

BACKGROUND

An estimated 250,000 to 300,000 U.S. veterans of Operation Desert Storm/Operation Desert Shield, also called the Persian Gulf War (PGW) took pyridostigmine bromide (PB), used as a pretreatment adjunct to protect troops in the event of chemical warfare using the nerve agent soman (Brake, 1997). This report examines the evidence regarding whether PB may be linked to illnesses in Persian Gulf War veterans.

Veterans of the Persian Gulf War have reported such symptoms as joint pains, sleep disorder, memory loss, and fatigue more frequently than those who were not deployed (Joseph, 1997) (Table 1.1). The exact number of veterans reporting symptoms that they attribute to involvement in the PGW is difficult to characterize; about 100,000 have enrolled in VA (Veterans Affairs) and DoD (Department of Defense) registries. However, some of those enrolled do not report symptoms (although most do). Some who report symptoms—perhaps as many as 80 percent—have been given a “diagnosis.” This has been presumed by some to imply that their symptoms have been “explained” and were thus unrelated to Gulf War involvement, but this does not necessarily follow. First, some “diagnoses,” such as “tension headache,” are little more than descriptors of symptoms, which may have any of a host of root “causes” or contributing factors. (For instance, headaches may result from drug or chemical exposures—e.g., nitrates or monosodium glutamate, insecticides, or caffeine withdrawal; from COPD or other factors producing reduced oxygen to the brain; from high or low blood pressure, from muscular injury or inappropriate muscular contraction; from conditions of the eyes, ears, teeth, or throat; from systemic infectious illness; from collagen vascular disease; from tumor; from cerebrovascular accident; or from endocrine conditions, such as hyperthyroidism, hypo- or hyperglycemia, among many other causes (Adler, Lam, et al., 1994)). Second, a “diagnosis” may be correct and may be unrelated to Gulf War

Table 1.1
Most Frequent Symptoms Among 3,558 Registry Participants
with a Primary Diagnosis of “Symptoms,
Signs, and Ill-Defined Conditions”

Symptom	As Chief Complaint (%)	As Any Complaint (%)
Fatigue	20.0	59
Headache	9.0	44
Memory problems	6.0	40
Sleep disturbances	5.0	40
Rash	4.0	30
Joint pain	4.0	47
Shortness of breath	2.0	19
Abdominal pain	1.0	16
Muscle pain	1.0	22
Difficulty concentrating	1.0	31
Diarrhea	0.5	18
Depression	0.3	22
Cough	1.0	1

SOURCE: Joseph, 1997.

involvement but may explain only one or several of a set of symptoms in a veteran—who may have additional unexplained symptoms. Third, many conditions—perhaps most possible diagnoses—have known (and certainly unknown) environmental risk factors, so that having a “diagnosis” does not in itself preclude a contribution from Gulf War involvement. (For instance, increasing evidence suggests that past infection with chlamydia pneumonia (Grayston, Kuo, et al., 1993; Melnick, Shahar, et al., 1993; Puolakkainen, Kuo, et al., 1993; Saikku, 1997; Muhlestein, Hammond, et al., 1996; Wimmer, Sandmann-Strupp, et al., 1996) or some herpes viruses (Nieto, Adam, et al., 1996; Dummer, Lee, et al., 1994; Melnick, Adam, et al., 1993; Sorlie, Adam, et al., 1994) increases the risk of atherosclerosis, heart attacks, and strokes—as do exposures to environmental cigarette smoke and many other factors.) Further complicating the characterization of the number of those with symptoms “associated with” Gulf War involvement is the fact that many personnel who have symptoms have elected not to participate in Gulf War registries, for a host of reasons, including fear of job discrimination and the belief that enrollment confers few tangible benefits. These factors have complicated the ability to assess the degree to which symptom reports are greater in PGW veterans than in controls. They have also complicated the ability to do studies to investigate the relationship of factors (such as exposure to PB) to development of illnesses in PGW veterans because it is hard to define who constitutes a “case” and who constitutes a “control.” (Some studies have used Registry participation per se to designate who is a case, and this strategy clearly produces misclassification. Others are beginning work on establishing a case definition for “Gulf War

Syndrome.” Nonetheless, PGW veterans who do not meet the case definition should not automatically be considered suitable “controls,” particularly if they report illness, because the validity of such case definitions remains to be ascertained.) This report will not cover the epidemiological evidence relating to illnesses in PGW veterans (which is the subject of a separate report). However, the available evidence does suggest that personnel deployed to the Gulf have an increase in self-reported symptoms compared to nondeployed controls, though they may have started out healthier. As a rough estimate, the number of PGW veterans—of the approximately 700,000 deployed—who may have “unexplained” symptoms, may range from 20,000 (those registered with no diagnosis to “explain” their symptoms) to 100,000 (those registered who are ill, assuming a small fraction of additional ill veterans who have not registered), or perhaps even higher.¹

¹For the purposes of study, subjects selected as representing ill PGW veterans should be those with more “characteristic” and more severe symptoms. It should be assumed that more than one illness or symptom complex may exist. (Separate study can ascertain whether the rates of these symptom complexes differ in ill PGW veterans and in controls). To define and distinguish among such illness complexes, statistical strategies to establish clustering should be performed. One group of investigators has performed a factor analysis of symptoms (Haley, Kurt, et al. 1997). Other viable strategies include cluster analysis, or use of unsupervised neural networks. After more-common symptoms in ill PGW veterans have been determined and “grouped,” “healthy” controls should be selected who have none of these symptoms. (Common symptoms described in ill PGW veterans have included headache, fatigue, and difficulty with sleep, concentration, and memory; other symptoms have included diarrhea, rash, mood alteration, and chemical sensitivities.) The goal is to separate groups at extremes of symptomatology, just as studies of cardiovascular risk factors often compare those in the highest quintile on some factor to those in the lowest quintile to offer greater potential for separation along lines of associated exposures. Because the criteria employed for the purpose of study are intended to identify the more extreme cases, it should not be presumed that others with lesser symptoms are “free” of illness.

Is There a Syndrome? There is debate regarding whether a “syndrome” exists in PGW veterans. Some symptoms are more common than others in veterans, and veterans have different combinations of these more common and less common complaints. Many of the complaints are “nonspecific,” such as fatigue, headache, rash, and diarrhea, which may occur in association with many known illnesses of infectious, collagen vascular, endocrine, toxic, or other causes. The picture of variable symptoms is not inconsistent with the presence of a single syndrome—many known medical conditions are characterized by a set of more common and less common symptoms, in which each individual with the syndrome has a different subset of symptoms and some have atypical presentations. (Conditions from widely varying categories of disease provide instances, such as tuberculosis, thyroid disease, B₁₂ deficiency, or lupus. Adverse effects in response to drugs and medications are also variable, although some drugs—such as theophylline and digoxin—may have common sets of symptoms on overexposure. Individual presentations may differ, but a pool of common symptoms is recognized.) A “syndrome” is often defined either when unusual symptoms are present or when an objective “marker,” such as a blood test, becomes available to which these varying symptoms can be tied. (It may also be defined by statistical grouping techniques such as those described above.) At present, there is no such marker in PGW veterans (see *A Review of the Scientific Literature As It Pertains to the Gulf War, Volume 3: Immunizations* (Golomb, forthcoming), section on mycoplasma, for one candidate). But the absence of an identified marker does not preclude the existence of a predominant syndrome; a marker or test for illness could, for instance, be identified in the future. Thus, at present the situation may be compatible with no predominant syndrome (but with a host of unrelated conditions having nonspecific symptoms, it remains necessary to explain why they are more common in PGW veterans); with one predominant syndrome and a smattering of less-common and unrelated complaints; or with several syndromes. Certainly, illness in PGW veterans includes incidental illness, which some

Although symptoms reported by ill veterans have not been accompanied by a demonstrable increase in hospitalizations (Gray, Coate, et al., 1996) or illness mortality (Kang and Bullman, 1996; Kang and Bullman, 1995), they are a source of continued concern to veterans, and efforts, including the present one, are under way to evaluate whether exposures of these veterans during the PGW might be linked to current reported symptoms.

This report presents PB's characteristics, the circumstances of its use, and an overview of theories relating PB to illnesses in PGW veterans; later chapters review these theories in detail. (A literature review was conducted first to identify theories that may relate PB use to illnesses in PGW veterans and then to identify evidence to allow assessment of these theories.) Current theories relating use of PB to illnesses in PGW veterans include, first, theories that suggest how the effect of PB may have been heightened in some individuals in the circumstances of the PGW. Mechanisms that have been theorized to promote heightened susceptibility in some individuals include individual differences in susceptibility to PB (and to other exposures), interactions between PB and other exposures present in the PGW, and increase in the permeability of the blood-brain barrier due to other exposures experienced by PGW veterans (such as stress), allowing access of PB (and other substances) to the brain. One or a combination of these factors may have acted to enhance the effect and the toxicity of PB and to enable access of PB to the brain, where additional toxic effects might have occurred. The next set of theories concerns what these hypothetical toxic effects, resulting from enhanced toxicity of PB, might have been. These include the possible relationship of PB to development of "multiple chemical sensitivity," effects of PB on the neuromuscular junction, and production of cholinergic dysregulation by administration of PB. One additional chapter reviews the evidence that such substances as PB could produce chronic neuropsychiatric effects. A final chapter briefly discusses other theories and considerations.

veterans would have been expected to develop irrespective of their involvement in the PGW. Certainly also some syndromes are associated with exposures experienced in the PGW: Posttraumatic stress syndrome has been diagnosed in a minority of ill veterans, as has viscerotropic leishmaniasis, providing examples of syndromes that account for symptoms in a few but not most ill veterans. Whether there are in addition one or a few dominant syndromes has not been settled. Despite the debate regarding existence of a syndrome, some groups have created working definitions of "Gulf War Syndrome" for research purposes.

The present review is concerned primarily with whether the existing scientific evidence is compatible with a contribution by PB to symptoms reported by PGW veterans. The term "syndrome" will be avoided; rather, we will refer simply to illness in PGW veterans, which intends no implication about the underlying causes.

METHODS

This effort can be divided conceptually into several parts. The first element concerns background information on characteristics of pyridostigmine bromide. This element comprises reviews of the nature, function, and past medical and military use of pyridostigmine.

The second element is a review of the circumstances surrounding the use of PB in the PGW. Information is presented regarding the production, storage and transport, and delivery of PB to troops, as well as decisions regarding who received PB. This information is important insofar as it demonstrates, or fails to demonstrate, irregularities in the circumstances of use that may have contributed to illnesses or differential effects among veterans. Data pertaining to circumstances of use have been gleaned primarily from government reports and interviews.

The third element consists of a review of theories and concerns associated with use of PB in the PGW. Existing theories were identified by searching the Internet, a popular venue for the airing of Gulf War hypotheses (see particularly the GulfLink and Chronic Illness sites) as well as through interviews with investigators of PGW illnesses, comments by veterans and veterans' advocate groups, and examination of the scientific literature.

The final conceptual element, comprising the bulk of the report, consists of chapters discussing evidence pertaining to specific theories regarding a relationship between PB and PGW illnesses. For this element, additional limited reviews of the literature were performed to identify data pertaining to theories that have been advanced concerning how PB and symptoms in PGW veterans are related.

The literature review process has been essential to every stage of this report and is particularly critical for the analysis of evidence pertaining to theories. A systematic literature review conducted by an experienced RAND librarian employed the following databases: Medline, Embase, Scisearch, Chemtox, CASearch, Pesticide fact file (for PB interaction with pesticides), Registry of Toxic Effects of Chemical Substances, Pharmaceutical News Index, Toxline, ADIS Newsletters, SEDBASE, BIOSIS Previews, PNI, RTECS, PASCAL, DTIC, the *New York Times* (via NEXIS), the *Wall Street Journal*, and the *Washington Post* (via DIALOG). The initial search was restricted to English language articles or those with English language abstracts, using the search word *pyridostigmine*. Articles and reports that appeared relevant, based on title, were identified and accessed. Initially, many additional articles were retrieved related to the Persian Gulf War and to diverse putative causes of illnesses in PGW veterans in order to gain an understanding of the topic's background and context. Subse-

quent, limited searches directed at specific theories were performed. These were supplemented by articles identified from a review of past reports on illnesses in PGW veterans (e.g., the Presidential Advisory Committee (PAC) and the Institute of Medicine (IOM)), articles identified by discussion with experts, and citations in evaluated articles. Cited government reports are restricted to those that are unclassified or declassified.