

This report endeavors to identify theories which may relate use of PB to development of chronic illnesses in PGW veterans and to review the evidence regarding these theories. The theories on safety are sorted into two categories: those that discuss mechanisms for heightened susceptibility to effects of PB or increased effective exposure to PB and those that suggest mechanisms by which PB exposure—perhaps enabled by such heightened susceptibility—could produce chronic illnesses. Theories relating to mechanisms of increased susceptibility to PB include the following:

- Conditions of stress in the PGW may have produced breaches of the blood-brain barrier, allowing PB to enter the brain, producing effects of PB that would not normally occur, or would occur only at far higher doses.
- Different individuals have physiological variations that result in marked individual differences in processing of, and susceptibility to, PB.
- Interactions between PB and other chemicals to which veterans may have been exposed may result in toxic effects occurring at far lower doses than if exposures had occurred separately.

Theories suggesting mechanisms by which PB exposure could produce subsequent chronic symptoms—in the face of these factors that enhance susceptibility—include the following:

- Ingestion of bromide in PB may (according to the theory) produce bromism, which can cause multiple neuropsychiatric symptoms.
- PGW veterans may have developed a (not universally accepted) condition termed “multiple chemical sensitivity,” which is associated with many of the symptoms seen in ill PGW veterans.
- PB may lead to disruption of the neuromuscular junction.

- PB, which abnormally elevates ACh, may cause changes in regulation in the ACh and perhaps other neurotransmitter systems.

Some other considerations are discussed in less detail, relating PB to changes in hormones, sleep, serotonin, violence, and other factors, although these can be viewed as consequences of the mechanisms mentioned here.

THEORIES OF HEIGHTENED SUSCEPTIBILITY

We now describe the theories regarding heightened susceptibility in slightly more detail.

The first postulate suggests that permeability of the blood-brain barrier in PGW veterans may have been enhanced due to stress and other conditions of war, permitting increased access of PB to the brain and that, moreover, PB itself may increase access of other agents to the brain. (The “blood-brain barrier” refers to special ability of certain cells to exclude access to the brain of chemicals and organisms that circulate in the blood—including PB.) Data demonstrating breach of the blood-brain barrier, allowing increased access of PB to the brain in conditions of stress, derive from rodents. (Some evidence suggests that heat may potentiate permeability effects.) However, human data suggest a possible increase in central side effects of PB during the war compared to peacetime, which could reflect increased access of PB to the brain in circumstances of stress in humans. The degree to which the blood-brain barrier may have been infringed, thus allowing entry of PB into the brain, determines the possible contribution of several other of the theories that have been discussed. For example, “downregulation” of the cholinergic system, at least central downregulation (described in more detail below), is not likely to result from administration of PB unless PB gains access to the brain. Therefore, if central cholinergic downregulation is to be proposed as a contributing mechanism for memory, learning, and sleep deficits in ill PGW veterans, then PB must have entered the brain—or other AChE inhibitors must have done so, perhaps facilitated by PB. Another animal study reports that PB itself may enhance permeability of the blood-brain barrier.

The next postulated factor that may contribute to a connection between PB and chronic illnesses concerns individual differences in processing of PB, leading to individual differences in susceptibility. How is it, if PB is a contributor to chronic illnesses in PGW veterans, that some PGW veterans who received PB became ill, while others who received a similar amount did not? Evidence was found for individual differences in PB processing at many levels. Differences occurred in the dose of PB actually taken by troops and the duration of treatment. Moreover, individual differences in “absorption” of PB pills from the gut

to the blood contribute to different blood levels for the same administered dose. Different rates of clearance of PB from the blood also contribute to different blood levels of PB. These different rates of clearance occur because of enzyme “polymorphisms” and individual differences in enzyme quantities. (Different individuals have different DNA coding for the enzymes, producing enzymes that are different in structure and function. Moreover, the same enzyme may be present in widely differing amounts.) Differences in AChE enzyme inhibition may occur, even if the same blood level of PB is obtained. Finally, differences in toxic effects may occur, even for the same degree of AChE inhibition—perhaps resulting from underlying differences in the ACh system—and in cholinergic “responsiveness”—which have been shown to occur in people.

These widespread differences in intake and processing of PB could contribute to important differences in the effect of administered PB from one individual to another. Indeed, from a clinical standpoint, individual differences in *acute* susceptibility to PB obviously occur, as reflected in differences in side effects experienced in response to PB. (Individual differences in “tolerance” to PB given therapeutically are also seen in patients with myasthenia gravis, a medical condition in which there is low action of ACh at the muscle, leading to weakness.) The same differences in susceptibility that lead to acute differences in response—or perhaps other differences in susceptibility, unrelated to those producing acute differences in response—may be postulated to condition development of long-term effects, if any, in response to PB. There is weak evidence that the acute susceptibility differences may arise from mechanisms relevant to differences in chronic symptoms in PGW veterans, since one study finds a relation between certain chronic illness “syndromes” (derived from factor analysis) in ill PGW veterans and self-reported adverse acute response to administration of PB. If PB is a contributor to chronic illnesses in some PGW veterans (perhaps for reasons discussed below), then individual differences in susceptibility almost certainly (and almost tautologically) play a role in determining which individuals are affected.

Another postulated factor that may play a role in the connection between PB and illnesses in PGW veterans involves possible toxic interactions between PB and other exposures. Studies performed in animals indicate that toxicity of PB is enhanced—indeed, in a synergistic fashion—with concomitant exposure to other chemicals, such as pesticides, to which some troops may have been exposed. (Synergistic toxicity means the toxic effects from a group of chemicals is more than the sum of the toxic effects from the individual chemicals.) These other exposures may include pesticides and insect repellents, as well as caffeine, perhaps nerve agents, and stress (which also figures in the relation of PB to illness in the blood-brain barrier theory—and which could be considered to have a role in the individual differences theory, since responses to stress may

differ from one individual to another based on individual differences in neurochemistry and experience). The degree to which these interactions between PB and other factors may play a role in PGW veterans is unclear, for several reasons. First, we do not have good data regarding who received which exposures, which complicates performance of epidemiological studies looking for the effect of these interactions. (Epidemiological studies using self-report data could, however, look to see whether incorporating an “interaction term” between PB and other self-reported exposures increases the explanatory power of the statistical model.) Second, the data from animal studies are difficult to extrapolate to PGW veterans because extremely high doses of drugs—both of PB and of the interactants—were used in these animal studies, doses many times higher than those experienced by PGW veterans. To address the question of whether important synergistic effects would occur with lower doses—more comparable to those administered to PGW veterans—is not simple. Even supposing administration of those low doses in animals produced effects comparable to those reported by ill veterans, there is no good way to assess the presence of those effects. (We have enough trouble assessing them in humans, who can tell us what they feel; in humans we have not, or not yet, found good “objective” tests to coincide with reports of symptoms.) In existing animal studies, relatively crude measures, such as gross incoordination in walking or death, are often employed. If lower doses of drugs are studied, more sensitive measures will need to be found to gauge the possibility of synergistic effects between PB and other exposures. Because evidence of synergistic toxicity exists—albeit in animals, using high doses and different routes of administration from those experienced by PGW veterans—interactions between PB and other agents or exposures remain a possible avenue by which increased effect or toxicity of PB may have occurred in some veterans.

THEORIES CONCERNING POSSIBLE CONTRIBUTION BY PB TO CHRONIC SYMPTOMS

The relation of such increased effect to long-term illnesses requires introduction of other theories, discussed below.

The first seeks to link PB exposure to development of chronic illnesses and suggests that illness results from excessive accumulation of bromide following PB administration. However, bromism emerges as an unlikely cause of chronic illness, because the cumulative doses of bromide given and the time-course of illnesses in PGW veterans are incompatible with available knowledge regarding bromism. Although it is possible that bromism could have contributed to illness in a small number of veterans with specialized circumstances, bromism appears unlikely to be a significant contributor to chronic illness in most ill veterans.

The second proposes that symptoms in ill PGW veterans have much in common with those of patients with a putative—but not universally accepted—condition termed “multiple chemical sensitivity” (MCS). MCS is a symptom complex involving multiple self-reported “sensitivities” or adverse subjective responses to a host of apparently unrelated foods and chemicals. Many ill veterans are said to have new chemical sensitivities (though peer-reviewed data on frequency of these reports are not available); MCS patients have other symptoms in addition to chemical sensitivities, symptoms said to parallel those of ill PGW veterans (again, not peer-reviewed data); and many or most ill PGW veterans and MCS patients report prior exposure to AChE-inhibiting agents—PB and perhaps nerve agent and pesticides in Gulf War veterans and pesticides and organic solvents in MCS patients. Moreover, the genesis of MCS has been proposed to relate to exposure to excessive ACh activity, or reduced AChE activity, which may presumably have been experienced by PGW veterans exposed to PB. However MCS is poorly positioned to serve as an explanation for illness in PGW veterans, because MCS itself is not well understood (or even universally accepted as a syndrome by scientists or clinicians). Like illness in PGW veterans, there is no widely accepted case definition (though several have been proposed); and there is as yet no identified objective marker that distinguishes those who report symptoms from those who do not. At present, MCS cannot serve as an explanation for illnesses in any PGW veterans. However, it can be hoped, whether or not MCS and illnesses in PGW veterans are found to converge in any way, that ongoing research for each condition into possible cholinergic mechanisms will assist in pursuit of understanding for the other.

A third theory relating PB to development of chronic illnesses in PGW veterans involves effects of PB on regulation of ACh.

- The first component of this discussion relates to the effects of AChE inhibitors at the neuromuscular junction.

Nerves signal to skeletal muscles using ACh, at receptors termed “nicotinic” receptors. Binding of ACh to these nicotinic receptors at the neuromuscular junction causes the muscle to contract. Administration of AChE-inhibiting drugs, including PB (leading to excessive signaling by ACh at the neuromuscular junction), has been shown in animals to produce destructive changes to the muscle tissue and to produce “presynaptic” and “postsynaptic” changes in the neuromuscular junction. These changes begin after a single dose of PB. Though some effects of destruction (effects visible with light or electron microscope) begin to recede even if use of PB is continued, partially restoring the appearance of the muscle and of the neuromuscular junction, such restoration has not in all cases been complete even long after administration of PB has been stopped—indeed, as long out as anyone has looked. Findings at the neuromuscular junction are potentially important for two reasons: first, be-

cause some of the symptoms reported by PGW veterans include musculo-skeletal problems and fatigue—to which effects of PB at the neuromuscular junction could conceivably contribute—and second, because this junction is the most accessible cholinergic synapse and therefore is the best studied. It is partly presumed, partly hoped, that effects evident at the neuromuscular junction will accurately reflect effects at central acetylcholinergic synapses, at least the nicotinic ones, and may help to explain central effects from AChE inhibitors. (Evidence to date supports both similarities and differences between the skeletal muscle nicotinic receptor and central nicotinic receptors.)

Data from the neuromuscular junction support development of “dysregulation” of the nicotinic and muscarinic acetylcholinergic systems—particularly but not exclusively for “downregulation” (that is, attenuation or suppression of those systems)—following use of AChE-inhibiting drugs, such as PB. That is, effects occur that tend to counteract the abnormally high activity of ACh induced by delivery of PB (or other AChE inhibitors) by suppressing ACh production, release, and response. Such changes include “presynaptic” changes—changes associated with the nerve cell sending the signal—including withdrawal of nerve terminals from the muscle; reduced production of ACh; reduced release of ACh, including reduced number of packets or “vesicles” (also called “quanta”) of ACh released with a nerve signal; and reduced number of ACh molecules in each such packet. Such changes also include “postsynaptic” changes—changes at the cell (in this case, muscle cell, but in the brain, another nerve cell) that receives the signal—such as reduced number of ACh receptors (the receptor is a five-subunit protein to which ACh binds; this binding leads to fluxes of ions that produce a chemical signal to the muscle cell, signaling it to contract) and reduced affinity by, and sensitivity of, ACh receptors to ACh.

- The second component of this theory relates to effects on ACh regulation produced by AChE inhibitors “centrally,” in the brain.

Although changes consistent with dysregulation have been best demonstrated in the neuromuscular junction, evidence from the brains of rodents suggests that dysregulation changes (again, especially but not necessarily exclusively downregulation) may also occur centrally (that is, in the brain and perhaps spinal cord) for both the nicotinic and muscarinic systems. These central changes have been demonstrated in animals, using AChE inhibitors that gain central access and typically at doses that achieve higher levels of AChE inhibition than those to which veterans were exposed. Clinical effects of downregulation may be referred to as “tolerance” to a drug when they are reflected in reduced response to that drug or “rebound” when effects opposite to those produced by the drug occur when the drug is discontinued. Tolerance to PB has been described, in the form of reduced therapeutic effect of PB, and reduced production of side effects by PB with continued use has been

described. It is not known whether symptoms described by PGW veterans could in some instances be manifestations of a prolonged form of rebound effect.¹ If PB gains central access, therefore, discontinuation of PB might be associated with effects of abnormally reduced activity of the nicotinic and muscarinic systems in the brain.

Though evidence for this possibility is substantially less extensive, there may be—alternatively, or more likely in addition—ACh upregulation producing increased activity for some receptor types, in some brain areas.

Evidence indicates that different effects have different time-courses. Some are short-lived and may dissipate even while PB continues to be given. These cannot of themselves plausibly contribute to chronic illnesses in PGW veterans. However, other effects appear to be long-lasting and may continue long after discontinuation of PB. The normal coordinated functions of the brain could be disrupted by differentially altered elements, and the resulting interactions could, hypothetically, produce their own consequences and result in evolution of effects over time. Even if upregulation is not a significant factor (other than upregulation of nicotinic receptors, which may occur in some brain regions after acetylcholinergic stimulation), existing evidence that different degrees of downregulation occur in different brain (and peripheral) areas and with different receptor subtypes suggests that “dysregulation” rather than “downregulation” may more accurately characterize the full spectrum of alterations in regulation that might occur following exposure to AChE-inhibiting agents in susceptible individuals. Neurotransmitter “dysregulation” constitutes the fourth “theory” relating PB to illness (though actually it is really an extension of the findings at the neuromuscular junction—or, otherwise viewed, the findings at the neuromuscular junction are a lead-in to this theory).

The actual contribution of dysregulation to symptoms in humans is not known, because evidence for dysregulation derives primarily from animal studies and basic science research. However, it is known that the cholinergic system is vitally involved in regulation of muscle action, sleep, pain, and learning and memory. Thus, a downregulated “hypocholinergic” (or dysregulated “dyscholinergic”) state might be expected to lead to problems with muscle action (or fatigue), memory, learning, and sleep, and increased sensitivity to pain—problems that figure prominently in complaints of ill PGW veterans.

¹PB may affect many systems that interact, including not only the ACh neurotransmitter system but the GABA system, the glutamate system, the catecholamine systems, and the 5-hydroxytryptamine (5-HT or serotonin) system; because these systems have complex interactions and are characterized by an assortment of different time-courses of regulation, effects distinct from simple rebound, here given the general term “dysregulation,” may occur.

Indeed, treatment with ACh-activating drugs has been used in other populations to treat most of the symptoms most commonly reported by ill PGW veterans. Pyridostigmine itself has been used to treat fatigue from various causes. Moreover, nicotine, which stimulates the nicotinic subtype of ACh receptors, along with other cholinergic drugs, has been reported clinically to reduce diarrhea (in patients with ulcerative colitis), to enhance cognitive function (in animals (Abdulla, Bradbury, et al., 1996; Zarrindast, Sadegh, and Shafaghi, 1996; Arendash, Sanberg, and Sengstock, 1995; Socci, Sanberg, and Arendash, 1995); in patients with Parkinson's disease and Alzheimer's disease (Christie, Shering, et al., 1981; Fagerstrom, Pomerleau, et al., 1994; Lena and Changeux, 1997), in normal subjects (Davis, Mohs, et al., 1978; Baldinger and Schroeder, 1995; Foulds, Stapleton, et al., 1996), and especially in former smokers (Foulds, Stapleton, et al., 1996), and to improve attention (in smokers (Ghatan, 1998) and in patients with attention deficit disorder (Benowitz, 1996; Levin, Connors, et al., 1996; Lena and Changeux, 1997). Moreover, nicotine has been used in treatment of sleep apnea, which appears to be the most common sleep disorder identified in ill PGW veterans. (Sleep apnea has in turn been linked to fibromyalgia, particularly fibromyalgia in males, and to fatigue and to mood and cognitive dysfunction.) And recently it has been shown that nicotinic stimulation has powerful pain-relieving effects, stronger than those of morphine. Since nicotinic stimulation may lead to improvement in memory, attention, diarrhea, sleep, and pain—areas that figure prominently in complaints of ill PGW veterans—central nicotinic dysfunction or depression might reasonably be postulated to explain many symptoms in ill PGW veterans.

Little is known about the time-course of ACh dysregulation (centrally or peripherally), following pharmacologically heightened ACh activity, and more needs to be understood about the doses of drug and the durations of use that might produce such dysregulation. At present, the idea of cholinergic down-regulation (or neurotransmitter dysregulation) as an explanation for illness in PGW veterans is speculative. Although existing literature supports the possibility of a link between ACh dysregulation and each of the symptoms commonly reported by ill PGW veterans and some evidence suggests that such dysregulation may occur with PB in animals, this does not mean that ACh dysregulation necessarily occurred in PGW veterans or is in fact the cause of any of these symptoms. (The consistency across many symptoms is suggestive, however.) Additional research is needed to clarify what role, if any, such dysregulation might have in development of chronic symptoms.

Issues relating to whether chronic symptoms might plausibly arise from acute administration of PB are discussed in a separate chapter. Evidence suggesting the possibility of chronic effects by AChE inhibitors, including but not confined to PB, is reviewed. Data regarding chronic effects, particularly from low-dose

exposures not producing acute symptoms, are meager, and studies are frequently of poor quality. Bearing this in mind, some evidence suggests the possibility of chronic effects, at least for some AChE inhibitors, perhaps even at dosage levels that do not produce obvious symptoms acutely. Some such studies have suggested the possibility of chronic changes in nerve and muscle function, EEGs, regional cerebral blood flow, or neuropsychological tests, typically with exposure to AChE-inhibiting pesticides or to nerve agents. Other studies fail to show such findings. Of course, if chronic effects, and particularly neuropsychological effects (which, along with musculoskeletal effects might be the effects most plausibly related to PB, stemming from PB's prominent action on acetylcholinergic function), are not present in PGW veterans, then neither PB nor any other exposure will need to be invoked as an explanation. Therefore, we have reviewed some evidence regarding chronic neuropsychological findings in ill PGW veterans.

Several studies suggest that selected ill veterans have statistically lower scores on neuropsychological batteries than do well controls. Often, although they do less well than controls, their scores remained in the "normal" range. Although it appears that *some* ill veterans do have diminished neurocognitive function compared to healthy controls when sensitive tests are selected, we would expect that some *non*veterans reporting similar complaints of memory and attention problems would also have lower scores. The extent to which an excess number of veterans do so remains to be clarified. The reductions in function that have been observed do not appear to relate to one or a small number of neurocognitive abilities. However, since the acetylcholinergic system plays a prominent role in many functions of the brain, if effects were mediated through dysregulation of the ACh system, the effects might be expected to span many functions.² The additional important issue is whether such impairment is related to use of—or adverse response to—PB. One small study (mentioned above) suggested a connection between adverse acute response to PB and current neuropsychological syndromes. Moreover, a recent

²Moreover, there are large differences from one skill to another in where one person "ranks" compared to other people. For instance, in school one person may have been good in spatial reasoning but bad in algebra; excellent in computation but average in mathematical abstraction; a person may have an adequate short-term memory but abysmal visual tracking ability. Therefore even if the drug's effects were in some sense "uniform" across the functions affected (presumably primarily the many functions influenced by the acetylcholinergic system; perhaps to a lesser degree by serotonergic, glutaminergic, GABAergic, or monoaminergic systems), depressing all by the same amount on some hypothetical standardized scale and to the same degree in all individuals, different individuals would still be expected to dip to below par on different functions. Which functions test as normal and which as subnormal could well depend on how far below or above average subjects were on that function to start with and would therefore be expected to differ from one person to another. The result would be the appearance of a haphazard "scattering" of the effect across tested functions, with different individuals testing abnormally low on different functions but an overall trend toward worse function in symptomatic PGW veterans than controls on many functions. This is consistent with the pattern described by some researchers.

study found that among British PGW veterans, self-reported exposure to PB was strongly and significantly related to current CDC-defined Gulf War Illness (Unwin, Blatchley, et al., 1999). However, these studies are limited by the use of self-report to determine exposure to PB because many individuals do not remember what agents they took (reducing precision and reducing the ability to detect an association) and individuals who are ill may remember use of PB differentially from individuals who are not ill (potentially producing bias). Ill individuals may have thought about it more and therefore be more likely to remember PB and other exposures (or think they remember) than do individuals who are not ill, or they may simply be more likely to respond positively, thinking an exposure must have been present. Also, the presence of serious illness may influence their thinking about how much they probably used. However, one study found that mean exposure estimates (for a set of exposures that did not include PB) in PGW veterans did not correlate with symptom scores, which militates against a strong role for recall bias. Moreover, in the British study, the observed increased risk associated with self-reported exposure to risk factors did not differ among those who had record-confirmation of exposure and the group as a whole, again suggesting that recall bias did not play a major role. In any event, no more accurate method of determining exposure to PB is currently available.

In short, there is suggestive evidence that some AChE inhibitors may cause chronic neurological changes. There is some objective evidence that chronic neurological changes exist in some ill PGW veterans compared to healthy controls. (Evidence is limited regarding whether new deficits are more common in PGW veterans—absence of relevant predeployment data renders this determination more difficult. However, whether or not this can be shown with certainty, efforts to understand the origin of deficits in those who have them are important.) Current evidence cannot rule out the possibility that long-term effects of PB might occur and might participate in production of neurological deficits reported in some PGW veterans.

Finally, one chapter mentions briefly several other considerations not reviewed in detail: these include hormone and stress effects, effects on sleep, the serotonergic system, and injury from accidents. Many PGW veterans report difficulties with sleep. Sleep is prominently regulated by the ACh and serotonin/melatonin systems, both of which might be influenced by PB if PB were to gain central access. PB, in addition to augmenting ACh by inhibiting AChE, also may “mimic” serotonin by binding to a specialized site on the ACh receptor for which the “endogenous ligand”—that is, the chemical that normally binds there—is serotonin. (Just as action by PB on the ACh system may lead to altered regulation of that system, so binding by PB on a site normally bound by serotonin could possibly affect regulation of the serotonergic system.) For these

reasons, an association between PB use and sleep difficulties in PGW veterans is possible, though certainly not demonstrated. Of note: A form of sleep apnea appears to be common in tested ill PGW veterans who report sleep disorders. Sleep disruption, particularly sleep apnea, has been linked to increased motor vehicle accidents, and deaths from motor vehicle accidents have been shown to be significantly increased in PGW veterans. Moreover, sleep disruption, including sleep apnea, has also been shown to have a role in production of some pain syndromes, in particular a syndrome termed “fibromyalgia,” which bears much in common to pain syndromes reported by many ill PGW veterans. It is also of note that nicotine, a nicotinic ACh receptor activating drug, has been used as a treatment for sleep apnea.

On a separate note, there remain some concerns regarding the efficacy of PB in protection against nerve agent threats. For some nerve agents, such as sarin, evidence was not adequate to exclude a possible harmful effect by use of PB as a pretreatment. A modest and “militarily” unimportant reduction in efficacy of postexposure treatments is seen when PB is used in rodents, but if the reduction in protection is exaggerated in primates—as the enhancement in protection for soman is exaggerated in primates—then it is possible that a meaningful reduction in protection against death would occur. (There is no evidence that this is the case, but neither is evidence adequate to confidently exclude this possibility.) Moreover, with regard to soman, one study compared the protective efficacy of PB against soman *in vitro* in muscles of monkeys and humans. Ten times the dose of PB had to be applied to human muscle to produce comparable protection—although oral doses in monkey studies to produce “comparable” AChE inhibition are three to ten times as high as in people. These findings suggest by comparison that the doses given to people may be inadequate to confer benefit against lethality (and it has never been proposed that PB will enhance mission completion). Although several plausible reasons suggest that these findings might be misleading, the studies have not been done that would lay these concerns to rest.

In summary, present evidence cannot exclude a role of PB as a contributor to chronic illnesses in PGW veterans mediated through several possible pathways, individually or in concert. First, one or a combination of several factors might participate in increasing susceptibility to PB—or effective exposure to PB. These factors include increased permeability of the blood-brain barrier in conditions of stress, allowing abnormal access of PB and other chemicals to the brain; individual differences in native susceptibility to PB and/or to other exposures that interact with PB; and enhanced toxicity (effect) of PB resulting from interactions of PB with pesticides, stress, caffeine, alum adjuvant of vaccines, or other exposures. Once exposure to PB occurs, particularly central exposure, PB could conceivably produce chronic illness by engendering dysregulation in

neurotransmitter systems and in particular in the ACh system. Although there is evidence that such dysregulation takes place in animals exposed to AChE inhibitors, whether some of the effects of dysregulation are chronic remains unknown. Moreover, for central dysregulation to occur, PB (or other AChE inhibitors) would (probably) need to gain access to the CNS, which would suggest that postulating PB as a plausible contributor to chronic illness would most likely require concomitant exposure to stress or other exposures that may enhance entry of PB to the brain. Alternatively, PB may enhance central entry or toxicity of other exposures, including centrally acting AChE inhibitors, such as pesticides or perhaps sarin). (Of note: The blood-brain barrier permeability is itself variable, perhaps independent of these forms of exposure.) Finally, PB could influence peripheral factors that in turn have central effects. Another form of dysregulation that has been postulated to link use of PB to later chronic illness is development of abnormal “sensitivity” of certain neurons in the brain, leading among other consequences to heightened aversive conditioning, possibly with somatic effects—that is, effects involving bodily symptoms. Evidence suggests that some parts of the brain may exhibit opposite direction effects on some aspects of the ACh system compared to other parts of the brain, so that changes consistent with both upregulation and downregulation could occur simultaneously.

LIMITATIONS AND FUTURE DIRECTIONS

The combined literature related to PB, to Persian Gulf illnesses, and particularly to acetylcholinergic function is quite extensive, and decisions were made to emphasize some factors at the expense of others. The chief “new” contribution of this report, compared to previous discussions of PB as a cause of illness in PGW veterans, is the comparatively more in-depth discussion of the acetylcholinergic system and its relation to possible mechanisms of illness. (Even in this arena, the present effort barely scratches the surface of available evidence; it is hoped that future efforts are able to build on the foundation provided here.)

Several issues important to military use of PB were reviewed but are given less attention in this report—including data on acute physiological and performance effects of PB, as well as on acute side effects, and data on alternatives to PB. These issues are relevant to military use of PB, but they were given relatively less emphasis in the current report because they do not directly address the issue of development of chronic health effects in PGW veterans.

This effort is limited, too, by the available evidence. Concern regarding PB as a possible source of chronic symptoms is relatively new, and research in this area is in its infancy. Human data regarding chronic effects are mostly epidemiological (observational—not experimental), and these epidemiological studies

are complicated by lack of a consistent clinical case definition (by lack of a clear definition of which PGW veterans should be counted as “ill,” or as neurologically symptomatic resulting from involvement in the PGW) and by lack of good data regarding who received which exposures, including PB. When both the exposure and the outcome are not well characterized, it is doubly difficult to clearly evaluate the connection between the exposure (here, PB) and an adverse outcome. While some experimental data are available from humans, related to fairly short-term effects of use of PB in non-war volunteers, and while these data do not suggest that short-term effects are a major concern, such studies have not looked at long-term effects and have often not entailed conditions of stress, heat, exertion, sleep disruption, and interactions with certain other exposures that may have conditioned susceptibility to PB in the PGW. Most experimental studies relating to toxic effects, and involving stress and drug interactions, are done in animals—typically rodents, but occasionally other orders, such as hens or primates—and the degree to which this evidence extrapolates to humans is uncertain. Moreover, less sensitive clinical outcome measures—such as gross neurological abnormalities or death—must be used in animals, since one cannot question them regarding self-reported symptoms. It would be expected that doses needed to produce these more dramatic abnormalities would be greater than doses needed to produce symptoms more consistent with those reported by veterans—in whom objective indices of dysfunction are difficult to identify. Indeed, substantially higher doses are used in most animal studies than those employed in PGW veterans, and different modes of administration are also employed. How the effects grade with decreasing dose—that is, whether severe symptoms with quite high doses in animals imply subtle symptoms with the *much* lower doses used in veterans—is simply not known.

CONCLUDING REMARKS

This report reviews several factors that have been postulated to contribute to heightened susceptibility or exposure to PB in PGW veterans and several proposed mechanisms by which PB may cause illness. One postulated cause is dismissed. The other postulated causes and contributors remain possible; further study is needed to assess their role, if any, in development of illnesses in PGW veterans.

Three theories propose that exposure to effects of PB may have been augmented in the conditions of the PGW in some individuals, by each of three factors: breaches in the blood-brain barrier, presence of native differences in susceptibility, and drug/chemical interactions. There is sufficient support from the literature to suggest that each of these factors *may* condition susceptibility to PB—though studies using more similar doses and conditions to those expe-

rienced by PGW veterans are needed. Several theories describe or suggest mechanisms by which PB exposure—conditioned by the above factors—may lead to subsequent illness. The evidence from the literature appears to be adequately clear on issues of dose and time-course, in humans, to allow dismissal of the theory that excessive blood levels of bromide resulting from ingestion of PB led to bromism and that symptoms in PGW veterans are the consequence. For other theories relating use of PB to illnesses in PGW veterans, particularly for cholinergic dysregulation, evidence is inadequate to foreclose them. Particularly in the case of neurotransmitter dysregulation, evidence from animal studies is sufficiently suggestive that additional research is clearly warranted. The mechanisms noted are not mutually exclusive—two or more of the postulated factors influencing susceptibility may act together. This could in turn offer conditions favorable for development of long-term problems by PB, via one or more of the proposed mechanisms or other mechanisms not yet considered. However the studies supporting these mechanisms use doses, time-courses of follow-up, and conditions sufficiently dissimilar to those in veterans that it is impossible to extrapolate directly.

Additional investigation will be required to clarify the role of these factors in the contribution of PB, if any, to illnesses in PGW veterans.