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RAND

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

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

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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.

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

Testimony Presented to the Sub-Committees on Health and Oversight and Investigations, Committee on Veterans' Affairs, U.S. House of Representatives

Beatrice Alexandra Golomb, M.D., Ph.D.
C. Ross Anthony, Ph.D.
RAND Health

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

RAND was asked to summarize the scientific literature on the health effects of possible causes of illness. It was hoped that combining these sources of information would produce a more complete understanding of illnesses among veterans.

The PB report is the fourth of eight literature reviews published by RAND to date. Literature reviews on the health effects of wartime stress, oil well fires, and depleted uranium were published previously; while reviews on chemical and biological warfare agents, pesticides, immunizations, and infectious diseases are to follow. The PB report differs from the other reviews to date, in that we are unable to rule out an agent as a possible contributing factor to illnesses among some veterans. As Dr. Golomb will explain, she exhaustively examined seven hypotheses and found enough supporting evidence that she was not able to dismiss PB as a potential contributing factor.

These findings must be interpreted carefully. Even if enough evidence is found that a hypothesis can not be rejected, this does not necessarily imply that the agent in question is a causal factor. It only means that, based on the available scientific evidence, the possibility cannot be dismissed. Also note that although this report has clear policy implications, RAND was not asked to and did not examine the policy issues related to PB and its use.

Dr. Golomb will now summarize her study for you.

PB Report Background

Mr. Chairman and Members of the Sub-Committees, over the past several years, I have looked extensively at the scientific information as it relates to pyridostigmine bromide.

As the Committee knows, pyridostigmine bromide was a drug taken during the Persian Gulf War by an estimated 250,000 U.S. troops as a pretreatment to protect against the nerve agent soman. PB was approved by the Food and Drug Administration in 1955 for treatment of myasthenia gravis, an autoimmune disease that

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.

Theories on Individual Susceptibility

Regarding theories of possible heightened susceptibility to PB, one theory proposes that there may be widespread individual differences in processing of PB. Indeed, our review found evidence of differences at many levels. First, the desired dose of PB was not taken by all the veterans in the approved manner; some took more and many took less. However, even supposing the same oral dose of PB, there are 7-fold differences in the resulting steady-state blood level of PB in humans. Moreover, for the same blood level of PB, there are many-fold differences in the percent of enzyme inhibition induced by PB; thus depending when after PB administration one looks, there may be up to 15 to 25 fold differences in enzyme inhibition for the same oral dose. Finally, for the same measured enzyme inhibition, there are widespread differences in clinical effects, including toxic effects of PB. These widespread differences in processing of PB from one individual to another could potentially lead to substantial differences in susceptibility to effects of PB, including chronic effects if any occur.

The second theory notes that whereas ordinarily most PB is excluded from entering the brain by what is termed the “blood brain barrier,” which bars access of many substances, some of the recent evidence from animal studies suggests that quite a bit of PB may access the brain under some conditions, such as stress, heat, and chemical combinations. These are conditions to which some PGW veterans may have been exposed, thus increasing the chance for brain effects of PB to occur. In addition, there is literature that indicates PB itself may enhance access to the brain of normally excluded substances, such as infectious viruses.

A third theory notes that toxic effects of PB may be greatly enhanced, in some cases in a synergistic fashion, by concomitant exposure to other factors like pesticides and nerve agent, to which some veterans may have been exposed.

These three theories, which describe mechanisms by which some individuals may have increased susceptibility to effects of PB – due to differences in processing,

differences in environmental exposures, or combinations of these – were all found to be viable (i.e. had enough supporting evidence that they could not be rejected).

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.

Could such long lasting or permanent changes in regulation of ACh action relate to chronic symptoms reported by PGW veterans? The answer is, we don't know; much more needs to be understood about the specifics of these changes, and what their relation may be to clinical effects. However we do know that ACh is critical to regulation of muscle action, pain, memory, and sleep – domains that are disrupted in ill PGW veterans; thus it is plausible that chronic changes in regulation of ACh could produce symptoms of the types veterans report.

Conclusions

Three major conclusions emerged from the study:

- We can not rule out pyridostigmine bromide as a possible contributor to the increased health symptoms in some Gulf War veterans.
- Further research is needed to determine the effectiveness of the current dose of PB in protecting against soman.
- More research is needed to clarify the role, if any, of PB in chronic health effects in ill PGW veterans. Some research of this kind is already being funded by the DoD, VA, and HHS.

The issue now is the very complex one of trading off uncertain health risks – but risks now known to be biologically plausible – against uncertain gains from use of PB in the warfare setting.