A Review of the Scientific Literature As It Pertains to Gulf War Illnesses: Pyridostigmine Bromide

Beatrice Alexandra Golomb
C. Ross Anthony

Presented to the Sub-Committees on Health and Oversight and Investigations
Committee on Veterans’ Affairs
U.S. House of Representatives
November 1999

RAND Health

The RAND testimony series contains the statements of RAND staff members as prepared for delivery.

RAND is a nonprofit institution that helps improve policy and decisionmaking through research and analysis. RAND's publications do not necessarily reflect the opinions or policies of its research sponsors.
The mission of RAND Health is working to improve health care systems and advance understanding of how the organization and financing of care affect costs, quality and access. The nation's largest private health-care research organization, RAND Health has helped shape private- and public-sector responses to emerging health care issues for three decades. We pioneered the application of rigorous empirical research designs to health care issues. Our landmark studies of health care financing helped change the way America pays for health care services. We established the scientific basis for determining whether various medical and surgical procedures were being used appropriately. Our assessments of how organization and financing affect costs, quality, and access to care have addressed the population at large, as well as such vulnerable and hard-to-reach groups as the frail elderly, children with special health care needs, substance abusers, and HIV-positive individuals.

RAND Health research is supported by funding from federal government grants, foundations, professional associations, universities, state and local governments and private sector organizations. RAND Health specialized research centers embody partnerships with other institutions, including: RAND/UCLA/Harvard Center for Health Care Financing Policy Research, UCLA/RAND Center for Adolescent Health Promotion and Disease Prevention, UCLA/RAND Research Center on Managed Care for Psychiatric Disorders, VA/UCLA/RAND/UCSD Center for the Study of Healthcare Provider Behavior, and the Southern California Evidence-Based Practice Center.

RAND Health disseminates its work widely to the health practitioner and research communities, and to the general public.

For information about RAND Health, contact
RAND Health Communications
1700 Main Street
P.O. Box 2138
Santa Monica, CA 90407-2138
Phone: 310-393-0411, ext. 7775
FAX: 310-415-7027
Email: RAND_Health@RAND.org

A profile of RAND Health, abstracts of its publications, and ordering information can be found on the RAND Health home page on the World Wide Web at www.rand.org/organization/health/
Preface

This document presents the written testimony of Beatrice Alexandra Golomb, M.D., Ph.D., and C. Ross Anthony, Ph.D., as presented to the Sub-Committees on Health and Oversight and Investigations, Committee on Veterans' Affairs, U.S. House of Representatives, on Tuesday, November 16, 1999.
Mr. Chairman and distinguished Members of the Sub-Committees, it is a pleasure for us to address you today on RAND’s review of the scientific literature as it pertains to pyridostigmine bromide (PB) and illnesses among Gulf War veterans. RAND is a nonprofit institution that helps improve policy and decision making through research and analysis. At RAND I am the Director of the Center for Military Health Policy Research and Co-Leader of this project. I am joined today by Dr. Beatrice Golomb, who prepared this exhaustive new PB study. Dr. Golomb, a RAND consultant, is a physician who also has a Ph.D. in biology specializing in neurobiology. She is a staff physician at the San Diego VA Medical Center, an Assistant Professor of Medicine at the U.C. San Diego, and a Research Associate Professor in the University of Southern California’s Psychology Department. This statement is based on a variety of sources, including research conducted at RAND. However, the opinions and conclusions expressed are those of the author and should not be interpreted as representing those of RAND or any of the agencies or others sponsoring its research.

I would like to describe briefly the context for this study. Dr. Golomb will then summarize her research findings.

After the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) was formed in late 1996, the Special Assistant determined that there were at least two key kinds of information that were needed in the office’s efforts to leave no stone unturned in looking into the possible causes of illness among Gulf War veterans. OSAGWI has extensively investigated what happened and what exposures occurred in the Gulf while
affects the muscles, and it is also approved for certain post-anesthesia applications. During the Gulf War, it was designated an "investigational new drug" for pretreatment for soman and was supplied to U.S. forces under a FDA waiver of informed consent with the possibility of an Iraqi nerve agent attack in mind. Technically, PB is a "pretreatment adjunct"—a drug that must be taken before exposure to be effective but that only confers benefit if post-exposure treatments are given as well.

RAND was asked to perform a literature review to evaluate whether PB could plausibly be related to increased health symptoms experienced by Persian Gulf War (PGW) veterans. I examined over 10,000 titles, 6,000 abstracts, several thousand papers and reports, interviewed over 80 people, and reviewed dozens of declassified British studies and reports. This extensive review has resulted in the lengthy report before you, which includes more than 1,000 citations.

The literature review was used first to identify theories that might link PB to symptoms in ill PGW veterans, and then to assess the evidence pertaining to these theories. (In addition, the issue of efficacy of PB as a pretreatment for nerve agent was addressed, but will not be reviewed here due to time constraints.) A total of 7 theories were identified that pertain to a link between PB and health effects. Each has its own chapter in the report, but two are closely related and will be discussed together.

These theories fall roughly into two categories each containing three theories.

- The first group of theories describes possible mechanisms that may produce heightened individual susceptibility to effects of PB in some circumstances—so that some individuals might experience effects, including perhaps toxic effects, while others do not.

- The second group of theories describes ways that PB may actually lead to chronic symptoms, perhaps selectively in those with heightened susceptibility.

I will discuss each of these theories briefly.
Mechanisms Linking PB with Chronic Symptoms

Of the theories in this category, the literature allowed us to reject bromism (from accumulation of the bromide in PB) as a likely factor in illnesses in Gulf War veterans, and the literature was inadequate to seriously evaluate multiple chemical sensitivity.

The most important theory regarding mechanisms by which PB may lead to chronic illness – perhaps selectively in those with heightened susceptibility – suggests that PB may change regulation of a key nerve signaling chemical called “acetylcholine” (ACh). ACh is known to be vitally involved in regulating muscle action, pain, mood, memory, and sleep, domains that figure prominently in complaints of ill PGW veterans.

PB acts by blocking the enzyme that normally breaks down excess ACh. The consequence is increased, unregulated action by this nerve-signaling chemical. The body responds to this inappropriate increase in ACh action by putting into place mechanisms to suppress the excess ACh activity. Thus, signaling cells may reduce production and release of ACh, and may withdraw nerve terminals from receiving cells. Receiving cells may reduce the number of receptors to which ACh may bind, and reduce the affinity of these receptors for binding to the signaling chemical. And there may be increased breakdown of ACh.

Since these mechanisms designed to suppress ACh action occur in response to the excess ACh action induced by PB, one might expect that they would go away as PB is withdrawn. But in fact, existing evidence from studies in animals suggests that the timecourses of these effects differ widely from one another. Some are short lived, and are unlikely to explain chronic illness in PGW veterans. However other effects are long lasting or permanent, lasting in some instances as long after stopping PB as anyone has looked.