventions and provides a clear connection to statistical evidence as it bears on causal claims. Below we present the briefest possible introduction to this theory. More detail is available in Robins (1986, 1988), Pearl (2000), Spirtes et al. (2000), Dawid (2004), Cox and Wermuth (2004), and many other sources.

[1] Sander Greenland, Jamie Robins, and others.

[2] Judea Pearl, David Heckerman, Greg Cooper, and many others.

[3] Peter Spirtes, Clark Glymour, Richard Scheines, Jim Woodward, Dan Hausmann, and many others.

[4] David Cox, Nanny Wermuth, Phil Dawid, Paul Rosenbaum, Thomas Richardson, Larry Wasserman, and many others.

CAUSAL STATISTICAL MODELS

The kind of causal theories and statistical evidence relevant to presumptive service-connection decisions involve a population and a set of variables, or factors. A population denotes a (potentially infinite) group of individuals, such as Vietnam War veterans, or American men over the age of 60, or all possible offspring of a heterozygous and homozygous pea plant. A set of variables describe properties of such individuals that might cause each other, such as exposed to Agent Orange (yes, no), smoked (no, lightly, heavily), lung cancer (yes, no), yearly income (in dollars), and so on.

The *qualitative* part of a causal theory, that is, which variables are causes of which other variables and which are not, can be represented with a *causal graph*, that is, a diagram involving arrows that connect the variables. See Neapolitan (2004), Pearl (2000), Spirtes et al. (2000), and Glymour and Cooper (1999). For example, consider the causal graph in Figure J-3.

To be concrete, let us assume that this model is meant to apply to a population of 4-year-old American children. Further, suppose the variables are the following:

- Exposure (yes, no)—Yes, if exposed to another child who was within 2 days of symptomatic chicken pox.
- Infection (yes, no)—Yes, if chicken pox virus was active in bloodstream.
- Rash (yes, no)—Yes, if rash appeared.

Then each arrow in the causal diagram depicts a claim about direct causation relative to this set of variables and this population. In this case, the diagram claims that

- exposure is a direct cause of infection, and
- infection is a direct cause of rash, and
- that no other direct causal claims hold among these variables in this population, including the claim that exposure is a direct cause of rash.

DEFINITION OF DIRECT CAUSATION

The presence of an arrow from one variable, such as exposure, to another, such as infection, means that, holding all the other variables in the system fixed, changing the assignment of exposure will result in *some* change in the probability of infection.[5] The absence of an arrow, for example the absence of an arrow from exposure to rash, means that, holding the other variables (infection) fixed, changing the assignment of exposure will *not* result in any change in the probability of rash.

FIGURE J-3 Chicken pox.

[5] More fully, X → Y just in case there exists any set of assignments for the variables besides X and Y such that there exists some change of assignments for X such that the probability distribution for Y changes.

Notice the role of possibly counterfactual interventions. When we say "holding fixed," or "changing the assignment," we are referring to hypothetical interventions in which we *set* or *assign* the value of a variable.

The *quantitative* part of a causal theory involves specifying a probability model that accords with the qualitative model. The full model with both graph and probability distribution is called a Causal Bayes Network. See Pearl (2000), Spirtes et al. (2000), and Neopolitan (2004). For each variable in the system, we express its probability distribution as a function of its direct causes. That is, we specify the way in which each effect responds to any set of values its direct causes might take on, and, since it is a population we are talking about, we need to express this response probabilistically. For example, in the chicken pox case, we might give the whole causal model—both its qualitative and quantitative parts—with a causal diagram and a table expressing the response structure for each variable (Figure J-4).

Because exposure has no immediate causes in our model, the hypothetical quantitative table just gives how probable it is for a 4-year-old American child to be exposed to another child who is infected and within 2 days of exhibiting chicken pox symptoms. Note that the numbers in this table are purely for illustration and do not reflect actual data. The probability of infection is given as a function of its immediate causes—in this case exposure. It claims that if a child is exposed to another child with chicken pox, then they have an 80 percent chance of becoming infected themselves, but if they are not exposed to another child with chicken pox, they have just a 3 percent chance of becoming infected.

We compute the joint probability distribution over the variables V as the product of the conditional probability of each variable on its direct causes:

$$P(\mathrm{V}) = \prod_{V \in \mathbf{V}} P(V \mid \text{direct causes of } V)$$

Having the joint distribution allows us to compute the probability of any variable conditional on an observation for any other variable or set of variables. For example, in the chicken pox model, we can compute the probability of exposure conditional on observing that a child is infected or conditional on having a rash, or the probability of rash conditional on observing exposure, and so on.

Most importantly, these models allow us to explicitly represent hypothetical interventions. The rule is simple: add an "intervention" variable to the system and draw an arrow to the variables targeted by the intervention. If the intervention determines the probability of its targets—for example, a randomizer that assigns subjects to treatment or control—erase the other arrows that previously went into these targets, and change the quantitative model accordingly.

For example, suppose we wanted to model an intervention in which we assigned everyone in our population of 4-year-old children to be infected with the chicken pox virus (by injection). Then the resulting "intervened upon" system would be as shown in Figure J-5.

Computing the joint distribution after an intervention goes the same way as for preintervention systems, but the results will sometimes differ, and *it is this difference that captures the causal part of the model*. For example, in the chicken pox model prior to our intervention (Figure J-4), the probability of exposure given infection is higher than 0.1, as in P(Exposure = yes | Infection = yes) > 0.1, but in the intervened-upon version of the system (Figure J-5), P(Exposure = yes | Infection set = yes) = 0.1 = P(Exposure). This is because the intervention on infection eliminated the causal connection between exposure and infection, and thus changed their informational relationship as well.

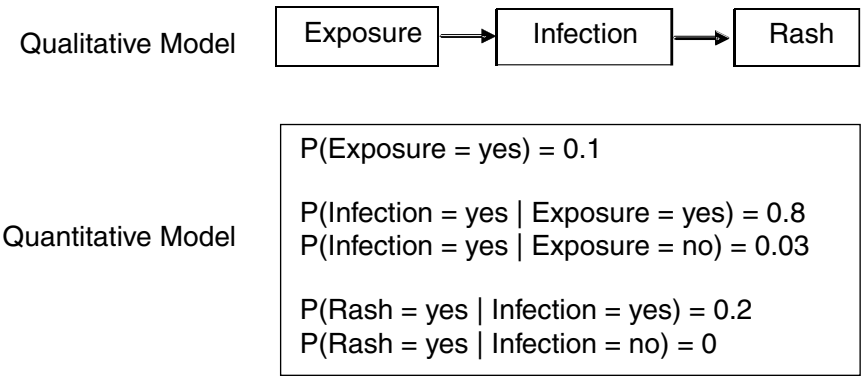

FIGURE J-4 Hypothetical statistical causal model for chicken pox.

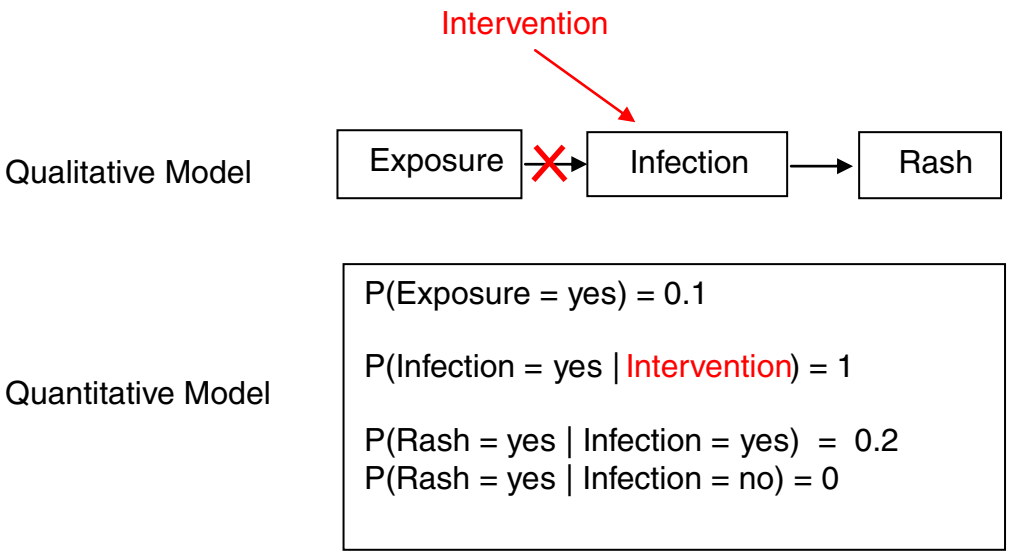

FIGURE J-5 Hypothetical intervention in the chicken pox system.

As this point cannot be emphasized enough, and as it underlies the difference between association and causation, consider another case in which two models agree about things prior to an intervention but differ about things after an intervention. Consider two distinct causal models of the relationship between a child's exposure to environmental lead and their cognitive function measured by IQ (Figure J-6).

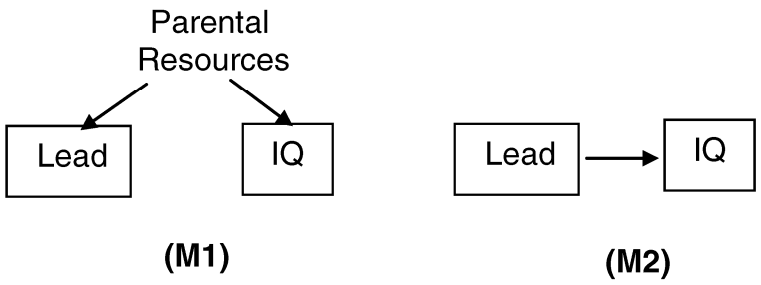

FIGURE J-6 Two hypothetical models of lead exposure and cognitive function.

In model 1 (M1), lead and IQ are effects of a common cause, parental resources, but have no influence on each other. We assume that parents with more resources will choose environments with less lead, and provide the stimulation necessary to increase their child's measured IQ. In model 2 (M2), lead is a direct negative cause of IQ. Supposing that the level of parental resources remains unmeasured, it is easy to attach quantitative values for both models such that the probability distributions over the measured variables lead and IQ are *identical*. In that case, $P(IQ \mid Lead)_{M1} = P(IQ \mid Lead)_{M2}$. That is, predictions about IQ from *observations* of lead exposure are implied to be *identical* in both models. Put another way, the association between lead and IQ implied by M1 can just as well be implied by M2 and vice versa.

It is *not* possible, however, for the models to agree about the relationship *after* a hypothetical intervention that sets the value of lead exposure: $P(IQ \mid Lead_{\text{set by intervention}})_{M1} \neq P(IQ \mid Lead_{\text{set by intervention}})_{M2}$. That is because a hypothetical intervention, or treatment, on lead, changes M1 in a way that makes lead and IQ independent, but leaves the causal dependence of lead and IQ unperturbed in M2 (Figure J-7).

So M1 and M2 can agree completely on the population we *observe*, but differ on the sorts of counterfactuals that underlie presumptive service connections. M2 supports counterfactuals of the sort: "Had Jonathan not been exposed to lead, he wouldn't have scored below average on the IQ test," but M1 does not. If M1 is true (and clearly that is a big *if*), then hypothetically changing the amount of lead Jonathan was exposed to leaves his IQ the same, for in M1 it is not lead that

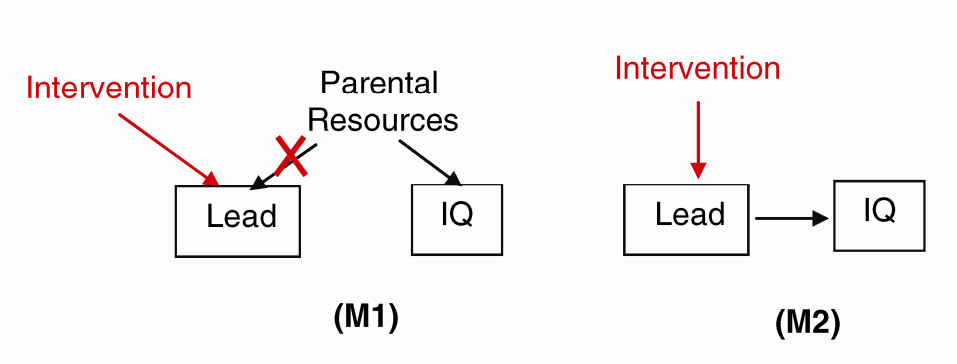

FIGURE J-7 Hypothetical postintervention models of lead and IQ.

causes IQ but parental resources. In all likelihood the "correct" model is a combination of M1 and M2: one in which any observed negative association between lead exposure and IQ is due to both a common cause and a direct causal influence.

Equipped with the correct causal model connecting military service (or a particular exposure in service) for an identified group and a health outcome, both qualitatively and quantitatively, we can compute the probability of this outcome in the counterfactual world in which the group *was not* exposed to the conditions and substances of military service and compare this to the probability of the outcome that we actually observed. This computation, of course, depends crucially on the model we consider "correct."

For example, consider the three hypothetical causal models shown in Figure J-8. Suppose that we didn't know which of these models was an accurate representation of the world. Suppose further that we collected a sample of 255 subjects, and for each recorded whether they had been exposed to some substance (Exposure), whether they had the disease in question (Health Outcome), and whether or not they showed evidence of some covariate, for example low income. We show purely hypothetical data table in Table J-1. The analysis of this dataset under the three models in Figure J-8 would yield three quite different estimates of the relative risk (RR) and any of the other epidemiologic parameters derived from it, for example, the population attributable risk (PAR). Under model M1, which asserts that Exposure causes Health Outcome and that the relationship is not confounded, we would ignore the covariate and estimate the RR from the crude odds ratio between exposure and disease, [(155/45) / (100/100)] = 3.44 (95% confidence interval [CI] 2.23-5.31). Under model M2, on the other hand, which asserts that Exposure is not a cause of Health Outcome at all, and that any observed association is due entirely to confounding, we would ignore the apparent association in the data and conclude based solely on the model that there was no causal association between exposure and disease (i.e., OR = 1.0). Finally, under model M3, which asserts that Exposure causes Health Outcome but that the two are also confounded, we would have to adjust for the confounder and obtain the adjusted OR = 3.03 (95% CI 1.93-4.73).

For these data, neither model M1 nor M2 fits the observed data very well, so we would need very compelling prior knowledge to accept them over M3. If, however, we had no recorded data on the covariate, then we could not distinguish between the three models.

TABLE J-1 Hypothetical Exposure and Health Outcome Data

Exposure	Covariate	Health Outcome = No Disease	Health Outcome = Disease
No	No	60	19
	Yes	40	26
	Total	100	45
Yes	No	40	39
	Yes	60	116
	Total	100	155

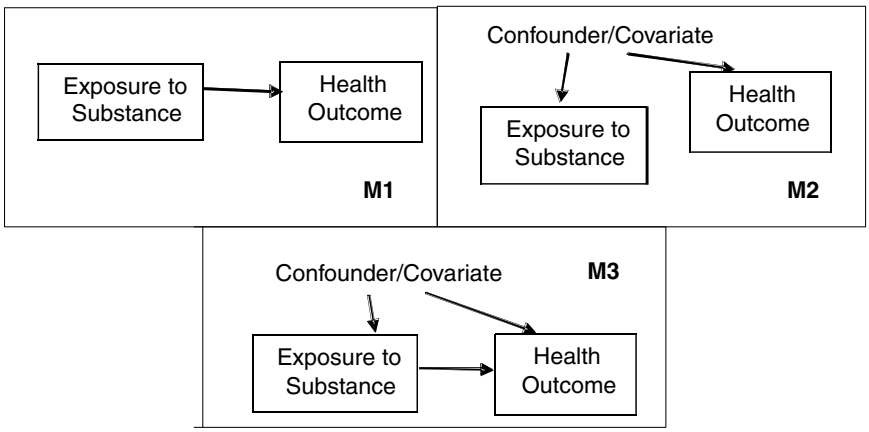

FIGURE J-8 Three hypothetical causal models connecting exposure/disease.

So given the correct causal model, and the knowledge that it *is* the right causal model, we can compute the quantities we need to entertain questions about service connection and presumptive service connection.

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Appendix K

Sources of Health and Exposure Data for Veterans

APPENDIX K-1

BIBLIOGRAPHY OF DEPARTMENT OF VETERANS AFFAIRS EPIDEMIOLOGIC STUDIES OF VETERANS

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APPENDIX K-2
SELECTED NATIONAL ACADEMIES REPORTS ON U.S. VETERANS' HEALTH[2] (IN CHRONOLOGICAL ORDER)

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IOM. 1999. *Potential radiation exposure in military operations: Protecting the soldier before, during, and after*. Washington, DC: National Academy Press.

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APPENDIX K-3
VIETNAM EXPERIENCE STUDY AND OTHER CDC STUDIES ON VIETNAM VETERANS AND GULF WAR VETERANS

Vietnam Experience Study

Background

Conducted by the Centers for Disease Control and Prevention (CDC), the Vietnam Experience Study compared the morbidity and mortality among Vietnam veterans and non-Vietnam veterans.

[2] Not intended to be a comprehensive list. See www.nap.edu for additional reports.

Vietnam veterans were concerned that their service in Vietnam adversely affected their health, and the health of their families. However, data did not exist comparing those who served in Vietnam and those who served during the Vietnam War in other countries. In 1979 President Jimmy Carter signed the Veterans Health Programs Extension and Improvement Act of 1979 that called for the Veterans Administration (VA) to "conduct an epidemiological study of persons who, while serving in the Armed Forces of the United States during the period of the Vietnam conflict, were exposed to any of the class of chemicals known as 'the dioxins' produced during the manufacture of the various phenoxy herbicides (including the herbicide known as 'Agent Orange') to determine if there may be long-term adverse health effects in such persons from such experiences" (Veterans Health Programs Extension and Improvement Act of 1979. Public Law 96-151. 96th Cong., 1st Sess.; as referenced in CDC VES, 1989b, pp. 4-5).

In 1981 an amendment was passed to the law above to include "an evaluation of any long-term adverse health effects in humans of such [military] service as such health effects may result from other factors involved in such [military] service, including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions" (Veterans' Health Care, Training, and Small Business Loan Act of 1981. Public Law 97-72. 97th Cong., 1st Sess.; as referenced in CDC VES, 1989b, p. 5).

The responsibility of designing, conducting, and analyzing such an investigation was originally bestowed upon VA and then transferred, by an Interagency Agreement, to the CDC. The CDC was then authorized to conduct three studies: the Agent Orange Exposure Study, the Selected Cancers Study, and the Vietnam Experience Study (CDC VES, 1989a, p. 3). This section will focus on the Vietnam Experience Study (VES).

VES Main Objectives

> Is there an excess risk of postservice mortality for the Vietnam group? (If so, due to what causes?)
> 1. Is there an excess risk of specific illnesses (including psychological) or groups of postservice illnesses for the Vietnam group?
> 2. Is there an excess of adverse reproductive outcomes or childhood illnesses among children of the Vietnam group?
>
> (CDC VES, 1989a, p. 4)

VES Cohort

The VES cohort included a random sample of male Vietnam and non-Vietnam veterans (limited to those who served in the United States, Germany, or Korea). The random selection process was based on "a computerized list of accession numbers taken from military personnel files of Army veterans discharged during the relevant time period" (CDC VES, 1987a). Sample sizes are given in Figure K-1. The inclusion criteria for this study were

- Army veterans (Marine, Air Force, and Navy personnel were not included);
- military occupational specialty (MOS) other than "duty soldier" and "trainee";
- single term of enlistment;
- minimum of 16 weeks of active duty time;
- pay grade E-1 (Private) to E-5 (Sergeant-Specialist 5);

- entered military service for the first time during 1965-1971; and
- discharged alive (CDC VES, 1989a, pp. 5, 7).

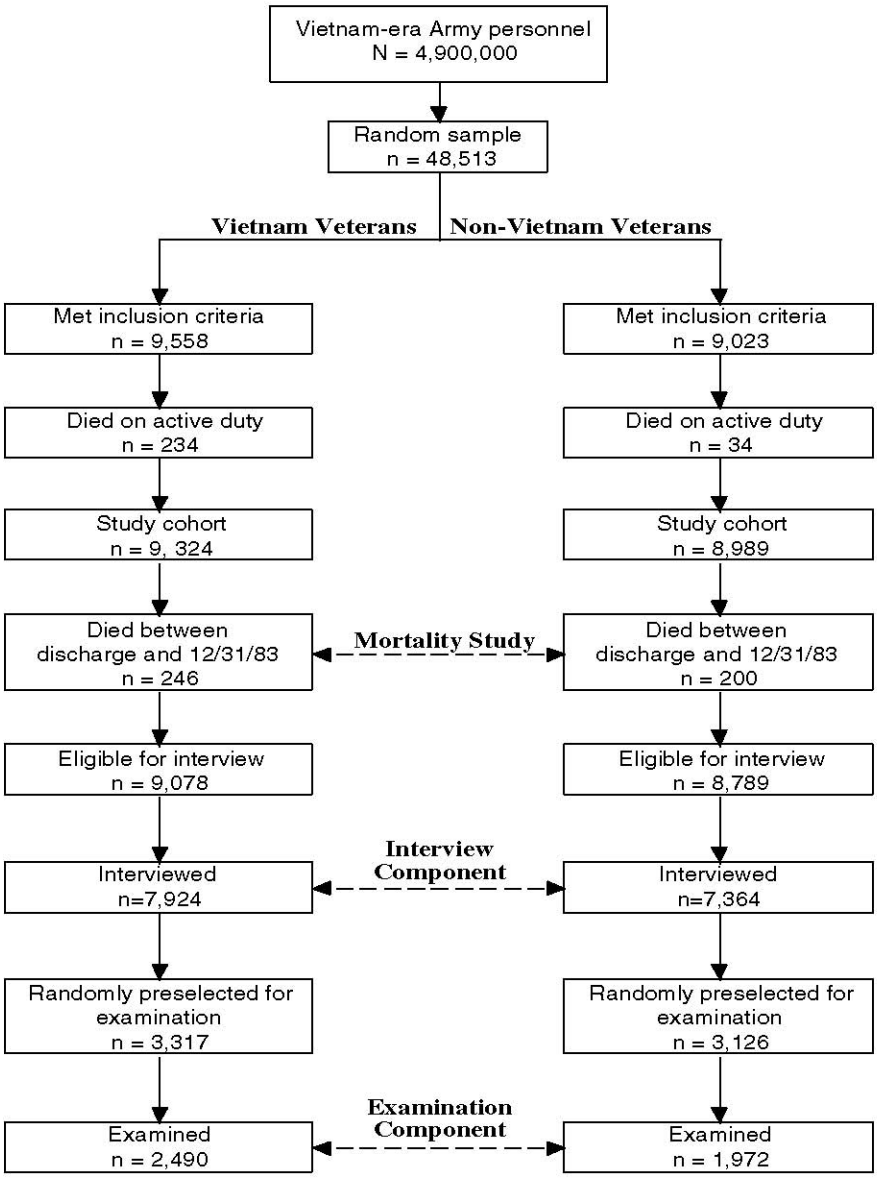

FIGURE K-1 Sample sizes for each component of the VES.
SOURCE: Adapted from CDC VES, 1989a.

Demographics[3]

- Vietnam veterans were more likely than non-Vietnam veterans to have
  - lower General Technical (GT) test scores;
  - entered the Army before 1969;
  - been volunteers;
  - had a tactical operation primary MOS;
  - been in a combat unit;
  - honorable discharges;
  - been discharged at pay grades >E3;
  - lower educational attainment at time of interview;
  - more unemployment at time of interview;
  - lower income in year immediately preceding the interview;
  - used drugs (marijuana only, or hard drugs) at least once/week in past year;
  - received therapy for drug, alcohol, or emotional problems in past year; and
  - drank, on average, ≥90 drinks per month (CDC VES, 1989a, Tables 2-4).
- Vietnam veterans were significantly less likely than non-Vietnam veterans to have an executive/managerial professional specialty (OR = 0.9, 95% CI 0.8-0.9) (CDC VES, 1989b, p. 44).
- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to
  - region of birth, region of residence at time of interview;
  - year of birth, age at interview;
  - race;
  - mean age at enlistment;
  - percent with some AWOL or confinement time;
  - current martial status; and
  - cigarette smoking.

Components of the VES

The VES included a mortality study, a telephone interview, an examination (medical, psychological, and laboratory), and a reproductive outcomes and child health component.

Primary potential confounders The primary potential confounders adjusted for in all analyses listed below are as follows:

- Race = white (referent), black, other
- Age at entry into the Army = <20 years (referent), ≥20 years
- Year of entry into Army = 1965-1966 (referent), 1967-1969, 1970-1971
- Primary MOS = tactical, other (referent)

[3] These results are from the telephone interview only. However, the demographic results did not significantly differ between the telephone interview and the medical history questionnaire (as part of the examination).

- Enlistment status = drafted (referent), volunteered
- GT test score = 40-89, 90-109 (referent), 110-129, 130-160 (CDC VES, 1989b, p. 23, Table 4)

For this summary on the VES analytical results, if the significance levels are not reported here, they were not reported in the documentation obtained from the CDC. Also, the VES full documentation presents both models: (1) the model only adjusting for the primary potential confounds listed above and (2) a multivariable model that adjusts for further potential confounders as appropriate. However, since the two models offer similar results, this summary only lists the results from the first model.

The Mortality Study: Postservice mortality among Vietnam veterans Mortality among the Vietnam veterans (n = 9,324) was compared to that of the non-Vietnam veterans (n = 8,989), based on information from personal physicians as well as hospital records, autopsy reports, and coroner and law enforcement files. The data showed that, over the entire follow-up period, total mortality in the Vietnam veterans was 17 percent higher than for the non-Vietnam veterans (http://www.cdc.gov/nceh/veterans/default1a.htm; CDC VES, 1987a,b). "The excess in postservice mortality due to external causes among Vietnam veterans is similar to that found among men returning from combat areas after World War II and the Korean War" (CDC VES, 1987b). Selected findings on mortality are given in Table K-1. Other findings on mortality included the following:

- When all drug-related deaths were analyzed together, "the rate ratio between Vietnam and non-Vietnam veterans appeared to increase with the number of years since discharge." This difference was found "almost exclusively among draftees; those assigned to tactical military occupational specialties; and those serving in Vietnam during 1968 or 1969, the years of heaviest combat activity."
- Alcohol did not seem to account for the difference in motor vehicle crashes between the Vietnam veterans and the non-Vietnam veterans.
- Vietnam veterans were significantly less likely than non-Vietnam veterans to die from circulatory system diseases (OR = 0.5, 95% CI 0.25-0.99).

TABLE K-1 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Die from the Following Conditions

Condition	Risk Ratio (RR)	95% Confidence Interval (CI)
Mortality[a] within 5 years of discharge	1.45	1.08-1.96
Suicides within 5 years of discharge	2.56	1.11-5.87
Motor vehicle crashes	1.48	1.04-2.09

[a]Mortality mostly due to motor vehicle accidents, suicide, homicide, and accidental poisonings.
SOURCE: CDC VES, 1987a,b.

- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to mortality from unintentional poisonings, most of which were due to the use of illicit drugs.
- After the initial 5 years after discharge, there were no significant differences in mortality among the Vietnam veterans and the non-Vietnam veterans, except that drug-related deaths continued to be elevated in the Vietnam veterans.

The telephone interview Under contract with the CDC, Research Triangle Institute (RTI) located, contacted, and interviewed the veterans with the help of Equifax, Inc. which provided multilevel locating and contacting services. To locate veterans these companies used the permanent addresses provided by the veterans at the time of discharge, the names and addresses of family members provided by the veterans upon entry into the service, the address on the veterans' most recent tax return, and the address provided by the veterans when filing for benefits (CDC VES, 1989a, pp. 7-8; CDC VES, 1989b, p. 9).

Eventually, 9,078 Vietnam veterans and 8,789 non-Vietnam veterans were found to be eligible for the interview (i.e., those not known to have died before December 31, 1983). Of these, veterans were not interviewed if they could not be located, refused to be interviewed, were unable to contact, were incarcerated, died after December 31, 1983, or were mentally or physically incapable of being interviewed. Thus, 7,924 Vietnam veterans and 7,364 non-Vietnam veterans were ultimately interviewed (CDC VES, 1989a, p. 7, Figure 1; CDC VES, 1989b, p. 31, Table 6).

It is important to note that there were differences between those interviewed and those not interviewed. On average, compared to those interviewed (Vietnam and non-Vietnam veterans combined, unless otherwise stated), those not interviewed (Vietnam and non-Vietnam veterans combined, unless otherwise stated) were more often nonwhite (21.5 percent vs. 11.6 percent), younger at enlistment (56.2 percent <20 years vs. 48.8 percent <20 years), volunteers (41.0 percent vs. 34.2 percent), having lower scores on the GT test (mean score about 100.0 vs. 105.2), and more likely received non-honorable discharges (8.0 percent for Vietnam veterans and 21.2 percent for non-Vietnam veterans vs. 1.8 percent for Vietnam veterans and 6.2 percent for non-Vietnam veterans) and discharged at lower pay grades (23.7 percent for Vietnam veterans and 40.1 percent for non-Vietnam veterans vs. 9.3 percent for Vietnam veterans and 15.9 percent for non-Vietnam veterans) (CDC VES, 1989b, pp. 31-33, Table 8). However, significance levels for these differences were not reported in the documents.

> Although the unlocatable subset of the non-respondent group appears to be very different from respondents with respect to demographic and military characteristics, about the same degree of divergence is seen for both Vietnam and non-Vietnam veterans. Thus, absence of interview data from the lost-to-follow-up group should not adversely affect the findings presented here.
>
> (CDC VES, 1989b, p. 33)

Selected findings from the telephone interviews are shown in Tables K-2, K-3, K-4, and K-5.

TABLE K-2 Current Health Status: Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Have the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
Perceived fair/poor health	1.8	1.7-2.0
Higher mean BMI	BMI = geometric mean 25.7 vs. 25.5	p = 0.004
Limitations in activities	1.3	1.2-1.4
≥3 prescribed medications	1.3	1.1-1.6
General symptoms	2.5	1.7-3.6

SOURCE: CDC VES, 1989b, Tables 18, 19, 20, 22, 102.

TABLE K-3 Health Status Between Discharge and Time of Interview: Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Have Experienced/Suffered from the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
≥1 hospitalization	1.1	p <0.05
Hypertension	1.3	1.2-1.4
Benign growths	1.2	1.1-1.3
Chloracne	3.9	2.5-6.2
Excessive hair growth	1.9	1.6-2.3
Other skin conditions	1.8	1.7-2.0
Gastrointestinal ulcers	1.2	1.1-1.3
≥4 Neurologic symptoms	2.0	1.8-2.3
Hepatitis B	1.5	1.3-1.8
Other liver conditions	1.4	1.1-1.8
Urinary tract problems	1.2	1.1-1.3
Fertility difficulties	1.3	1.2-1.5

SOURCE: CDC VES, 1989a, p. 18, Table 5; 1989b, pp. 100, 371-373, Table 73, Table I-I.

TABLE K-4 Reported Medical Care: Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Report Medical Care While in the Army for the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
Intestinal infections	2.7	2.1-3.5
Malaria	104.0	33.3-324.4
Sexually transmitted disease	2.0	1.7-2.4
Mycoses	6.5	4.8-9.0
Ear disorders	1.7	1.4-2.0
Hepatitis B	1.8	1.3-2.5
Skin infections	2.1	1.7-2.7
Other skin disease	1.3	1.1-1.6
Rash	3.3	2.5-4.3
Fever	2.3	1.7-3.0

Open wounds	3.5	3.1-4.0
Superficial injuries	1.6	1.1-2.1
Burns	1.8	1.2-2.5

SOURCE: CDC VES, 1989b, pp. 37-39, Table 12.

TABLE K-5 Vietnam Veterans Were Significantly Less Likely Than Non-Vietnam Veterans to Report Medical Care While in the Army for the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
Strep infections	0.6	0.5-0.8
Acute respiratory infection	0.8	0.7-0.9
Other upper respiratory disease	0.6	0.4-0.8
Influenza	0.8	0.7-0.9
Osteopathy	0.7	0.5-0.9

SOURCE: CDC VES, 1989b, pp. 37-39, Table 12.

There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to postdischarge cancer, diabetes, and cirrhosis (CDC VES, 1989a, p. 18, Table 5).

There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to viral exanthemas; neoplasms; endocrine, nutritional, and metabolic disease; mental disorders; disease of the nervous system; eye disorders; circulatory disease; pneumonia; digestive diseases (except for hepatitis B); genitourinary disease; dermatitis; musculoskeletal disease (except for osteopathy); head and neck symptoms; cardiorespiratory symptoms; fractures, dislocations, sprains and strains, intracranial injuries, contusions, other and unspecified injuries; and poisoning (CDC VES, 1989b).

The examination At the end of the telephone interview, veterans were told if they were preselected by RTI to be examined. The preselection process was done randomly by RTI and names and information were then transferred to the Lovelace Medical Foundation (LMF) in Albuquerque, New Mexico. LMF was under contract with the CDC to schedule the examination appointments which were conducted at LMF, arrange the veterans' round-trip travel to Albuquerque, and provide food and lodging during the examination period (CDC VES, 1989c, p. 16). Over 3,300 Vietnam veterans and over 3,100 non-Vietnam veterans were invited for the examination. However, veterans were not examined if they could not be contacted, refused to be examined, were incarcerated, died after December 31, 1983, were mentally or physically incapable of being examined, or were in a mental institution. Ultimately 2,490 Vietnam veterans and 1,972 non-Vietnam veterans were examined (CDC VES, 1989c, pp. 31, 32). See the demographics section above for differences between the Vietnam and non-Vietnam veterans.

It is important to note that there were also some differences between those examined and those not examined. Higher participation rates were observed among blacks compared to whites, those in the youngest age group compared to those in the older age groups, those with higher levels of education, those in the lowest income category, and those not married compared to those currently married. However, the documentation did not present significance levels (CDC VES, 1989c, pp. 33-34).

For the 3 days before the examination, the veterans were instructed not to eat red meat, pork, or sweets; drink any alcohol or use any mouthwash; take any multivitamins or vitamin C supplements; take any nonprescription drugs; or start a new exercise program. However, participants could continue current prescription medications and exercise programs. From 7pm the night before the first day of examinations, the participants were asked to fast, permitting only water, and during the night they began a 12-hour urine sample (CDC VES, 1989c, p. 17).

Participants were in Albuquerque for 4 days. The first day included an orientation session. The next day started with a morning blood draw, followed by a medical examination (including a medical history questionnaire and general physical, dermatologic and neurological clinical tests), special medical tests (chest roentgenogram, electrocardiogram, pulmonary function, Doppler evaluation of peripheral vasculature, hypersensitivity skin test, nerve conduction velocities, vibratory sensation, audiometry, visual acuity), and laboratory tests (hematologic assays, serum analytes, hepatitis B, endocrine, immunology, urinalysis, 12-hour urine, semen analysis, erythrocyte sedimentation rate, prothrombin time, rapid plasma regain test, stool occult blood, melioidosis antibody titer, breath alcohol level). The third day focused on psychological and neurological tests conducted in a special center at their hotel. On the fourth day the veterans met with an internist and a psychologist to discuss their individual results (CDC VES, 1989c, p. 17). Selected results from the examinations are shown in Tables K-6, K-7, K-8, K-9, and K-10.

TABLE K-6 Current Health Status: Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Currently Have the Following Conditions

Condition	Odds Ratio (OR)	p-value
Perceived fair/poor health	1.9	$p < 0.05$
Somatic symptoms	1.7	$p < 0.05$

SOURCE: CDC VES, 1988a,b; 1989a, p. 18, Table 5.

TABLE K-7 Postdischarge Health Status: Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Have Experienced/Suffered from the Following Conditions Postdischarge

Condition	Odds Ratio (OR)	p-Value
Hypertension	1.2	$p < 0.05$
Chloracne	7.3	$p < 0.05$
Other skin conditions	1.7	$p < 0.05$
Other liver conditions	1.7	$p < 0.05$
Fertility difficulties	1.5	$p < 0.05$

SOURCE: CDC VES, 1989a, p. 18, Table 5.

TABLE K-8 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Have Experienced the Following Conditions

Condition[a]	Odds Ratio (OR)	95% Confidence Interval (CI)
Alcohol abuse or dependence	1.5	1.2-1.8
Generalized anxiety	1.5	1.1-2.1

Depression	2.0	1.4-2.9
≥1 of the above conditions	1.5	1.3-1.8
≥2 of the above conditions	1.9	1.2-2.8

[a]Based on the Diagnostic Interview Schedule.
SOURCE: CDC VES, 1989a, pp. 24-26, Tables 13-15.

TABLE K-9 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Have Elevated Levels on the Minnesota Multiphasic Personality Inventory Clinical Scales

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
Scale 1 (Hypocondriasis)	1.7	1.4-2.1
Scale 2 (Depression)	1.6	1.3-1.8
Scale 3 (Hysteria)	1.5	1.2-2.0
Scale 7 (Obsessive-compulsive syndrome)	1.6	1.3-1.9
Scale 8 (Schizophrenia)	2.0	1.6-2.4
≥1 or more scales elevated	1.3	1.2-1.5
≥2 or more scales elevated	1.5	1.2-1.7

TABLE K-10 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Experience the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
High-frequency hearing loss		
Right ear	1.4	1.2-1.7
Left ear	1.4	1.2-1.6
Both ears	1.4	1.1-1.8
Peripheral nervous system abnormalities—leg absent pinprick (distal dorsal)	1.6	1.1-2.4

SOURCE: CDC VES, 1989a, pp. 20-21, Tables 8-9; 1989c, pp. 110, 113, Tables 7.9, 7.12.

Medical history questionnaire

- These results are somewhat different than those from the telephone interview.
- Vietnam veterans reported more current health problems than non-Vietnam veterans, particularly for mental disorders; diseases of the nervous system; diseases of the skin; symptoms, signs, and ill-defined conditions. However, significance levels were not reported in the document.
- Vietnam veterans reported more physician-diagnosed alcohol-related liver damage, hepatitis B, gastritis, and stomach or duodenal ulcer, and less physician-diagnosed cirrhosis than non-Vietnam veterans. However, significance levels were not reported in the document.

- There were no significant differences between Vietnam veterans and non-Vietnam veterans with respect to *current* limitation in activities or prescribed medications. These results are different than those from the telephone interview listed above.
- There were no significant differences between Vietnam veterans and non-Vietnam veterans with respect to post-discharge hospitalization, cancer, benign growth, diabetes, gastrointestinal ulcers, hepatitis B, cirrhosis, and urinary tract problems. These results are somewhat different than those from the telephone interview listed above.

Cardiac tests There were no significant differences between the Vietnam and non-Vietnam veterans with respect to hypertension, altered peripheral arterial hemodynamics, electrocardiogram findings (ischemia, left ventricular hypertrophy, any finding), chest roentgenogram findings (pulmonary, cardiac, any finding), or pulmonary function parameters (CDC VES, 1989a, p. 19, Table 7).

Dermatologic examinations There were no significant differences between the Vietnam and non-Vietnam veterans with respect to chloracne-like lesions, acneiform lesions, hyperpigmentation, skin cancer, infections, and postinflammatory scars. These results are somewhat difference than those from the telephone interview (CDC VES, 1989a, p. 19, Table 6; CDC VES, 1989b, pp. 56-58).

Psychiatric examinations

- There was no significant difference between the Vietnam veterans and the non-Vietnam veterans with respect to drug abuse or dependence.
- Combat-related PTSD analysis was restricted to Vietnam veterans since non-Vietnam veterans had a low likelihood of experiencing combat. Almost 15 percent Vietnam veteran had experienced PTSD prior to examination while over 2 percent experienced PTSD the month before the examination.
- There were no significant differences between the Vietnam veterans and non-Vietnam veterans with respect to MMPI scale 4 (psychopathic personality disorders), scale 5 (male sexual inversion), scale 6 (Paranoia), scale 9 (hypomania), or scale 0 (uneasiness in social situations or dealing with others).

Neurological examinations/tests

- Vietnam veterans had a significantly lower mean score on the Army Classification Battery (ACB) General Technical Test at examination, Rey-Osterreith Test (RO) Complex Figure-Copy, Wechsler Adult Intelligence Scale-Revised (WAIS-R) block design subset ($p < 0.05$), and a significantly higher average number of cards per sort on the Wisconsin Card Sorting Test ($p < 0.05$).
- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to peripheral neuropathy.
- There were no significant differences between the Vietnam veterans and non-Vietnam veterans with respect to a mean score on the California Verbal Learning Tests, Grooved Pegboard, Paced Auditory Serial Addition Test, short-delay recall and long-delay recall

on the RO Complex Figure, the information subset of the WAIS-R, and Word List Generation.

Hematological/laboratory tests (CDC VES, 1989c, pp. 174, 176, 187, 190, Tables 11.5, 11.8, 12.6, 12.8)

- Vietnam veterans had significantly higher fasting serum glucose (difference = 0.9mg/dl, 95% CI 0.2-1.6) and thyroid-stimulating hormone (difference = 4.3mIU/L, 95% CI 0.5-8.2).
- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to
  - mean red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white cell count, segmented neutrophil, band neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet count and prothrombin time;
  - free thyroxine index, cortisol, dehydroepiandrosterone, testosterone, follicle-stimulating hormone, or luteinizing hormone;
  - blood urea nitrogen or serum creatinine; and
  - diabetes or hypothyroidism.

Semen tests (CDC VES, 1989c, pp. 208-209, Tables 13.5, 13.6)

- Vietnam veterans had significantly lower sperm concentrations (mean difference = –20.2 million cells/mL, 95% CI –34.5 to –2.8) and a lower percent of normal cell morphology (mean difference = –3.8 percent, 95% CI –6.6 to –0.9) compared to non-Vietnam veterans.
- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to movement characteristics (percent motile cells, mean linear velocity, mean straight line velocity, mean linearity, mean amplitude lateral head displacement, mean beat/cross frequency).

Reproductive outcomes and child health During the interview, data on the following topics were collected:

- Basic data for all veterans' biological children, including month and year of birth, sex of child, live-born or stillborn status
- Birth defects of malformations diagnosed by a physicians—up to two per child
- Physician-diagnosed major health problems or impairments occurring in the first 5 years of life, not including normal childhood diseases and injuries—up to three per child
- Leukemia and other types of cancer
- Infant and child mortality
- Pregnancies fathered by the veteran that ended early, including miscarrages, induces abortions, and tubal pregnancies

(CDC VES, 1989d, p. 9)

Selected results from the interview are as follows are shown in Tables K-11, K-12, and K-13.

TABLE K-11 The Offspring of Vietnam Veterans Were Significantly More Likely Than Those of Non-Vietnam Veterans to Have the Following Conditions

Condition	Odds Ratio (OR)	95% Confidence Interval (CI)
Been miscarried	1.3	1.2-1.4
Anomalies (total)	1.3	1.2-1.4
Anemia	1.9	1.1-3.2
Diseases of the ear	1.3	1.1-1.6
Diseases of the skin	1.5	1.1-2.0
Symptoms and signs	1.5	1.2-1.8
Injuries and poisonings[a]	1.6	1.2-2.1

[a]Standardized for race.
SOURCE: CDC VES, 1989d, pp. 22-28, Tables 10, 11, 14, 15, 16, 17, 19, 21, 23.

TABLE K-12 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Father Children with Birth Defects of These Organ Systems

	No. of Children		Odds Ratio	95% Confidence
Organ System	Vietnam	Non-Vietnam	(OR)[a]	Interval (CI)
Total anomalies	826	590	1.3	1.2-1.4
Nervous	33	13	2.3	1.2-4.5
Hydrocephalus	11	2	5.1[b]	1.1-23.1
Musculoskeletal	426	309	1.2	1.1-1.5
Integument	41	17	2.2	1.2-4.0

[a]Adjusted for primary potential confounders listed above, as well as years between entry into Army and birth of the child.
[b]Crude OR because the number of cases is not sufficient for multivariable modeling.
SOURCE: CDC VES, 1989d, pp. 22-28, Tables 10, 11, 14, 15, 16, 17, 19, 21, 23.

TABLE K-13 Vietnam Veterans Were Significantly More Likely Than Non-Vietnam Veterans to Report the Following Birth Defects

Birth Defect	Odds Ratio (OR)	95% Confidence Interval (CI)
Children with 1 birth defect	1.3	1.1-1.4
Children with >1 birth defect	1.6	1.1-2.5
1 child with 1 birth defect	1.2	1.1-1.4

SOURCE: CDC VES, 1989d, pp. 22-28, Tables 10, 11, 14, 15, 16, 17, 19, 21, 23.

- There were no significant differences between the Vietnam veterans and the non-Vietnam veterans with respect to induced abortions, and tubal pregnancies, stillbirths, and childhood cancer among the offspring.
- There were no significant differences between the offspring of the Vietnam veterans and the non-Vietnam veterans with respect to infectious and parasitic diseases, benign and unspecified neoplasms, endocrine diseases, mental disorders, nervous system diseases (except for diseases of the ear), circulatory system diseases, respiratory system diseases,

digestive system diseases, genitourinary system diseases, urinary tract infection, musculoskeletal disease, perinatal conditions, and supplementary classifications.

- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to total serious health problems, infant mortality or child mortality.
- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to birth defects of the eye; ear, face, and neck; circulatory system; respiratory system; digestive system; genitals; urinary system; or other unspecified systems.
- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to veterans reporting more than one child with a birth defect.

The General Birth Defects Sub-Study

The General Birth Defects (GBD) Sub-Study was designed to compare the rates of birth defects, as presented in hospital birth records, among offspring of Vietnam veterans and those among non-Vietnam veterans. This comparison was also used to validate the data from the telephone interview (see data above). Selected results from this substudy are as follows:

- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to major, minor, or suspected birth defects.
- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to defects of the ear, face, and neck; digestive system; genitals; musculoskeletal system; or integument system.
- There were no significant differences between the offspring of the Vietnam veterans and those of the non-Vietnam veterans with respect to having a child with low birth weight or perinatal deaths. (CDC VES, 1989d, p. 46, Tables 16, 19, 21, 23, 24)

The Cerebrospinal Malformations Sub-Study

The Cerebrospinal Malformations (CSMs) Sub-Study also used hospital birth records to identify all children with possible cerebrospinal malformations (i.e., a reported CSM, a reported condition that suggested a possible CSM, and all children reported as stillborn) (CDC VES, 1989d, p. 46). Selected results from this sub-study are as follows:

- Among reported stillbirths, 5 CSMs in the offspring of Vietnam veterans and 6 CSMs in the offspring of non-Vietnam veterans were found; 10 of which were not reported during the time of the interview.
- Among reported live births, 21 CSMs in the offspring of Vietnam veterans and 6 CSMs in the offspring of non-Vietnam veterans were found.
- The CSMs observed in Vietnam veterans were anencephaly ($n = 10$), spina bifida ($n = 9$), and hyrocephalus ($n = 7$).
- The CSMs observed in non-Vietnam veterans were anencephaly ($n = 7$), spina bifida ($n = 2$), and hyrocephalus ($n = 3$). (CDC VES, 1988c)

"Because record retrieval rates varied considerably by cohort status and because negative responses were not verified, we did not calculate or compare rates of CSM cases in the two cohorts; the results are expressed as numbers of verified cases" (CDC VES, 1988c).

Strengths of the VES

As listed in the VES documentation (CDC VES, 1989a, p. 32), the major strengths of the VES are as follows:

- The random sampling method used to identify large representative samples of Vietnam and non-Vietnam veterans
- The measures used to assure good comparability of the two cohorts
- The rigorous vital status ascertainment and cause of death classification methods
- The high participation rates in the interview component
- The comparability of the examined cohorts (in the face of differential participation rates)
- The attempt at independent validation of certain interview outcomes
- The meticulous data control and bias-avoidance methods used in all components of the study

Limitations of the VES

As listed in the VES documentation (CDC VES, 1989a, p. 32), the major limitations of the VES are as follows:

- The long time that has elapsed since the end of the Vietnam conflict
- The differential participation rates in the examined cohorts
- The lack of any reliable indirect estimate of the Agent Orange exposure (the study was not designed to focus on Agent Orange exposure)
- The fact that the VES "exposure," the Vietnam experience, represents a large variety of individual experiences (e.g., combat exposure) that are probably not homogeneous

Selected Cancers Study

Background

Vietnam veterans are concerned that exposure to Agent Orange and especially its TCDD contaminant may negatively impact their health. in response to this concern and to the Veterans Health Programs Extension and Improvement Act of 1979 (Public Law 96-151. 96th Cong., 1st Sess.) and the Veterans' Health Care, Training, and Small Business Loan Act of 1981 (Public Law 97-72. 97th Cong., 1st Sess.), the CDC conducted the Vietnam Experience Study (see above) and the Selected Cancers Study (CDC VES, 1989a, p. 3).

The Selected Cancers Study is a case-control study of veterans' risk to six rare cancers (non-Hodgkin's lymphoma, Hodgkin's disease, soft-tissue and other sarcomas, nasal cancer, nasopharyngeal cancer, and primary liver cancer among Vietnam veterans) thought to be associated with TCDD exposure based on published literature (see http://www.cdc.gov/nceh/veterans/default1d.htm). This study "focuses on the risk of cancer after service in Vietnam in general. We only indirectly examine any possible association with

herbicide exposure through investigation of service characteristics such as military branch, region of service in Vietnam, calendar years of service, and specific duties that involved the handling of herbicides" (Selected Cancers Cooperative Study Group, 1990b, p. 2474).

Methodology

The three investigations within this study follow the same methodology and control series. The study includes a consensus diagnosis from three experts to confirm the cases (only these are included in the analysis), a standardized telephone interview, and microscopic slides or tissue blocks for 97 percent of lymphoma cases interviewed from pathology department where diagnosis was given (Selected Cancers Cooperative Study Group, 1990a, pp. 1, 12; Selected Cancers Cooperative Study Group, 1990b, p. 2474). The Environmental Support Group also reviewed the medical records of those stationed in Vietnam, when permission was granted (Selected Cancers Cooperative Study Group, 1990b).

The cases and controls were randomly assigned to interviewers so each interviewer had a similar number of cases and control (see Table K-14). The telephone interviews took about 50 minutes to complete, and were conducted in English, Spanish, and Cantonese by fluent speakers. Those who served in Vietnam were asked about dates of tour, branch of service, rank, unit, location in Vietnam, job duties, and self-perceived exposure to herbicides while in Vietnam. They were also asked to name the specific herbicides that they used on crops, in landscaping, in right-of-way maintenance along power lines, rail lines, and in forestry. in this study "stationed in Vietnam" includes those stationed off the coast. The U.S. Army and Joint Services Environmental Support Group then classified veterans' units into those likely to be combat, combat support, or support based on information provided during the interview (they were not aware of the veterans' control and case status) (Selected Cancers Cooperative Study Group, 1990a, pp. 16, 18-19; Selected Cancers Cooperative Study Group, 1990b, p. 2475).

TABLE K-14 Sample Size for the Cases and Controls in the Selected Cancers Study

		Cases					
	Controls	**Non-Hodgkin's Disease**	**Soft-Tissue and Other Sarcomas**	**Hodgkin's Disease**	**Nasal Cancer**	**Nasopharyngeal Cancer**	**Liver Cancer**
Controls Selected or Cases Identified	2299	2354	612	2354	89	131	310
Interviewed	1910	2073	521	2073	80	115	263
Specimen Obtained	N/A[a]	2004	511	2004	78	113	233
Diagnosis Confirmed	N/A	1511	386	343	70	113	168
Excluded from Analysis							
Military/Vietnam service status unknown	7	5	4	0	0	1	2
In/off coasts of Vietnam but not stationed there	27	13	8	1	1	1	2
AIDS or related condition	1	290	3	17	3	1	0

Not a U.S. resident before 1969	99	56	23	15	4	21	34
History of von Recklinghausen's neuro-bibromatosis or postirradiation osteosarcoma	N/A	N/A	6	N/A	N/A	N/A	N/A
Total Available for Analysis	**1776**	**1157**	**342**	**310**	**62**	**89**	**130**

[a]N/A = Not applicable.
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 12-13, 1990b,c,d.

Regression models Three models were used for the analysis (Selected Cancers Cooperative Study Group, 1990a,b,c,d) and they are as follows:

- Model 1 = registry and age in 1968
- Model 2 = registry, age in 1968, race/ethnicity, educational achievement
- Model 3 = registry, age in 1968, race/ethnicity, educational achievement, spraying or mixing any herbicide other than in Vietnam, occupational contact with phenoxyherbicide other than in Vietnam, occupational contact with chlorophenols or dioxin other than in Vietnam, medical irradiation, having been raised in the Jewish religion, marital status, cigarette smoking, reported immunodeficiency disease other than AIDS, rheumatoid arthritis, systemic lupus erythematosus, use of immunosuppressive drugs, and use of phenytoin or related compounds, and other relevant potential confounders of Agent Orange exposure

Study Strengths

The strengths of this investigation are that the participation rates were high, only 7.5 percent of controls selected actually reported serving in Vietnam, and the fact that the same study design and control group was used for all six cancers proves against a general selection bias (Selected Cancers Cooperative Study Group, 1990b, p. 2481).

Study Limitations

The limitations of this investigation are that the researchers "could not measure serum TCDD levels in men recently diagnosed to have cancer because of the large quanitity of blood required" and like in any case-control study there is possible bias, residual confounding, and possible misclassification of the exposure or disease (Selected Cancers Cooperative Study Group, 1990b, pp. 2481-2482).

Cases and Controls

Part I: Non-Hodgkin's lymphoma (NHL) This part of The Selected Cancers Study investigates the association between military service in Vietnam and exposure to phenoxy-herbicides and NHL.

Cases and Controls The inclusion criterion for the cases includes

- had an initial diagnosis of NHL, Hodgkin's disease, or "lymphoma, not otherwise specified";
- men first diagnosed with NHL between December 1, 1984, and November 30, 1988;
- lived in geographic location areas covered by the population-based cancer registries for five metropolitan areas (Atlanta, GA; Detroit, MI; San Francisco, CA; Seattle, WA; Miami, FL) and three states (Connecticut, Iowa, and Kansas); and
- born between 1929 and 1953. (Selected Cancers Cooperative Study Group, 1990a, p. 28, 1990b, pp. 2474-2475)

The exclusion criterion includes

- unknown military or Vietnam service status;
- been in or off the coast of Vietnam but not stationed there;
- have AIDS or AIDS-related illness; and
- not residents of the United States before 1969 and were thus unlikely to have been eligible for U.S. military service in Vietnam. (Selected Cancers Cooperative Study Group, 1990a, p. 28, 1990b, pp. 2474-2475)

The controls were selected based on random digit dialing and frequency-matched to lymphoma cases by geographic areas (registries) and age in 1968, and were the same controls for the other cancers investigated.

Part II: Soft-tissue and other sarcomas This part of the Selected Cancers Study investigates the association between military service in Vietnam and exposure to phenoxyherbicides and soft-tissue and other sarcomas.

Cases and controls The inclusion criterion for the cases includes

- men first diagnosed with sarcoma between December 1, 1984, and November 30, 1988;
- lived in geographic location areas covered by the population-based cancer registries for 5 metropolitan areas (Atlanta, GA; Detroit, MI; San Francisco, CA; Seattle, WA; Miami, FL) and three states (Connecticut, Iowa, and Kansas); and
- born between 1929 and 1953. (Selected Cancers Cooperative Study Group, 1990a, p. 42, 1990c, p. 2486)

The exclusion criterion includes

- diagnosis of Kaposi's sarcoma or mesothelioma;
- unknown military or Vietnam service status;
- been in or off the coast of Vietnam but not stationed there;
- had AIDS or AIDS-related illness;
- not residents of the United States before 1969 and were thus, unlikely to have been eligible for U.S. military service in Vietnam; and

- reported a history of von Recklinghausen's neurofibromatosis or a possible postirradiation osteosarcoma. (Selected Cancers Cooperative Study Group, 1990a, p. 42, 1990c, p. 2486)

The controls were selected based on random digit dialing and frequency-matched to lymphoma cases by geographic areas (registries) and age in 1968, and were the same controls for the other cancers investigated.

Part III: Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer
This part of the Selected Cancers Study investigates the association between military service in Vietnam and exposure to phenoxyherbicides and the following cancers: Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer.

Cases and controls The inclusion criterion for the cases includes

- men first diagnosed with Hodgkin's disease, nasal cancer, nasopharyngeal cancer, or liver cancer between December 1, 1984, and November 30, 1988;
- lived in geographic location areas covered by the population-based cancer registries for 5 metropolitan areas (Atlanta, GA; Detroit, MI; San Francisco, CA; Seattle, WA; Miami, FL) and three states (Connecticut, Iowa, and Kansas); and
- born between 1929 and 1953. (Selected Cancers Cooperative Study Group, 1990a, pp. 53, 63, 70, 76-77, 1990d, pp. 2496-2497)

The exclusion criterion includes

- unknown military or Vietnam service status;
- been in or off the coast of Vietnam but not stationed there;
- had AIDS or AIDS-related illness;
- not residents of the United States before 1969 and were thus, unlikely to have been eligible for U.S. military service in Vietnam; and
- reported a history of von Recklinghausen's neurofibromatosis or a possible postirradiation osteosarcoma. (Selected Cancers Cooperative Study Group, 1990a, pp. 53, 63, 70, 76-77, 1990d, pp. 2496-2497)

The controls were selected based on random digit dialing and frequency-matched to lymphoma cases by geographic areas (registries) and age in 1968, and were the same controls for the other cancers investigated.

Results

Part I: Non-Hodgkin's lymphoma (NHL)

Demographics Compared to the controls, NHL cases were distributed differently among the 8 registries, were significantly older, had significantly less formal education, smoked more cigarettes, were more likely to be never married, had systemic lupus erythematosus, took more

immunosuppressive drugs following an organ transplant and intravenous drugs not prescribed by a physician ($p < 0.05$) (Selected Cancers Cooperative Study Group, 1990a, pp. 29-30, 1990b).

There were no significant differences between the cases and controls with respect to being stationed in or off the coast of Vietnam, racial/ethnic group, sprayed or mixed any herbicide on a farm or ranch, sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work, occupational exposure to phenoxyherbicides, occupational exposure to chlorophenols, raised in the Jewish religion, exposure to medical radiation ≥5 years before the date of diagnosis, diagnosed with rheumatoid arthritis, had an immune disease other than AIDS ≥3 years before the data of diagnosis, had malaria, took medication to treat or prevention malaria, or took phenytoin or related compounds for epilepsy of seizures (Selected Cancers Cooperative Study Group, 1990b).

Part II: Soft-tissue and other sarcomas

Demographics Compared to controls, cases were distributed differently among the 8 registries and were significantly less likely to be white non-Hispanic, more likely to have occupational exposure to chlorophenols and more likely to work in a meat packing or processing plant ($p < 0.05$) (Selected Cancers Cooperative Study Group, 1990a, p. 42, 1990c).

There were no significant differences between the cases and controls with respect to age in 1968, being stationed in or off the coast of Vietnam, highest level of education completed, regular smoking of cigarettes, sprayed or mixed any herbicide on a farm or ranch, sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work, occupational exposure to phenoxyherbicides, had an immune disease other than AIDS ≥3 years before date of diagnosis, took drugs to suppress the immune system, had Gardner's syndrome, or took clofibrate or a related compound (Selected Cancers Cooperative Study Group, 1990c).

Part III: Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer

Demographics Compared to controls, cases of Hodgkin's disease were significantly younger, had less formal education, and were more likely to have reported ever having smoked cigarettes regularly ($p < 0.05$). However, there were no significant differences between the cases of Hodgkin's disease and the controls with respect to the distribution within the 8 registries, being stationed in Vietnam or off the coast of Vietnam, race/ethnicity, reported having sprayed or mixed any herbicide on a farm or ranch, reported having sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work, reported occupational exposure to phenoxyherbicides, reported occupational exposure to chlorophenols, raised in the Jewish religion, number of siblings lived with while growing up, raised in an urban setting, exposure to medical radiation ≥5 years before the date of diagnosis, had chemotherapy ≥5 years before the date of diagnosis, had mononucleosis, had a tonsillectomy, or had an appendectomy (Selected Cancers Cooperative Study Group, 1990a, p. 54, 1990d).

Compared to controls, cases of nasal cancer were significantly older, had less formal education, and were more likely to have reported ever having smoked cigarettes regularly ($p < 0.05$). However, there were no significant differences between the cases of nasal cancer with respect to the distribution within the 8 registries, being stationed in Vietnam or off the coast of Vietnam, race/ethnicity, reported having sprayed or mixed any herbicide on a farm or ranch, reported having sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or

forestry work, reported occupational exposure to phenoxyherbicides, reported occupational exposure to chlorophenols, working in a pulp, saw or planning mill, worked around wood dust, worked with or around plywood, worked in metal planting, working with or around nickel, worked with or around chromium, or worked with wood as a hobby (Selected Cancers Cooperative Study Group, 1990a, p. 64, 1990d).

Compared to controls, cases of nasopharyngeal cancer were significantly older, were less likely to be white non-Hispanic, had less formal education, were more likely to have reported ever having smoked cigarettes regularly, and more likely to have reported occupational exposure to chlorophenols ($p < 0.05$). However, there were no significant differences between the cases of nasopharyngeal cancer with respect to the distribution within the 8 registries, being stationed in Vietnam or off the coast of Vietnam, reported having sprayed or mixed any herbicide on a farm or ranch, reported having sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work, reported occupational exposure to phenoxyherbicides, nasopharyngeal cancer in blood relatives, or had an infectious mononucleosis ≥5 years before the date of diagnosis (Selected Cancers Cooperative Study Group, 1990a, p. 71, 1990d).

Compared to controls, cases of liver cancer were distributed within the 8 registries differently and were significantly older, less likely to be white non-Hispanic, have less formal education, more likely to have reported ever having smoked cigarettes regularly, less likely to have reported having sprayed or mixed any herbicide on a farm or ranch, less likely to have occupational exposure to phenoxyherbicides, more likely to have had hepatitis ≥3 years before the date of diagnosis, more likely to had had cirrhosis ≥3 years before the date of diagnosis, and less likely to have worked with chemical solvents ($p < 0.05$). However, there were no significant differences between the cases of liver cancer and the controls with respect to being stationed in Vietnam or off the coast of Vietnam, reported having sprayed or mixed any herbicide for right-of-way maintenance, lawn care, or forestry work, reported occupational exposure to chlorophenols, reported ever drinking alcohol regularly, taking androgenic steroids, or working in a dry-cleaning plant (Selected Cancers Cooperative Study Group, 1990a, p. 77, 1990d).

All investigations (Part I, II, III)

Association between military service in Vietnam and cancer There was a significant association between military service in Vietnam and NHL in the Selected Cancers Study based on Model 1, Model 2, and Model 3 (see above for covariate in each model) (Table K-15). However, there were no significant associations found between military service in Vietnam and soft-tissue and other sarcomas, Hodgkin's disease, nasal cancer, nasopharyngeal cancer, or liver cancer (see Tables K-15, K-16, K-17, and K-18 for the results for various associations) (Selected Cancers Cooperative Study Group, 1990a,b,c,d).

Histological Classification There was no significant differences between men with NHL stationed in or off the coast of Vietnam and those not stationed in or off the coast of Vietnam with regards to histological classification of the malignant neoplasms (i.e., low grade, intermediate grade, high grade [$p = 0.73$]) (Selected Cancers Cooperative Study Group, 1990b, p. 2478).

There were no significant differences between men with soft-tissue and other sarcomas stationed in or off the coast of Vietnam and those not stationed in or off the coast of Vietnam with regards to histological classification of the malignant neoplasms (i.e., fibromatous,

TABLE K-15 Association Between Military Service in Vietnam and Cancer

Model	Non-Hodgkin's Disease OR (95% CI)	Soft-Tissue and Other Sarcomas OR (95% CI)	Hodgkin's Disease OR (95% CI)	Nasal Cancer OR (95% CI)	Nasopharnygeal Cancer OR (95% CI)	Liver Cancer OR (95% CI)
Model 1	1.45 (1.08-1.93)	1.02 (0.65-1.61)	1.20 (0.76-1.90)	0.70 (0.08-2.95)	0.60 (0.12-1.93)	1.22 (0.55-2.67)
Model 2	1.46 (1.09-1.96)	1.01 (0.64-1.60)	1.17 (0.74-1.86)	0.67 (0.15-2.96)	0.57 (0.17-1.93)	1.27 (0.56-2.89)
Model 3	1.47 (1.09-1.97)	1.00 (0.63-1.58)	1.14 (0.71-1.83)	0.66 (0.15-2.91)	0.52 (0.15-1.75)	1.16 (0.50-2.68)

NOTE: See above for covariates for each of the three models.
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 32, 45, 57, 66, 73, 79, 1990b,c,d.

TABLE K-16 Risk of Cancer Among Vietnam Veterans Compared to the Risk Among Four Unexposed Referent Groups

Unexposed Referent Groups	Non-Hodgkin's Disease OR (95% CI)	Soft-Tissue and Other Sarcomas OR (95% CI)	Hodgkin's Disease OR (95% CI)	Nasal Cancer OR (95% CI)	Nasopharnygeal Cancer OR (95% CI)	Liver Cancer OR (95% CI)
Men who did not serve in Vietnam	1.47 (1.09-1.97)	1.00 (0.62-1.59)	1.14 (0.71-1.83)	0.66 (0.15-2.91)	0.52 (0.15-1.75)	1.16 (0.50-2.68)
Men who served in the military at any time but not in Vietnam	1.63 (1.14-2.33)	0.88 (0.51-1.52)	1.09 (0.62-1.91)	0.37 (0.08-1.83)	0.68 (0.18-2.65)	0.87 (0.33-2.28)
Men who served at any time from 1964-1972 in the military but not in Vietnam	1.52 (1.00-2.32)	0.74 (0.39-1.41)	1.23 (0.65-2.36)	0.31 (0.04-2.20)	Could not be calculated	0.53 (0.14-1.94)
Men who never served in the military	1.41 (1.03-1.93)	1.05 (0.64-1.71)	1.17 (0.71-1.92)	1.38 (0.28-6.81)	0.48 (0.14-1.71)	1.34 (0.52-3.44)

NOTE: Data from Model 3 (see above for covariates).
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 33, 45, 57, 67, 74, 80; 1990b,c,d.

TABLE K-17 Association Between Branch of Military Service and Cancer[a] for Non-Vietnam and Vietnam Veterans

Branch of Military Service	Non-Hodgkin's Disease OR (95% CI)	Soft-Tissue and Other Sarcomas OR (95% CI)	Hodgkin's Disease OR (95% CI)
Non-Vietnam Veterans			
Army	0.82 (0.66-1.02)	0.89 (0.64-1.25)	0.78 (0.52-1.17)
Air Force	0.91 (0.67-1.25)	0.58 (0.32-1.04)	1.36 (0.81-2.29)
Marines	0.77 (0.45-1.32)	0.85 (0.36-1.99)	1.77 (0.86-3.63)
Navy	0.79 (0.57-1.11)	1.25 (0.77-2.01)	1.34 (0.81-2.24)
Coast Guard	1.45 (0.39-5.38)	1.35 (0.15-12.2)	N/A
Vietnam Veterans			
Army	1.19 (0.79-1.80)	0.70 (0.35-1.43)	1.00 (0.51-1.97)
Air Force	1.02 (0.47-2.24)	1.40 (0.49-3.99)	1.69 (0.58-4.89)
Marines	1.84 (0.78-4.34)	1.71 (0.57-5.15)	1.73 (0.51-5.88)
Navy	1.89 (1.11-3.24)	0.83 (0.30-2.24)	1.06 (0.43-2.59)
Coast Guard	N/A	N/A	N/A

NOTE: Data from Model 3 (see above for covariates). N/A = Odds ratio could not be calculated.
[a]Due to the small number of Vietnam veterans with nasal cancer, nasopharyngeal cancer, and liver cancer, the analysis in Part III was completed for Hodgkin's disease only.
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 34, 48, 58, Tables 3.6, 4.6, 5.6; 1990b,c,d.

TABLE K-18 Association Between Self-Reported Agent Orange Contact and Cancer[a] Among Those Who Reported the Exposure and Served in Vietnam Compared to Those Who Did Not Report the Exposure but Who Served in Vietnam

Type of Contact with Agent Orange	Non-Hodgkin's Disease OR (95% CI)	Soft-Tissue and Other Sarcomas OR (95% CI)	Hodgkin's Disease OR (95% CI)
Reported passing though a defoliated area	0.82 (0.45-1.49)	1.60 (0.63-4.12)	0.65 (0.25-1.67)
Reported any possible contact with Agent Orange	1.08 (0.58-2.02)	0.68 (0.23-2.05)	0.76 (0.28-2.07)
Reported being present when other were spraying Agent Orange	0.98 (0.39-2.48)	0.38 (0.05-3.11)	0.74 (0.15-3.67)
Reported getting Agent Orange in skin or clothes	1.08 (0.40-2.96)	0.52 (0.06-4.39)	0.47 (0.06-3.99)
Reported handling equipment or containers that had been used with Agent Orange	0.41 (0.04-4.07)	N/A	N/A

NOTE: Data from Model 3. N/A = Odds ratio could not be calculated.
[a]Due to the small number of Vietnam veterans with nasal cancer, nasopharyngeal cancer, and liver cancer, the analysis in Part III was completed for Hodgkin's disease only.
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 36, 48, 60, Tables 3.8, 4.8, 5.8; 1990b,c,d.

TABLE K-19 Association Between Selected Characteristics of Military Service in Vietnam and Cancer[a]

Characteristics	Non-Hodgkin's Disease OR (95% CI)	Soft-Tissue and Other Sarcomas OR (95% CI)	Hodgkin's Disease OR (95% CI)
Military service in Vietnam	1.47 (1.09-1.97)	1.00 (0.63-1.58)	1.14 (0.71-1.83)
Duration of service in Vietnam (years)			
<1	1.05 (0.70-1.57)	0.77 (0.41-1.47)	0.86 (0.45-1.65)
1-1.4	1.98 (1.00-3.94)	1.28 (0.45-3.66)	2.43 (0.98-5.99)
1.5-1.9	2.99 (1.41-6.31)	0.92 (0.20-4.26)	1.14 (0.30-4.37)
≥2	1.54 (0.79-3.01)	1.24 (0.44-3.45)	1.11 (0.36-3.45)
	p for trend = 0.06	p for trend = 0.80	p for trend = 0.33
Calendar years stationed in Vietnam			
Before 1966	1.38 (0.54-3.55)	0.46 (0.05-3.93)	0.41 (0.05-3.44)
1966-1969	1.41 (1.01-1.98)	0.95 (0.56-1.62)	1.11 (0.64-1.93)
After 1969	1.64 (0.79-3.39)	1.30 (0.45-3.69)	1.63 (0.66-4.02)
	p for trend = 0.93	p for trend = 0.66	p for trend = 0.42
Age at beginning of first tour in Vietnam (years)			
<21	1.73 (1.11-2.70)	0.97 (0.47-2.01)	1.15 (0.61-2.18)
21-25	1.20 (0.74-1.94)	1.34 (0.68-2.66)	1.06 (0.49-2.29)
≥26	1.45 (0.81-2.60)	0.44 (0.13-1.52)	1.31 (0.42-4.10)
	p for trend = 0.52	p for trend = 0.26	p for trend = 0.95
Rank at end of last tour in Vietnam			
E1-E3	1.29 (0.61-2.72)	0.67 (0.19-2.35)	1.07 (0.37-3.04)
E4-E9	1.44 (1.02-2.03)	1.11 (0.65-1.89)	1.19 (0.70-2.04)
Officer	1.78 (0.80-3.96)	0.69 (0.15-3.22)	1.33 (0.28-6.26)
	p for trend = 0.84	p for trend = 0.66	p for trend = 0.97
Type of unit in Vietnam			
Support	1.50 (1.02-2.21)	0.76 (0.37-1.53)	1.58 (0.90-2.77)
Combat support	1.18 (0.65-2.15)	1.03 (0.44-2.41)	0.50 (0.14-1.76)
Combat	1.25 (0.63-2.45)	0.76 (0.25-2.28)	0.94 (0.34-2.59)
	p for trend = 0.76	p for trend = 0.85	p for trend = 0.17
Corps in Vietnam			
I	2.25 (1.21-4.18)	1.61 (0.69-3.76)	1.67 (0.67-4.18)
II	1.22 (0.66-2.26)	0.74 (0.25-2.18)	0.52 (0.15-1.81)
III	0.89 (0.50-1.58)	0.50 (0.17-1.44)	1.25 (0.57-2.75)
IV	0.90 (0.15-5.41)	N/A	0.93 (0.09-9.82)
Blue-water Navy	2.17 (1.22-3.86)	0.64 (0.18-2.21)	1.39 (0.56-3.46)
	p for trend = 0.11	p for trend = 0.33	p for trend = 0.59
Ever in III Corps in Vietnam			
No	1.70 (1.07-2.71)	1.15 (0.57-2.32)	1.27 (0.60-2.67)
Yes	0.96 (0.59-1.57)	0.67 (0.30-1.54)	1.12 (0.55-2.27)
Blue-water Navy	2.18 (1.23-3.88)	0.63 (0.18-2.20)	1.42 (0.57-3.52)
	p for trend = 0.06	p for trend = 0.73	p for trend = 0.92

Land vs. sea duty in Vietnam			
All land-based men	1.30 (0.93-1.83)	1.07 (0.65-1.76)	1.08 (0.64-1.82)
Sea-based blue-water Navy	2.18 (1.23-3.87) p for trend = 0.11	0.64 (0.18-2.21) p for trend = 0.41	1.41 (0.57-3.50) p for trend = 0.61

NOTE: Data from Model 3.
[a]Due to the small number of Vietnam veterans with nasal cancer, nasopharyngeal cancer, and liver cancer, the analysis in Part III was completed for Hodgkin's Disease only.
SOURCE: Selected Cancers Cooperative Study Group, 1990a, pp. 37, 49, 59, Tables 3.7, 4.7, 5.7; 1990b,c,d.

lipomatous, myomatous, and other soft-tissue sarcomas [p = 0.82]) (Selected Cancers Cooperative Study Group, 1990c, p. 2488).

Conclusions

Part I: Non-Hodgkin's lymphoma (NHL) "Compared with the other malignant neoplasms under investigation in the Selected Cancer Study, previous studies of Vietnam veterans more strongly support an association with NHL." "Results of this study strongly suggest that Vietnam veterans have a roughly 50 percent increased risk of developing NHL approximately 15 to 25 years after military service in Vietnam (OR = 1.47, 95% CI 1.09-1.97). The results do not show a similar increased risk among veterans who served in other locations during the Vietnam ear, suggestions that this association is specific to Vietnam service rather than military service in general." "Although we could not test such hypotheses and we cannot completely rule out the role of chance or unrecognized bias, our results strongly suggest that Vietnam veterans are at increased risk of NHL and that this increased is not due to Agent Orange exposure" (Selected Cancers Cooperative Study Group, 1990b, pp. 2479-2480, 2482).

Part II: Soft-tissue and other sarcomas "The results of this study do not indicate that the risk of sarcoma is increased among men who served in the U.S. military in Vietnam." "The military service characteristics of men with sarcoma did not suggest that Vietnam veterans who might have been exposed to Agent Orange are at higher risk for the development of sarcoma." "Our results are in agreement with those of most other studies and suggest that Vietnam veterans are not at increased risk for the development of sarcoma 15 to 25 years after service. We also failed to identify any subgroup of Vietnam veterans at higher risk or any subtype of soft-tissue sarcoma with greater risk for Vietnam veterans" (Selected Cancers Cooperative Study Group, 1990c, pp. 2489, 2491-2492).

Part III: Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer "Our results provide no evidence of higher risk of Hodgkin's disease, nasal cancer, nasopharyngeal cancer, or primary liver cancer among Vietnam veterans." "Except for Hodgkin's disease, the malignant neoplasms described in this report have not received extensive attention in other studies of Vietnam veterans." "Because most of the Vietnam veterans in this study were probably not (or were only minimally) exposed to Agent Orange, the results should not be considered an adequate test of the hypothesis that exposure to Agent Orange of TCDD is

associated with the development of these malignant neoplasms" (Selected Cancers Cooperative Study Group, 1990d, pp. 2503-2504).

Agent Orange Validation Study

Background

The CDC conducted the two studies above (the VES and the Selected Cancer Study) in response to veterans' concern that their service in Vietnam adversely affected their health. To study Agent Orange more directly, and to "determine if exposure scores based on military records of troop locations and spray locations can identify a large number of men exposed to Agent Orange, as would be needed for a large cohort study," the CDC also conducted the Agent Orange Validation Study (CDC, 1988, p. 1253; see http://www.cdc.gov/nceh/veterans/default1b.htm).

Agent Orange Validation Study Cohort

The sample size of the study is given in Figure K-2. The Agent Orange Validation Study cohort included Vietnam veterans with the following inclusion criteria:

- U.S. Army combat battalions
- Single term of enlistment
- Minimum or 16 week of active duty time
- Served 18 months or more in the III Corps military region (includes Saigon) during 1967-1968 (heavy spraying in this year during these years)
- Military occupational specialty (MOS) other than "duty soldier" or "trainee"
- Discharged at pay grade E-5 or lower
- No deceased veterans (CDC, 1988, p. 1250)

The Agent Orange Validation Study cohort included the following non-Vietnam veterans:

- All who entered the U.S. Army between 1965 and 1971
- Sample of men interviewed near the end of the Vietnam Experience Study, but were not invited for the medical examination (see description above)
- Served in the continental United States or Germany

Three hundred and sixty-seven non-Vietnam veterans met the criteria above and were frequency-matched by race and age to the Vietnam veterans originally selected. Two hundred non-Vietnam veterans were invited to participate in both the telephone interview and the medical examination (CDC, 1988, p. 1250).

Demographics

The demographics (mean age, race, region of residence, smoking, alcohol use, mean BMI, and mean total serum lipid level) of the Vietnam veterans were not significantly different than those of the non-Vietnam veterans.

Many more Vietnam veterans self-reported direct herbicide exposure (25 percent) than non-Vietnam veterans (6 percent) and indirect herbicide exposure (71 percent and 6 percent,

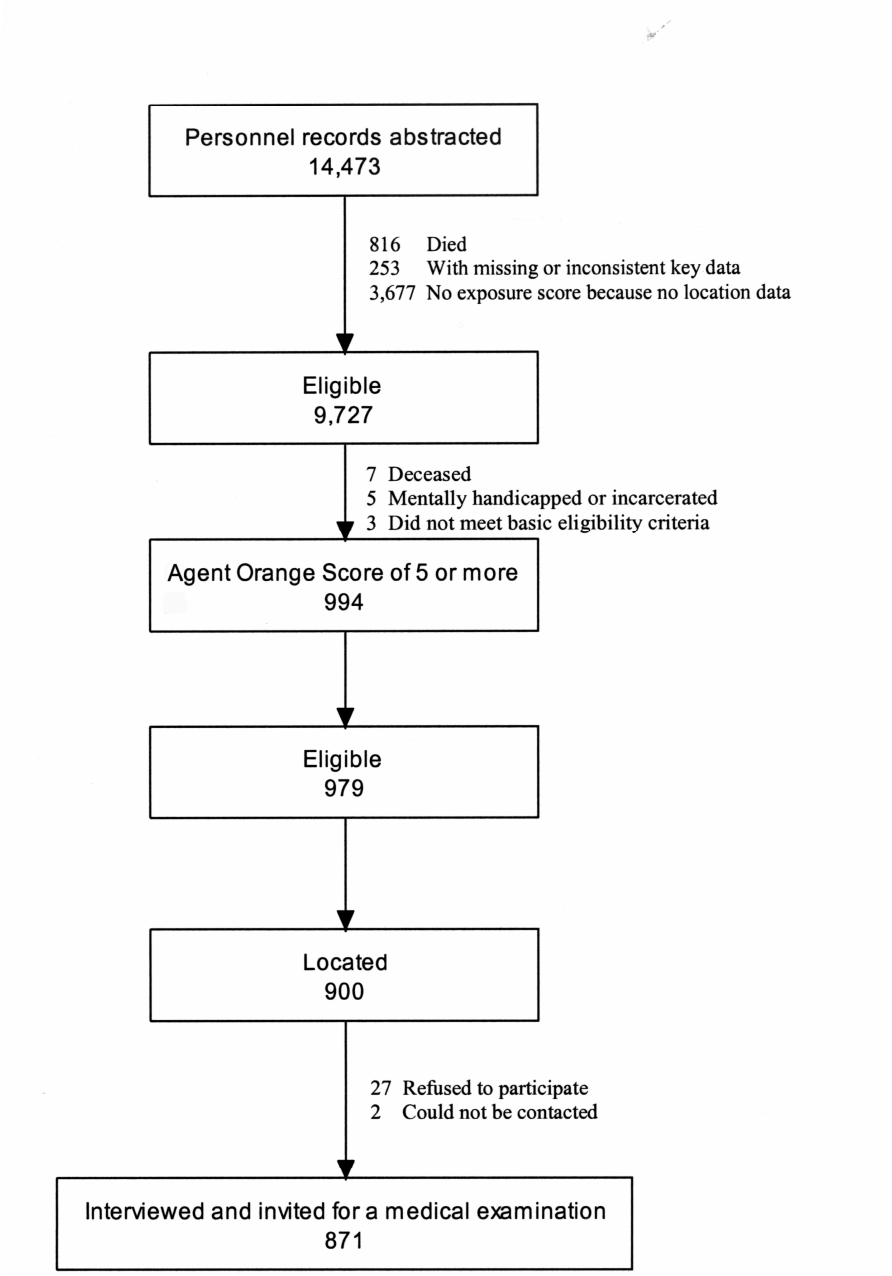

FIGURE K-2 Sample size of the Vietnam veterans in the Agent Orange Validation Study.
SOURCE: CDC, 1988, pp. 1250-1251.

respectively). However, fewer Vietnam veterans self-reported any civilian occupation or home use exposure to herbicides compared to non-Vietnam veterans (20 vs. 33 percent and 33 vs. 44 percent, respectively) (CDC, 1988).

Data from the Agent Orange Validation Study

Potential confounders A priori potential confounders are age, race, body mass index, and self-reported civilian occupational and home exposures to herbicides. Preliminary data analysis showed that smoking history, alcohol consumption, and region of residence are also potential confounders (CDC, 1988, p. 1251).

General methods The methods followed in this study are similar to those of the VES (see above). Briefly, RTI (and Equifax Inc, its subcontractor) located veterans and performed telephone interviews and the medical examinations were performed at the Lovelace Medical Foundation. The data were then abstracted by the U.S. Army and Joint Services Environmental Support Group (CDC, 1988, pp. 1249-1250).

Exposure data Dates and locations of herbicide sprays in South Vietnam for Operation Ranch Hand missions and other sprays were abstracted from military records. Military unit locations were abstracted from military and personnel records. These data were then used to access the herbicide locations of the exposed compared to the unexposed (CDC, 1988, p. 1249).

Exposure score The exposure score was calculated for each day of the study and for each company in 50 of the 65 battalions with abstractable data. The exposure score was calculated by 5 methods (CDC, 1988, p. 1250) as follows:

- Agent Orange intermediate score
  - "Weighted number of days on which at least one location for a company was within 2 km of a recorded Agent Orange spray within 6 days after the spray" (where the weight is the number of different sprays within 2 km of a company location)
  - Unknown intermediate scores are also calculated since some unknown agents are actually Agent Orange
- Agent Orange slow score
  - "Weighted number of days a company was within 2km of an Agent Orange spray after any earlier spray" (where the weight is the 5-year half life of Agent Orange)
  - Unknown slow scores are also calculated since some unknown agents are actually Agent Orange
- Number of days a company was in one of the five large, heavily sprayed regions
- Number of days of self-reported direct exposure during military service(spraying herbicide or being present during spraying, handling herbicide, getting herbicide on skin or clothing)
- Number of days of indirect exposure to herbicides during military service (walking through or clearing vegetation in a previously sprayed area) (from interviews)

Telephone interview Eight-hundred and seventy-one Vietnam veterans completed the interview. Men were asked about exposure to herbicides during military service, civilian work, and at home. Only 5 percent of Vietnam veterans reported spraying herbicides or handling spray equipment during military service (CDC, 1988, pp. 1251, 1254).

There were no significant differences in median current serum TCDD levels in the Vietnam veterans among those with low, medium, and high exposure scores, based on self-reported

indirect exposure (p = 0.08). However, there was a borderline significant difference based on self-reported direct exposure (p = 0.05) (CDC, 1988).

Medical examination The medical examination includes serum samples for TCDD measurements. Each participant fasted overnight; ate a low-fat, low-cholesterol breakfast; and the blood samples were collected 2 hours later. Current TCDD levels of Vietnam veterans are then compared to those of non-Vietnam veterans.

Six-hundred and sixty-five Vietnam veterans and 103 non-Vietnam veterans gave blood samples, and 646 of the samples in Vietnam veterans and 97 samples in non-Vietnam veterans had TCDD results that met laboratory quality control criteria.

Service in Vietnam was not associated with TCDD level after adjusting for age, race, region or residence, body mass index, smoking history, alcohol consumption, and reported civilian herbicide exposure (p = 0.23) (CDC, 1988, p. 1251).

Conclusions

"It seems . . . that most U.S. Army ground combat troops who did not handle or spray herbicides were not heavily exposed to TCDD in Vietnam" (CDC, 1988, p. 1254). "This study is consistent with other studies and suggests that most U.S. Army ground troops who served in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides" (CDC, 1988).

Strengths of the Agent Orange Validation Study are that there are

- no indications of selection bias or confounding; and
- participation rates were modest at 66 percent for Vietnam veterans and 48 percent for non-Vietnam veterans, but they were "unlikely to cause bias."

Limitations of the Agent Orange Validation Study are that it

- cannot be generalized to other Vietnam veterans since sample was not random;
- did not include veterans from the chemical corps, a relatively small group with a high potential for exposure; and
- military records could not only be used since "records may be unavailable for many of the herbicide applications most likely to have exposed troops" (CDC, 1988, pp. 1253, 1249).

Studies on Gulf War Veterans

For the purposes of this report, short summaries of CDC studies on Gulf War veterans were taken directly from the CDC website (http://www.cdc.gov/nceh/veterans/default2.htm) and provided below.

Health Effects of Exposure to Smoke from Oil Well Fires

> Researchers from the Centers for Disease Control and Prevention (CDC) and several other federal agencies conducted surveys of workers in Kuwait City in May 1991, and of firefighters in the oil fields in October 1991. Blood samples were tested for 31 volatile organic compounds (VOCs) and were compared with samples from a group of people

living in the United States. The samples from people living in the United States were collected as part of the Third National Health and Nutrition Examination Survey (NHANES III), a national survey of the health of Americans. The median concentration of VOCs among the firefighters was quite elevated. However, among the non-firefighting personnel, VOC con-centrations were equal to or lower than the levels found among the people living in the United States.

(http://www.cdc.gov/nceh/veterans/default2a.htm)

NCEH also collaborated with the U.S. Department of Defense on a study of 30 members of an Army unit located in Germany. Blood from these military personnel was tested for VOCs at three points in time: before, during, and after their deployment to Kuwait. Tetrachloroethylene, a compound found in degreas-ing agents used to clean equipment, was the only VOC found to be elevated.

(http://www.cdc.gov/nceh/veterans/default2a.htm)

Birth Defects

In 1994, CDC collaborated with the Mississippi Department of Health and the U.S. Department of Veterans Affairs to investigate reports of adverse birth out-comes among members of two Mississippi National Guard Units that served in the Gulf War. This investigation found no increase above expected rates in the total number of birth defects or in the frequency of premature births and low birth-weight babies. The frequency of other health problems, such as respiratory infections, gastroenteritis, and skin diseases among children born to these veterans also did not appear to be elevated.

(http://www.cdc.gov/nceh/veterans/default2b.htm)
(See also Penman et al., 1996)

In 1995, the Naval Health Research Center asked CDC to assist in a study of Goldenhar syndrome. Goldenhar syndrome is characterized by abnormal prenatal development of facial structures. Two clinicians from CDC reviewed birth records of 75,414 infants conceived after the Gulf War and born in military treatment facilities (34,069 infants born to Gulf War veterans and 41,345 born to nondeployed veterans). They identified five infants with Goldenhar syndrome who were born to Gulf War veterans and two infants born to nondeployed veterans. Because of the small number of cases found by the study, the statistical power of the study was low. It was not possible to conclude solely from this study whether there is a higher or lower risk for Goldenhar syndrome among infants born to Gulf War veterans.

(http://www.cdc.gov/nceh/veterans/default2b.htm)
(See also Araneta et al., 1997)

Air Force Study

Various members of a Pennsylvania Air National Guard unit reported illnesses potentially associated with their previous deployment to the Gulf War. in November 1994, the Pennsylvania State Health Department, the U.S. Department of Veteran Affairs, and the U.S. Department of Defense requested that CDC conduct an independent investigation of those illnesses. The investigation, carried out by CDC's National Center for Infectious Diseases, involved three phases:

1. Interviews with and examination of ill Gulf War veterans from the Air National Guard unit (the index unit) and review of medical records to verify and characterize illness
2. A survey of 3,723 military personnel from four Air Force units, including veterans who were and were not deployed to the Gulf War, to determine the relative prevalence of symptoms and to develop a working case definition of illness
3. A clinical evaluation of 158 Gulf War veterans from the index unit to further clinically characterize illness and to identify risk factors (by examination and laboratory tests)

(http://www.cdc.gov/nceh/veterans/default2c.htm)

A case was defined as a person having one or more chronic symptoms from at least two of three symptom categories (fatigue, mood-cognition, and musculoskeletal). A case was further classified as severe if each case-defining symptom was rated as severe; otherwise, the case was classified as mild-to-moderate. Cases were more likely to demonstrate poorer functioning, depression, and post-traumatic stress disorder. However, no consistent abnormalities were found by physical examination, routine laboratory tests, or tests for several infectious agents endemic to the Middle East. The prevalence of mild-to-moderate and severe cases was 39 percent and 6 percent, respectively, among Gulf War veterans versus 14 percent and 0.7 percent among nondeployed veterans. Fifty-nine (37 percent) clinically evaluated Gulf War veterans did not qualify as cases, 86 (54 percent) were mild-to-moderate cases, and 13 (8 percent) were severe cases. The investigators identified a chronic multisystem condition that was significantly associated with deployment to the Gulf War, but was not associated with specific Gulf War exposures, and that also affected nondeployed personnel.

(http://www.cdc.gov/nceh/veterans/default2c.htm)
(See also CDC, 1995; Fukuda et al., 1998; Nisenbaum et al., 2000)

Health Assessment of Gulf War Veterans from Iowa

In April 1994, Senator Tom Harkin of Iowa requested that CDC conduct a health assessment of Gulf War veterans his state. The study was initiated in December 1994 and was conducted through a cooperative agreement between the Iowa Department of Public Health and CDC's National Center for Environmental Health. The Iowa Department of Public Health contracted with investigators at the University of Iowa who took the lead in designing and conducting the study. From September 1995 through May 1996, a telephone survey was administered to 1,896 Gulf War veterans and to 1,799 military personnel who were not deployed to the Persian Gulf.

(http://www.cdc.gov/nceh/veterans/default2d.htm)

This was one of the first population-based epidemiologic studies to document that Gulf War veterans are reporting more medical and psychiatric conditions than their military peers.

(http://www.cdc.gov/nceh/veterans/default2d.htm)

The study identified several conditions that need to be studied in more detail, including cognitive dysfunction, depression, chronic fatigue, post-traumatic stress disorder, and respiratory illness (asthma and bronchitis). The conditions identified in this study appear to have measurably affected the functional activity and daily lives of these Gulf War veterans. However, these conditions may not be unique to Gulf War veterans and may be similar to the experience of veterans in other wars. Among Gulf War veterans, minimal

differences were observed between the National Guard or Reserve troops and the regular military personnel.

(http://www.cdc.gov/nceh/veterans/default2d.htm)

(See also Barrett et al., 2002; Black et al., 1999, 2000; Doebbeling et al., 2000, 2002; Iowa Persian Gulf Study Group, 1997; Zwerling et al., 2000)

Iowa Asthma Follow-Up Study

The original Iowa study was extended to collect physical examination data on a subset of the telephone survey participants to validate the self-report of asthma. Data were collected on 32 Gulf War veterans who reported asthma during the telephone survey, 42 Gulf War veterans who reported no illnesses during the tele-phone survey, and 20 non-Gulf War veterans who reported asthma during the telephone survey. The two groups of subjects with reported asthma were similar in symptoms, baseline pulmonary function tests, and bronchial hyperreactivity. The Gulf War veterans who reported asthma had significantly more current symptoms compared with the Gulf War veterans who reported no illness during the telephone survey. They also had comparatively lower baseline spirometry (a measure of how well the lungs exhale) and increased bronchial hyperreactivity. No differences in smoking history were found between the two groups with asthma. However, Gulf War veterans who reported asthma were more likely to be current and past smokers than the Gulf War veterans who did not report illness.

(http://www.cdc.gov/nceh/veterans/default2e.htm)

Cognitive Function and Symptom Patterns in Gulf War Veterans

In November 1997, CDC funded a study by the Boston University School of Public Health to examine potential reasons for the memory and thinking problems reported by Gulf War veterans. in one component of this study, functional magnetic resonance imaging (fMRI) was used to examine possible differences in brain activation patterns within specific areas of the brain. Gulf War veterans and their nondeployed peers with differing levels of symptoms were compared. in another component of this study, Danish armed forces personnel were tested to determine whether they are experiencing the same types of memory and thinking problems reported by U.S. troops who participated in the Gulf War. The Danish troops were also asked about any symptoms that they may be experiencing. Both Danish troops who participated in the Gulf War and troops who were not deployed to the Gulf War were tested. The results will be compared with results from a group of U.S. Gulf War veterans that the Boston University School of Public Health and the Boston VA Medical Center have been following since they returned from the Gulf War. Findings have been published regarding the neuropsychological functioning of the Danish Gulf War troops. No significant differences in neuropsychological test performances were found between the Gulf War-deployed and non-Gulf War-deployed groups. Danish troops deployed to the Gulf War reported significantly more mood complaints (i.e., fatigue and confusion) than their nondeployed counterparts. Publications are still pending for the fMRI component of this study.

(http://www.cdc.gov/nceh/veterans/default2f.htm)

(See also Proctor et al., 2003)

Defining Gulf War Illness

In November 1997, CDC funded a study to characterize and compare different approaches for defining the medically unexplained illnesses of Gulf War veterans. This study by the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School compared the symptoms of two groups of Gulf War veterans at two points in time. The study subjects included Gulf War veterans from the Department of Veterans Affairs' Gulf War Registry who had participated in a previous study conducted by the New Jersey researchers, and veterans who had participated in the CDC Air Force study. Data-driven case definitions for illness previously derived from these two groups of Gulf War veterans were compared with standard or existing case definitions for unexplained multi-symptom illnesses (such as chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity) to determine which definition best characterized Gulf War veterans' unexplained illnesses. The study also tried to determine how well the derived and existing case definitions could be generalized in a new random sample of deployed and nondeployed Gulf War era veterans and active duty soldiers. The investigators are preparing manuscripts for publication which are expected by the end of 2005.

(http://www.cdc.gov/nceh/veterans/default2g.htm)

Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members

This study, initiated in 1999, involved a collaborative effort of health researchers from the United States (U.S. Department of Defense and CDC) and Saudi Arabia. The team examined hospitalization data for 15,612 Saudi Arabia National Guard (SANG) troops. The goal of this study was to compare hospitalization rates and health outcomes among a group of SANG soldiers who were stationed in a combat area in January 1991 (Al Khafji) with soldiers who were stationed in a non-combat area (Riyadh). The investigators identified 148 SANG soldiers who had at least one hospitalization between 1991 and 1999. The adjusted rate of hospitalization was higher in the combat-exposed group (risk ratio = 1.80, 95% confidence interval = 1.25-2.59). No unusual patterns of diagnoses were found. Because the overall number of hospitalizations was low, the absolute difference in risk was found to be very small.

(http://www.cdc.gov/nceh/veterans/default2h.htm)
(See also Gackstetter et al., 2005; Hooper et al., 2005)

Epidemiologic Study of the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans

In June 1999, the Department of Veterans Affairs and U.S. Department of Defense requested that CDC assist in a study of amyotrophic lateral sclerosis (ALS) among Gulf War veterans. ALS is a fatal neurodegenerative disease that destroys the brain and spinal cord nerve cells that control muscle movement. As the brain and spinal cord nerve cells die, muscles weaken and shrink, and rapid severe paralysis occurs. Neither a cause nor a cure for ALS is known at this time. This investigation of ALS was initiated to determine if there is a higher than expected incidence of ALS among veterans of the 1991 Gulf War and to examine possible risk factors for the disease. CDC's Environmental Health Laboratory conducted laboratory analyses of blood and urine specimens to look for signs of exposure to heavy metals. Initial results found military personnel who were deployed to the Gulf region during the 1991 Gulf War experienced a greater post-war risk of ALS

than those who were not deployed to the Gulf. Among approximately 2.5 million eligible military personnel, 107 confirmed cases of ALS were identified (an overall occurrence of 0.43 per 100,000 persons per year). Overall, the attributable risk associated with deployment was 18 percent (95% CI = 4.9 to 29.4%). Findings regarding exposure to heavy metals are pending.

(http://www.cdc.gov/nceh/veterans/default2i.htm)
(See also Horner et al., 2003)

Deployment to the Gulf War and Subsequent Development of Cancer

In 2002, George Washington University School of Public Health and Health Services began a study to determine if cancer patterns among veterans of the 1991 Gulf War veterans differ from the patterns found among Gulf War era veterans not deployed to the Persian Gulf. CDC and the Association of Schools of Public Health funded the study. Initial work by the study investigators using data from the District of Columbia and the New Jersey Cancer Registries found a statistically significant excess of testicular cancer in Gulf War deployed veterans compared to non-Gulf War veterans. The current study is focusing on extending the analysis to include cancer data from additional states. These states include Texas, California, Florida, New York, Maryland, and Illinois. This study is expected to continue through July 2005.

(http://www.cdc.gov/nceh/veterans/default2j.htm)
(See also Levine et al., 2005)

Gulf War Research Planning Conference

In early 1999, CDC helped sponsor *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*. The U.S. Department of Health and Human Services' Office of Public Health and Science, the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry cosponsored the conference with CDC. The intent was to obtain broad public input into the development of a multi-year research plan for investigating the relationship between chemical exposures during the Gulf War and illnesses affecting Gulf War veterans. Concurrent workgroups developed research recommendations in the following areas:

- Pathophysiology/etiology of illnesses among Gulf War veterans
- The most appropriate methods for assessing and diagnosing the health effects of chemical exposures
- The most appropriate treatment approaches
- Ways to prevent similar illnesses in future military deployments

(http://www.cdc.gov/nceh/veterans/default2k.htm)

A final report summarizing conference recommendations was released in March 2000 and is accessible at http://www.cdc.gov/nceh/publications/gulfwar/report.pdf. The background document prepared for the conference that reviews Gulf War-related research conducted before 1999 is accessible at http://www.cdc.gov/nceh/publications/gulfwar/bdgw65.pdf.

Web Based Central Library (Medsearch)

CDC, the U.S. Department of Defense's Deployment Health Support Directorate, and the Department of Veterans Affairs collaborated to create a centralized Internet site, known

as Medsearch. Veterans and members of the armed forces can visit the site to find information on Gulf War-related medical research developed by or for government agencies. The idea for the online medical library came from a recommendation at a CDC conference in 1999. The conference participants called for a central location where both veterans and researchers could access the latest research on illnesses among Gulf War veterans. The Internet site developers worked with veterans and researchers to ensure that Medsearch is easy to use. Many of the documents available on Medsearch are written in nontechnical language. Medsearch can be accessed at http://www.gulflink.osd.mil/medsearch.

(http://www.cdc.gov/nceh/veterans/default2l.htm)

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APPENDIX K-4

SELECTED STUDIES ON VETERANS FROM THE CRISP DATABASE[4]

(Table follows.)

[4] Not intended to be a comprehensive list. See http://crisp.cit.nih.gov for additional projects.

Primary Investigator	Project Name	Grant Number	Start Date	End Date
Beebe, G	Hepatitis B Virus and Liver Cancer in Army Veterans of WW II	1Z01CP005329-11		
Doebbeling, Bradley	Illness Among Persian Gulf War Veterans: Case Validation	5M01RR000059-411069		
Dohrenwend, Bruce	Social Status and PTSD in U.S. Vietnam Veterans	5R01MH059309-03	9/28/1999	12/1/2003
Giardina, Charles	Mustard Gas Exposure and Carcinogenesis of the Lung	1R21ES013775-01		
Golier, Julia	Psychobiologic Alterations in Persian Gulf War Veterans With/Without PTSD	5M01RR000071-400470	6/22/1905	
Haley, Robert	Pathophysiologic Studies of Ill Gulf War Veterans and Controls	5M01RR000633-310606	6/21/1905	
Hrubec, Zdenek	Resource Support of Medical Studies on Veteran Twins	5R01MH018820-04	4/1/1970	3/31/1974
Jablon, Seymour	Epidemiologic Studies in Etiology of Cancer in Veterans	3N01CP04333600174	6/28/1974	
Jerskey, Beth	Combat Trauma and Mid-Life Marital Outcomes: A Twin Study	5F31MH071017-02	3/1/2004	6/30/2005
King, Daniel	PTSD and Its Etiology: A Quintet of Inquiries	1R01MH049168-01	6/1/1992	5/31/1995
Laufer, Robert	A Study of Veterans: Impact of The Vietnam War	3R01MH026832-06S1	9/1/1980	12/31/1984
Lee, Chulhee	Exposure to Disease During Growing Ages and War Service	5P01AG010120-100001		
Linet, M	Studies of Radiation Related Cancer	1Z01CP010102-01		
McCaffery, Jeanne	SES, Health Behaviors and CVD Among Vietnam-Era-Twins	5R01HL072819-02	6/1/2004	5/31/2007
Murphy, Ronald	Combat Exposure, Early Trauma, and Alcohol Problems	1R03AA010027-01	5/1/1994	4/30/1996

Primary Investigator	Project Name	Grant Number	Start Date	End Date
Norman, James	Hepatitis "B" Virus and Liver Cancer in Veterans	5N01CP031021-00783	6/30/1983	
Page, William	Cancer in Navy Korean War Microwave (Radar) Workers	3N01CP040536-00694	9/15/1994	10/31/1997
Page, William	Studies of Cancer in Veteran Twin Registry	5N01CP015690-00591	3/15/1991	3/14/1994
Pitman, Roger	Twin Study of Biologic Markers for PTSD	5R01MH054636-09	9/30/1995	5/31/2007
Robinette, C	Studies of Cancer in Veteran Twin Registry	3N01CP015690-00191	3/15/1991	
Rose, Kathryn	Combat Stress and Cardiovascular Risk Among Aging Men	1R21HL080422-01A1	9/31/2006	11/30/2007
Schmidt, Silke	Genetic Epidemiology of ALS in Veterans	5R01ES013244-03	8/19/2004	6/30/2009
Schwartz, David	Iowa Persian Gulf Research Project: Follow-Up Study on Asthma	5M01RR000059-411045	12/1/2001	11/30/2002
Scrimshaw, Nevin	Exposure to Disease During Growing Ages and War Service	3P01AG010120-08S20001		
Tanner, Caroline	Genes, Environment and Parkinson's Disease: Studies in Four Unique Cohorts	1U54ES012077-010001	8/26/2002	7/31/2007
Vaccarino, L	Posttraumatic Stress Disorder and Cardiovascular	5R01AG026255-03		
Vandenborne, Krista	Evaluation of Muscle Function in Persian Gulf Veterans	5M01RR000040-420711	12/1/2001	11/30/2002
Vernon, Sally	A Cancer Study Among Female Veterans in Texas, 1979-2001	5R03CA103512-02	9/30/2004	8/31/2006
Yehuda, Rachel	Psychobiological Alterations in Aging Combat Veterans w/PTSD	5M01RR000071-400427		

SOURCE: Crisp Database, http://crisp.cit.nih.gov/.

Appendix L

Additional Classification and Secrecy Information

APPENDIX L-1

HISTORY OF RADIATION STUDIES CLASSIFICATION

The following paragraphs are excerpted from the ACHRE Report, Chapter 13 (1995):

> The Manhattan Project's "Security Manual" followed the Army rules, requiring classification of information as Confidential, and even at the higher level of Secret, in the absence of likely harm to national security (Manhattan Engineer District, 1945). Before the end of World War II, therefore, there was precedent for using the classification system to do more than protect national security.
>
> (p. 2)

> The era of atomic energy presented the government with unique questions of secrecy. The government built the atomic bomb behind an extraordinary shield of wartime secrecy. The very existence of the newly created communities surrounding AEC laboratories in Los Alamos, New Mexico; Hanford, Washington; and Oak Ridge, Tennessee; was a secret. Children at Oak Ridge schools did not use their full names, and houseguests were introduced as "Mr. Smith" (Warren, 1966). Following the Hiroshima bombing, the government faced the somewhat paradoxical task of protecting its single most important military secret while having to inform the public, if not the world, about both the hazards and peacetime spin-offs that the creation of the bomb had engendered—from radiation fallout and waste to nuclear power and radioisotopes for medical research and treatment.
>
> (p. 2)

> At the war's end, a committee (known after its chair as the Tolman Committee) convened to determine what information from the Manhattan Project should be declassified. In its report, the Tolman Committee concluded that "in the interest of national welfare it might seem that nearly all information should be released at once" (Committee on Declassification to Major General L. R. Groves, 1945). But national welfare had to be considered in light of national security. Still, "it is not the conviction of the [Tolman] Committee that the concealment of scientific information can in any long term contribute to the national security of the United States" (Committee on Declassification to Major General L. R. Groves, 1945). The progress of science, the committee reasoned, depends on the free flow of information, and long-term national security depends on the progress of science.

In the short term, however, the security of the nation required some secrecy. Thus, the Tolman Committee concluded that secrecy could be justified for reasons of national security and then only if "there is a likelihood of war within the next five or ten years" (Committee on Declassification to Major General L. R. Groves, 1945). Applying this general philosophy to the question of secrecy in medical research, it recommended that "all reports on medical research and all health studies" be immediately declassified except for those reports that contained information independently classified in the interest of short-term national security (Committee on Declassification to Major General L. R. Groves, 1945).

(p. 2)

While the Tolman Committee report generally advocated openness, it also set the precedent for keeping declassification guides secret. The report recommended that "the whole of the Declassification Guide should not, however, be generally distributed since it gives an overall picture of the whole project and makes mention in certain instances of extremely secret matters. The portions of the Declassification Guide needed for the work of anyone concerned with declassification should be made available" (Committee on Declassification to Major General L. R. Groves, 1945). By following this recommendation, the AEC, and later the Department of Energy, would keep from the public the ever-accumulating rules governing weapons-related information. Indeed, the first three declassification guides covering information on nuclear weapons, published in 1946, 1948, and 1950, were declassified only in 1995 (Manhattan Engineer District, 1946; Atomic Energy Commission, 1948, 1950).

(p. 2)

In 1946 Congress enacted the Atomic Energy Act, which, in creating the AEC, expressly addressed the protection of atomic energy information. The act provided that all information related to atomic energy was to be considered as Restricted Data (RD) until the AEC reviewed it and decided that it should be unprotected (RD was, therefore, said to be "born secret"). The act prohibited the unauthorized disclosure of RD (making it a capital crime to do so in the course of espionage) and prohibited anyone from receiving access to it without first receiving a security clearance. At the same time, however, the act instructed the AEC not to protect information if the AEC did not consider its disclosure harmful to the national security. Thus, the statute defined RD to mean "all data concerning the manufacture or utilization of atomic weapons, the production of fissionable material, or the use of fissionable material in the production of power, *but shall not include any data which the Commission from time to time determines may be published without adversely affecting the common defense and security*" (Atomic Energy Act, 1954).

(p. 2), [emphasis added]

When it began operation in 1947, the AEC was heir to two traditions: one in which official secrets could extend beyond national security to matters of prestige and another in which the interest in promoting openness and limiting secrecy to matters of national security was recognized. In public, AEC biomedical officials and advisers advocated the latter policy. In secret they embraced the former and even expanded it to encompass "embarrassment." Through as late as 1949, the declassification of reports on human experiments involved their review for public relations and legal liability implications. Documents revealing the dual tracks of public policy making and the secret review process did not become public until 1994. Important pieces of the story remain unclear, including the way in which AEC officials and advisers reconciled seemingly contrary principles.

(p. 3)

> . . . [W]hen Manhattan Project medical official Hymer Friedell recommended in late 1946 that one of the reports on the plutonium injection experiments be declassified, officials inside the new AEC reacted strongly. On March 19, 1947, AEC Medical Division chief Major B. M. Brundage countermanded the declassification decision, on grounds of "public relations." The plutonium report produced the strongest reaction, but it was not the only report on human data at issue. Brundage's March 19 memo also stated that further reports ("Studies of Human Exposure to Uranium Compounds" and "Uranium Excretion Studies") should remain classified. On March 21, an AEC declassification officer confirmed the reclassification on the ground that "these documents may involve matters prejudicial to the best interests of the Atomic Energy Commission in that experiments with humans are involved." The memo expressed hope that "a definite policy in this matter will be announced or explained in the near future" (Batson, 1947).
>
> (p. 3)

> In April 1947 that hope was partly fulfilled when Colonel O. G. Haywood of the Corps of Engineers wrote to H. A. Fidler, an AEC information officer, that "it is desired that no document be released which refers to experiments with humans and might have adverse effects on public opinion or result in legal suits. Documents covering such work should be classified as secret" (Haywood, 1947).
>
> (p. 3)

References

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Atomic Energy Commission. 1950. *Declassification guide for responsible reviewers.* ACHRE No. DOE-052595-B.

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Haywood, O. G. 1947. *Medical experiments on humans.* ACHRE No. DOE-051094-A-62. Memo to H. A. Fidler.

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APPENDIX L-2

LEVELS OF CLASSIFICATION, FROM PIKE, 2002

Unclassified—Limited: "the distribution category applied to the a wide range of unclassified types of official information, which although not requiring protection as National Security Information, is limited to official use and not publicly releasable. Other similar markings, such as For Official Use Only (FOUO) and Limited Official Use are not used to identify classified in-

formation . . . six Distribution Statements designated A through F, were approved establishing categories of Unclassified/Limited Data" (Pike, 2002):

A. Approved for Public Release: "available to the public, foreign nationals, companies, foreign governments, and may be exported without a license"
B. Limited to Government Agencies: "covers weapons test and evaluation data, contractor performance evaluation records, foreign government data and proprietary information"
C. Limited to Government Agencies and Their Contractors: involves "critical technologies which advance the state of the art in an area of significant or potentially significant military application"
D. Limited to DoD and DoD Contractors Only: "designed to protect information on system or hardware in the development of concept stage, which must be protected to prevent premature dissemination"
E. Distribution to DoD Components Only
F. Further Dissemination Only as Directed: "normally imposed only on classified documents, but may be used on unclassified documents where specific authority exists"

Information or material that requires additional protection against unauthorized disclosure in the interest of national security is classified in one of three designations namely: Top Secret, Secret or Confidential.

Confidential (C) is applied to information or material the unauthorized disclosure of which reasonably could be expected to cause damage to the national security. Examples of damage include the compromise of information that indicates strength of ground, air, and naval forces in the United States and overseas areas; disclosure of technical information used for training, maintenance, and inspection of classified munitions of war; revelation of performance characteristics, test data, design and production data on munitions of war.

Secret (S) is applied to information or material the unauthorized disclosure of which reasonably could be expected to cause serious damage to the national security. Examples of serious damage include disruption of foreign relations significantly affecting the national security; significant impairment of a program or policy directly related to the national security; revelation of significant military plans or intelligence operations; compromise of significant military plans or intelligence operations; and compromise of significant scientific or technological developments relating to national security.

Top Secret (TS) is applied to information or material the unauthorized disclosure of which reasonably could be expected to cause exceptionally grave damage to the national security. Examples of exceptionally grave damage include armed hostilities against the United States or its allies; disruption of foreign relations vitally affecting the national securely; the compromise of vital national defense plans or complex cryptology and communications intelligence systems; the revelation of sensitive intelligence operations, and the disclosure of scientific or technological developments vital to national security.

Special Access Program (SAP) is any program which imposes need-to-know or access controls beyond those normally required for access to Confidential, Secret, or Top Secret information. It is the policy of the Department of Defense to use security classification

categories to limit access to classified information on a need-to-know basis to personnel who have been determined to be trustworthy, and to apply the need-to-know principle in the regular system so that there will be no need to resort to formal Special Access Programs. Also, need-to-know control principles shall be applied within Special Access Programs. In this context Special Access Programs may be created or continued only on specific showing that normal management and safeguarding procedures are not sufficient to limit need-to-know or access, and the number of persons who need access will be reasonably small and commensurate with the objective of providing extra protection for the information involved. Each Special Access Program is assigned a classified code word, or an unclassified nickname, or both.

Sensitive Compartmented Information (SCI) is information and material that requires special controls for restricted handling within compartmented intelligence systems and for which Code Word compartmentation is established. Special Activity is an activity, or functions in support of such activity, conducted in support of national foreign policy objectives abroad that is planned and executed so that the role of the U.S. Government is neither apparent nor acknowledged publicly; but that is not intended to influence U.S. political processes, public opinion, polices, or media and does not include diplomatic activities or the collection and production of intelligence or related support functions.

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Pike, J. 2002. *Security and classification*. Gloucester, MA: Granite Island Group, Technical Surveillance Counter Measures. http://www.tscm.com/classification.html (accessed April 10, 2007).

APPENDIX L-3

NUREMBERG CODE OF 1947

Trials of War Criminals before the Nuremberg Military Tribunals, 1949; Nuremberg Code, 1947; Office on NIH History, Office of Intramural Research:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the natures, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests with each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problems under study that the anticipated results [will] justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians will also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even the remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

References

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Trials of war criminals before the Nuremberg military tribunals. 1949. *Control Council Law* 10(2):181-182. http://www.copernicusgroup.com/irbForms/NurembergCode.pdf (accessed March 7, 2007).

APPENDIX L-4

EXCERPTS FROM TAYLOR AND JOHNSON, 1975

This report was the result of a request to the Inspector General and Auditor General of the Department of the Army (DoA) by the Secretary of the Army to research the use and treatment of human volunteers in chemical agent research. The request was prompted by congressional inquiries, during 1975 and 1976, by the Senate Select Committee on Intel-

ligence Activities and joint hearings by the Senate's Labor and Public Welfare Committee and the Judiciary Committee, individual Members of Congress, private citizens, and the press regarding the use of human volunteers in testing of hallucinogenic substances in DoA chemical warfare research. Although the report focused largely on psychochemical testing programs and on testing programs from approximately 1950 to 1975, it also related certain specific aspects of the history of chemical warfare research in regards to treatment of human volunteers and general attitudes toward and compliance with the Nuremberg Codes of 1947. The major conclusion of these authors was that the secrecy, applied to the projects, to the overall research program, and even to the official guidelines governing use of human volunteers, left ample room for misinterpretation, lack of knowledge about, and outright disregard for established policies and guidelines.

The June 1942 request for human volunteers to the Secretary of War, and its subsequent approval, gave authority to the War Department to use human volunteers in the World War II sulfur mustard and Lewisite testing programs. The approval of this request became the basis on which such authority was retained by the Army and the Chemical Warfare Service to use human volunteers in all other World War II and later testing programs up to the mid 1950s. In July 1950, research was placed under the control of the Army by the Organization of the Army Act. Despite the establishment in 1947 of the Nuremberg Codes regarding the appropriate use and treatment of human subjects in research, Taylor and Johnson reported that no documentation could be found about whether the Army was explicitly bound by the Codes. By 1952, the Armed Forces Medical Policy Council filed a request to use human subjects and suggested that the Nuremberg Codes be used as guidelines.

The possible guidelines were discussed at a meeting at Edgewood Arsenal in March 1953. Recommendations were made at the conference that distinctions be made between hazardous and non-hazardous test situations so that non-hazardous procedures/tests would not require approval of the human-use research protocols. The examples given for non-hazardous situations were training exercises in which men, equipped with gas masks, went through gas chambers filled with high concentrations of sulfur mustard. A further proposal was that any human-use codes based on the Nuremberg Codes should only apply to biological warfare testing, not to chemical or radiological testing. This proposal was rejected.

Formalized guidelines were finally issued in June 1953 in a Chief of Staff Memo (MM385). These guidelines represented an official adoption of the Nuremberg Codes (although somewhat modified) and were meant to apply to all types of chemical, radiological, and biological warfare testing. Further, they required all projects to be approved by the Secretary of the Army. However, no detailed descriptions of what types of experiments required this approval were included, and the report authors argue later that this was a "loophole" that permitted "selective compliance" with the guidelines. For example, in August 1953 seven research projects were sent for approval, one on vesicants and other agents, one on phosgene, and five on nerve agents. Not sent for approval was a research project labeled a "local field exercise" at Fort McClellan, Alabama (Operation TOP HAT). This operation involved use of Chemical Corps personnel in tests of decontamination methods for biological warfare agents, sulfur mustard, and nerve gases. These personnel were not informed and were not volunteers. The justification for the lack of a request for approval was that the project fell under the "line of duty" definition and was not subject to protocol approval.

Another example given by Taylor and Johnson pointed out that protocols were often submitted to test a class of drugs, rather than a specific drug at defined dosage levels. One project entitled, "Retention of Nerve Gas in the Human Respiratory Tract" was given only a cursory examination prior to approval, despite the fact that the specific nerve agents to be used were not listed in the proposal. By 1955, when research into psychochemicals began, approvals were still being given for general research types and not for specific protocols. In 1957, more potent nerve agents were being tested, but the protocols for this research were not sent for examination and approval on the justification that they were simply extensions of projects already approved years earlier. By 1959, Secretary of the Army Brucker gave blanket approval for all projects utilizing "non-lethal incapacitating agents," and the period between 1959 and 1975 was typified by great inconsistency in policy and practices relating to research with human volunteers. The situation became so bad, and the outcry from Congress, the press, and the citizenry so intense, that all research with human volunteers was suspended in 1975 by Acting Secretary of the Army Norman Augustine.

References

Taylor, J. R., and W. N. Johnson. 1975. *Research report concerning the use of volunteers in chemical agent research.* DAIG-IN 21-75. Washington, DC: Department of the Army, Office of the Inspector General and Auditor General.

APPENDIX L-5

EXCERPTS FROM IOM, 1993

The lack of exposure data for the WWII human subjects caused the committee to attempt to gather as much information as possible about the experimental protocols, the equipment used, and any injuries from official reports of the testing programs. The committee found that an atmosphere of lingering secrecy still existed in the Department of Defense regarding some of the testing programs. Reports of the specific experimental protocols were not always easy to obtain; in some cases, reports were not available or were obtained as the study was almost complete. Fortunately, enough information was gathered to allow reasonable estimates of the exposures to human subjects, who were repeatedly exposed to mustard agents and Lewisite in gas chamber tests or under so-called field conditions.

(pp. vi-vii)

As the full scope of the WWII testing protocols was revealed, compelling ethical questions emerged. At times, it seemed as if every new discovery only posed more questions. As the study progressed, the bits and pieces of information finally coalesced into a picture of abuse and neglect that was impossible for the committee to ignore. One of the first discoveries was that the end point of all the WWII mustard agent and Lewisite experiments was tissue injury—from mild skin burns to severe, and widespread, skin burns that took more than a month to heal. The chamber and field tests were actually called "man-break" tests.

(p. vii)

Both veteran self-reports and official documents revealed that some subjects suffered damaging injuries to the lungs and upper respiratory system from inhalation of the agents. Committee analysis of expected gas mask efficiencies further showed that projected nor-

mal mask leakage under the hot, humid conditions of the gas chambers would have, in some cases, resulted in exposure levels as high as those reported on World War I battlefields.

(p. vii)

The first response of many of the committee members to these discoveries was to try to understand the actions of the investigators in historical context—it was a war and the experiments were conducted before the Nuremberg Code of 1947 established formal principles to govern the proper treatment of human subjects. However, examination of the treatment and care of WWII chemical warfare production workers, and the conduct of later military experiments with human subjects from 1950 to 1975, demonstrated a well-ingrained pattern of abuse and neglect. Although the human subjects were called "volunteers," it was clear from the official reports that recruitment of the WWII human subjects, as well as many of those in later experiments, was accomplished through lies and half-truths.

(p. vii)

Most appalling was the fact that no formal long-term follow-up medical care or monitoring was provided for any of the WWII human subjects, other exposed military personnel, or chemical warfare production workers, despite knowledge available by 1933 that mustard agents and Lewisite could produce long-term debilitating health problems, particularly in those people suffering severe burns and inhalation injuries. There was not even adequate short-term follow-up of the human subjects by the Department of Defense. Subjects in the chamber tests were sworn to secrecy and simply released on leave at the conclusion of the experiments. Some of these men still had blisters or evidence of skin burns upon release, but were not given any instructions about how to obtain knowledgeable medical care if they had needed it.

(p. vii)

Although the experiments began in a wartime climate of urgency and secrecy, it was clearly a mistake in this case to continue the secrecy after the conclusion of the war. Follow-up of the exposed human subjects could have provided a wealth of information on the effects of these war gases and could have served as a basis for legitimate disability claims by injured subjects. By the end of the war, the use of nitrogen mustard as a chemotherapeutic agent (developed as part of the WWII testing program) clearly showed the serious health effects that the previous "volunteers" might be expected to experience.

(p. viii)

In the face of the abuses uncovered, the committee members nevertheless sought to maintain an appropriate balance of their scientific responsibilities in assessing the available literature and their ethical responsibilities as physicians and scientists. In this effort, the committee members were guided by their stated task and their own individual judgments of the scientific and historical information examined. Thus, the committee believes that the findings and recommendations contained in this report are entirely justified by the scientific, medical, and historical evidence examined. There are, however, specific statements the committee wishes to offer as commentary on its findings.

(p. viii)

First, the committee believes that each veteran who served as a human subject in the WWII experiments deserves honor for his sacrifice. These men risked their health and safety to help develop better means of protection against chemical warfare. Yet, in most

> cases, their participation in these experiments was not even acknowledged in their service records and was, in fact, officially denied for decades. Further, these men were ordered to keep their participation secret. They did so for nearly 50 years, in some cases despite serious, disabling diseases that they believed were caused by their exposures. There can be no question that some veterans, who served our country with honor and at great personal cost were mistreated twice—first, in the secret testing and second, by the official denials that lasted for decades. They deserve recognition.
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> (p. viii)

> Second, the committee believes that any future military research with human subjects should be conducted according to publicly established ethical principles similar to those that apply to civilian research. The Department of Defense should consider including civilian medical experts in reviews of all proposed military research protocols involving human subjects. As was shown in the examination and evaluation by the Department of the Army Inspector General's report of the military drug and chemical testing programs from 1950 to 1975 . . . a climate of secrecy provides a permissive environment for the neglect of established rules of conduct. Such neglect should never be allowed to occur when human experimentation is involved.
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> (pp. viii-ix)

References

IOM (Institution of Medicine). 1993. *Veterans at risk: The health effects of mustard gas and lewisite*. Washington, DC: National Academy Press.

Appendix M

Biographical Sketches of Committee Members, Consultants, and Staff

Jonathan M. Samet, M.D., M.S. (*Chair*), is a professor and the Chair of the Department of Epidemiology of the Johns Hopkins University's Bloomberg School of Public Health. Dr. Samet also has joint Johns Hopkins' appointments in the Department of Medicine and the Oncology Center, and serves as the Director of the Institute for Global Tobacco Control and as the Co-Director for the Risk Sciences and Public Policy Institute. Before coming to Johns Hopkins, he was Professor and Chief of the Pulmonary and Critical Care Division in the Department of Medicine of the University of New Mexico School of Medicine. His research has emphasized the assessment of health effects of environmental pollutants using epidemiological approaches. His work addressing indoor and outdoor air pollution and occupational exposures, including asbestos and radon, has made use of risk assessment methods as a tool for translation of scientific findings into policy. Dr. Samet received his M.D. from the University of Rochester's School of Medicine and Dentistry and his M.S. from the Harvard School of Public Health. He interned at the University of Kentucky Medical Center and then served in the U.S. Army as an anesthesiologist at Gorgas Hospital (Balboa Heights, Canal Zone) from 1971 to 1973. Following his military service, Dr. Samet completed his internal medicine residency in Medicine at the University of New Mexico and then a research and clinical fellowship at Harvard Medical School's Channing Laboratory. He is board certified in internal medicine and the subspecialty of pulmonary medicine. Dr. Samet was elected to the Institute of Medicine in 1997 (Section 9) and has served as a member and chair of numerous committees for the National Academies. He currently chairs the Board on Environmental Studies and Toxicology. In addition, he is a member of the Committee on Science, Technology, and Law.

Margaret A. Berger, J.D., is the Suzanne J. and Norman Miles Professor of Law at Brooklyn Law School. Professor Berger's research interests focus on scientific evidentiary issues, and she has contributed to the field of postadmission legal education by developing new approaches to the judicial treatment of scientific evidence. She has authored numerous briefs, articles, chapters in books, and books which address the topic of the admissibility and interpretation of scientific evidence. Professor Berger holds a J.D. from Columbia University School of Law. She has held membership positions on the National Academies' Committees on Tagging Smokeless and Black Powder and the Committee on DNA Technology in Forensic Science: An Update. Professor Berger is currently a member of the National Academies' Committee on Science, Technology,

and Law and co-chairs a subcommittee on the Reference Manual on Scientific Evidence. She also serves on a National Academy Committee on Identifying the Needs of the Forensic Science Community, and on a Committee on Assuring the Integrity of Research Data.

Kirsten Bibbins-Domingo, Ph.D., M.D., MAS-CR, is an Assistant Professor of Medicine and of Epidemiology and Biostatistics at the University of California, San Francisco (UCSF). She is the co-director of the UCSF Center for Vulnerable Populations and an attending physician at San Francisco General Hospital. Dr. Bibbins-Domingo received her A.B. from Princeton University and her Ph.D. in biochemistry, her M.D. and her Masters of Clinical Research from UCSF. She completed her residency in internal medicine at UCSF that included training at the San Francisco Veterans Administration Medical Center (SFVAMC) and continues to have several active collaborations with researchers in epidemiology and health services at the SFVAMC. Dr. Bibbins-Domingo's research interests include the epidemiology of cardiovascular disease, race and gender health and health-care disparities, and the quality of cardiovascular care, particularly heart failure disease management. She has published original research on the development of risk factors for cardiovascular disease, including diabetes, impaired kidney function, and high blood pressure, as well as the use of novel biomarkers as diagnostic and screening tests for cardiovascular disease.

Eric G. Bing, M.D., Ph.D., M.P.H., is the Endowed Professor of Global Health and HIV Research at the Charles Drew University of Medicine and Science in Los Angeles. He is the Director of the Drew Center for AIDS Research, Education and Services (Drew CARES), the Institute for Community Health Research and co-director of the Center for HIV Identification, Prevention and Treatment Services (CHIPTS). Dr. Bing's research interests include mental health care, substance abuse treatment, community mobilization, service systems, and HIV prevention research in civilian and military settings in the United States and abroad. He works with militaries in multiple countries in developing disease prevention programs for soldiers. Dr. Bing received his M.D. from Harvard Medical School and his M.P.H. and Ph.D. in epidemiology from the University of California, Los Angeles's (UCLA's) School of Public Health. He completed his psychiatric training at the UCLA Neuropsychiatric Institute/West Los Angeles VA Medical Center. Dr. Bing served as a member of the National Academies' Ryan White CARE Act committee.

Bernard D. Goldstein, M.D., is the former Dean of the University of Pittsburgh's Graduate School of Public Health and remains active as a professor in the Department of Environmental and Occupational Health. Dr. Goldstein's research interests include risk assessment, toxicology, workplace hazards, internal medicine, preventive medicine, occupational and environmental medicine, and environmental health policy. He has conducted research on air quality and leukemia and various aspects of public health decision making. Dr. Goldstein was the founder and former Director of the Environmental and Occupational Sciences Institute at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School. Dr. Goldstein also served as Assistant Administrator for Research and Development at the U.S. Environmental Protection Agency. He received his M.D. from the New York University School of Medicine. Dr. Goldstein was elected to the Institute of Medicine in 1991 (Section 9) and has served as a member and chair of numerous committees for the National Academies which address subjects including risk assessment methodology, exposure to radioactive materials, and biological

markers. He currently serves as chair of the NRC Standing Committee on Risk Analysis Issues and Reviews, chair of the IOM Environmental and Occupational Health Interest Group, and as a member of the Roundtable on Environmental Health Sciences, Research, and Medicine. Dr Goldstein's residency training included a rotation through the Manhattan VA Hospital.

Guy H. McMichael III, J.D., is president of GHM Consulting which offers federal relations and management consulting advice. Mr. McMichael served as a senior official in the Department of Veterans Affairs (VA) for 30 years and provided advice and direction at the highest levels of VA in the development and execution of a complex array of programs administered by the agency. During his tenure with VA, he served as Acting Under Secretary for Benefits, Acting Chief Information Officer, Acting Chief of Staff, Chief Judge of VA's Board of Contract Appeals, VA General Counsel and head of Congressional Relations. He also served as the agency's designated Dispute Resolution Specialist. Prior to joining VA, Mr. McMichael served as General Counsel for the United States Senate Committee on Veterans Affairs for 6 years. Following his military service in the U.S. Army, he began his public service as a Deputy Prosecuting Attorney for the State of Indiana. Mr. McMichael holds a J.D. from University of Michigan Law School. He received the VA's Exceptional Service Award on three separate occasions and was also a recipient of the VA's Distinguished Career Award. Mr. McMichael also serves as a Director of the Wounded Warrior Project, a nonprofit organization.

John R. Mulhausen, Ph.D., M.S., C.I.H., is the Manager of Corporate Industrial Hygiene for the 3M Company. Dr. Mulhausen is responsible for the leadership of the Corporate Industrial Hygiene organization and oversight of its programs worldwide in a $21 billion per year global manufacturing company. Prior to joining 3M, Dr. Mulhausen worked for the U.S. Army Environmental Hygiene Agency. Dr. Mulhausen also holds an Adjunct Assistant Professor position in the Division of Environmental and Occupational Health, School of Public Health at the University of Minnesota. He has presented and published in the fields of exposure assessment, industrial hygiene and industrial hygiene statistics. He was one of the editors for the American Industrial Hygiene Association's "A Strategy for Assessing and Managing Occupational Exposures." Dr. Mulhausen is certified in the comprehensive practice of industrial hygiene and is a Fellow of the American Industrial Hygiene Association.

Richard Scheines, Ph.D., is professor and Head of the Department of Philosophy at Carnegie Mellon University. In addition, Dr. Scheines is a professor of the Human-Computer Interaction Institute as well as the Department of Machine Learning. Dr. Scheines' research focuses on the relationship between causal hypotheses and statistical evidence. Dr. Scheines has collaborated for more than two decades with statisticians and computer scientists on characterizing what can and cannot be learned about causal claims from statistical data in a variety of empirical settings, and to develop and implement algorithms for causal discovery that are practical and relevant. He has applied these techniques to the question of whether lead affects IQ, the efficacy of online courses, the effect of welfare reform on single mothers, and many other policy domains. Dr. Scheines received his Ph.D. in history and philosophy of science from the University of Pittsburgh in 1987, and has published 5 books and over 80 articles since joining Carnegie Mellon in 1988. Dr. Scheines was recently on the Institute of Medicine Committee on Food Marketing and the Diets of Children and Youth, where cause and effect relationships were examined involving marketing and its effects on children's preferences, purchase requests, and diets.

Kenneth R. Still, Ph.D., M.S., M.B.A., F.A.T.S., C.I.H., C.S.P., C.H.M.M., is a retired U.S. Navy Captain in the Medical Service Corps. Dr. Still served as the Senior Director of Safety and Occupational Health for the Commander of the U.S. Pacific Fleet, Pearl Harbor, Hawaii, as well as the Officer-In-Charge of the Navy's only Toxicology Research laboratory Program in Dayton, Ohio. Dr. Still retired from the U.S. Navy in November 2005 and is currently the Scientific Director and toxicology consultant for Occupational Toxicology Associates, Inc., chairs an Independent Toxicology Panel for an International corporation, and provides consulting services for several DoD programs, including the Breast Cancer Research Program under the aegis of the Congressionally Directed Medical Research Program. Dr. Still has held numerous adjunct faculty/associate professorships including the John Burns School of Medicine at the University of Hawaii, and the Uniform Services University of Health Sciences, Bethesda, Maryland. He held a visiting research scientist appointment at the Naval Health Research Center Environmental Health Effects Laboratory in Dayton, Ohio, for several years. Dr. Still's main research interests include human health risk assessment, exposure assessment, and regulatory and mechanistic toxicology. His research addresses the areas of neurobehavioral, reproductive, inhalation/respiratory, biochemical, and occupational toxicology. He has more than 250 publications in the areas of his research. Dr. Still received his Ph.D. in chemical/physiological ecology from Oklahoma State University, his M.S. from Portland State University in the same field, and his M.B.A. from Chaminade University of Honolulu in financial management. Dr. Still holds certifications in the comprehensive practice of industrial hygiene, safety, hazardous materials management, and several environmental arenas. Dr. Still is a Fellow of the Academy of Toxicological Sciences and the American Industrial Hygiene Association. He has served as a liaison on numerous committees for the National Academies which have addressed the topics of toxicology hazard evaluation, reproductive and developmental toxicants, and acute exposure guidelines. Dr. Still has also served on many working groups for governmental agencies. He received the Vice President Al Gore Hammer Award for Reinventing Government for work on the Environmental Protection Agency Acute Exposure Guidelines.

Duncan C. Thomas, Ph.D., M.S., is the Director of the Biostatistics Division within the Department of Preventive Medicine at the University of Southern California and holds the Verna Richter Chair in Cancer Research. Dr. Thomas was Co-Director of the Southern California Environmental Health Sciences Center (funded by the National Institute of Environmental Health Sciences) and is Director of its Study Design and Statistical Methods of Research Core. His research interests include the development of statistical methods in epidemiology, with special emphasis on cancer epidemiology, occupational and environmental health, and genetic epidemiology. He is also one of the senior investigators in the California Childrens Health Study, the only long-term cohort study of the chronic effects of air pollution in children. He has published more than 200 peer-reviewed journal articles in these areas of research and is the author of *Statistical Methods in Genetic Epidemiology* (Oxford University Press, 2004). Dr. Thomas is a Fellow of the American College of Epidemiology and a past President of the International Genetic Epidemiology Society. Dr. Thomas received his Ph.D. in epidemiology and health from McGill University and his M.S. in mathematics from Stanford University. He has served as a member of the National Academies' committees to review radioepidemiology tables and the biological effects of populations of exposures to low levels of ionizing radiation (BEIR V) and was a member of President Clinton's Advisory Committee on Human Radiation Experiments.

Sverre Vedal, M.D., M.Sc., is a professor in the Department of Environmental and Occupational Health Sciences, Occupational and Environmental Medicine Program, at the University of Washington School of Public Health and Community Medicine. Prior to joining the faculty of the University of Washington, Dr. Vedal worked as an academic pulmonologist at the University of British Columbia in Vancouver and then at the National Jewish Medical and Research Center in Denver, Colorado. Dr. Vedal is well published in the application of epidemiological methods to evaluating the health effects of air pollution and occupational lung disease, and is funded by National Institutes of Health in researching health effects of air pollution sources. Dr. Vedal received his M.D. from the University of Colorado's School of Medicine and his M.Sc. in epidemiology from Harvard University. He is board certified in internal medicine and pulmonary medicine. Dr. Vedal is a member of the Review Committee of the Health Effects Institute in Boston, Massachusetts, and a member of air pollution panels of the Clean Air Scientific Advisory Committee of the Environmental Protection Agency's Science Advisory Board. Dr. Vedal served as a member of the National Academies' committee addressing air quality management.

Allen J. Wilcox, M.D., M.P.H., Ph.D., is a Senior Investigator in the Epidemiology Branch of the National Institute of Environmental Health Sciences, where he served for 10 years as the Chief of the Epidemiology Branch. He also holds a professorship in epidemiology at the University of Bergen (Norway) and an adjunct appointment as Professor of Epidemiology at the University of North Carolina, Chapel Hill. Dr. Wilcox's research focuses on reproductive and perinatal epidemiology, a field to which he has made methodologic as well as etiologic contributions. Dr. Wilcox received an M.D. from the University of Michigan, and an M.P.H. in Maternal and Child Health and a Ph.D. in Epidemiology from the University of North Carolina. He is certified by the American Board of Preventive Medicine as a specialist in Public Health and General Preventive Medicine. He retired in 2001 as a Captain from the U.S. Public Health Service, Commissioned Corps, where he was awarded the Meritorious Service Medal, the highest honor granted by the Public Health Service. He has twice received the National Institutes of Health Director's Award. Dr. Wilcox has served as the President of the Society for Epidemiologic Research, the Society for Pediatric Epidemiologic Research, and the American Epidemiological Society. Dr. Wilcox has held numerous editorships, and since 2001 has served as the Editor-in-Chief of *Epidemiology*.

Scott L. Zeger, Ph.D., is the Hurley-Dorrier Professor of Biostatistics and Chair of the Department of Biostatistics of the Johns Hopkins Bloomberg School of Public Health. Dr. Zeger is jointly appointed to the Department of Epidemiology and served as the Senior Associate Dean for Academic Affairs. His research is on regression analysis for correlated responses. Dr. Zeger has focused in two areas: (1) when observations come in clusters, for example in longitudinal research, family studies in genetics or in sample surveys and (2) when a single time series is observed. His research has extended generalized linear models (logistic, linear, log-linear, and survival models) to be applicable in these cases. Dr. Zeger has published extensively in peer-reviewed journals and is co-author of two books. Dr. Zeger received his Ph.D. in statistics from Princeton University. He is a Fellow of the American Statistical Association and of the American Association for the Advancement of Science. He was a member of several committees for the National Academies, including the Committee on Applied and Theoretical Statistics, the Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution

Regulations, and the Committee on Gulf War and Health: Health Effects Associated with Exposure During the Persian Gulf War.

Lauren Zeise, Ph.D., is the Chief of the Reproductive and Cancer Hazard Assessment Branch in the Office of Environmental Health Hazard Assessment at the California Environmental Protection Agency. Dr. Zeise's main research areas of interest include cancer and reproductive risk assessment. Her current work addresses cancer and reproductive risk methodologies and characterizations, establishment of baseline risks, and guidance for evaluating risks to the fetus, children, and adolescents from environmental exposures. She is widely published. Dr. Zeise received her Ph.D. from Harvard University. She is currently serving on the U.S. Environmental Protection Agency's Science Advisory Board. Dr. Zeise has served as a member of numerous committees for the National Academies which have addressed topics such as air quality, assessing exposure of herbicides in Vietnam, copper in drinking water, and risk characterization. She currently serves on the Board on Environmental Studies and Toxicology and is also a member on the Committee on Toxicity Testing and Assessment of Environmental Agents.

Volunteer Scientific Consultant

Melissa A. McDiarmid, M.D., M.P.H., D.A.B.T., is a professor of Medicine and Director of the University of Maryland School of Medicine's Occupational Health Program. Dr. McDiarmid also directs the Department of Veterans Affairs surveillance program for veterans exposed to depleted uranium. Previously, Dr. McDiarmid was Director of the Office of Occupational Medicine for the U.S. Occupational Safety and Health Administration (OSHA) in Washington, D.C. Prior to OSHA, she was an Assistant Professor of Environmental Health Sciences at the Johns Hopkins School of Hygiene and Public Health. Principal career interests for Dr. McDiarmid have been the study of health effects and toxicology of metals and environmental reproductive and developmental hazards. She has authored numerous journal articles and book chapters on various occupational and environmental medicine topics related to health-care workers, medical surveillance and management, reproductive health, and occupational cancers. Dr. McDiarmid received her M.D. from the University of Maryland, her M.P.H. from the Johns Hopkins University School of Public Health where she also completed her fellowship training in Occupational Medicine. She is board certified in Internal Medicine, Occupational Medicine, and Toxicology. Dr. McDiarmid is serving as a Volunteer Scientific Consultant to IOM's Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans.

Consultant

Robert J. Epley is an independent consultant working in the areas of strategic planning, training, performance management, and the operations of federal entitlement programs. Mr. Epley served with the Department of Veterans Affairs for 31 years, dividing his tenure between positions in headquarters and in the field. In VA field offices, he progressed through positions as benefits counselor and claims examiner to director of two regional offices in Detroit and St. Louis. At VA headquarters, Mr. Epley was chief of field operations for the education program, and later he served as deputy director and director of the Compensation & Pension Service. His final position with VA was associate deputy under secretary for policy and program management, where he was responsible for administration and oversight of the Veterans Benefits Administration's business lines: compensation, pension, housing, insurance, vocational

rehabilitation, and education. During his tenure with VA, Mr. Epley received two Vice President Al Gore Hammer Awards for reinventing government and two Presidential Rank Awards.

Staff

Catherine C. Bodurow, M.S.P.H., holds a research faculty position at the Georgia Institute of Technology and serves as a Senior Research Scientist in the Deputy Director's Office of Georgia Tech Research Institute. She was on loan to the Institute of Medicine (IOM) of the National Academies as a Senior Program Officer and Study Director. Ms. Bodurow also served as a Senior Scientist in the Office of Science Coordination and Policy of the Office of Prevention, Pesticides and Toxic Substances at the U.S. Environmental Protection Agency. Her research interests include exposure and risk assessment, epidemiology, and the application of real-time sensor technology in occupational and environmental exposure assessment. She has presented and published in these fields. Ms. Bodurow received her B.A. in chemistry from Kalamazoo College and her M.S.P.H. from the University of North Carolina at Chapel Hill. She has served on numerous national and international committees and chaired several national technical committees.

Frederick (Rick) Erdtmann, M.D., M.P.H., is the Director of the Board on Military and Veterans Health and the Medical Follow-Up Agency at the Institute of Medicine (IOM) of the National Academies. Prior to joining the IOM he was a career military physician in the U.S. Army. While in the military he served as chief of several large departments of Preventive Medicine at U.S. installations at home and overseas. He also was commander of the military community hospital at Ft Carson, Colorado, and later served as Hospital Commander for the Walter Reed Army Medical Center. He had several assignments at the Army Surgeon General's Office working on military health care policies. He received his undergraduate degree from Bucknell University and his M.P.H. from the University of California, Berkeley. He is a graduate of Temple University Medical School and is board certified in the specialty of Preventive Medicine.