Several theories relate PB to illnesses in PGW veterans. Following a general discussion of these theories in this chapter, a chapter devoted to each theory will discuss the evidence in greater detail. The first three theories relate to how some individuals, or individuals in some conditions of the PGW, may have had increased susceptibility to effects of PB. The next four theories relate to how PB—perhaps enabled by heightened susceptibility in some individuals—could have produced chronic symptoms. One chapter discusses evidence relating to whether agents like PB could plausibly produce chronic effects, and a final chapter discusses other considerations or theories that have been examined in lesser detail. The descriptions of the theories and their presumed rationales in this chapter are not intended to reflect conclusions or balanced assessment of those theories after examination of the evidence. (See chapters corresponding to the respective theories for such assessment.)

**BLOOD-BRAIN BARRIER PASSAGE: DOES PB CROSS THE BLOOD-BRAIN BARRIER DURING CONDITIONS OF STRESS?**

PB is normally viewed as having minimum potential for CNS toxicity, due to its failure to cross the blood-brain barrier. However, recent evidence suggests this failure to cross the blood-brain barrier is vitiated under conditions of stress (Friedman, Kaufer, et al., 1996; Hanin, 1996) and possibly with administration of multiple chemicals. Therefore, central effects of PB may contribute to symptoms.

**INDIVIDUAL DIFFERENCES IN RESPONSE TO PB: DO PHYSIOLOGIC DIFFERENCES INFLUENCE SUSCEPTIBILITY TO PB?**

Genetic polymorphism or phenotypic differences in enzymes that may help to break down PB, as well as other individual differences in action of PB, influence its effect and toxicity. Examples of enzymes for which individual variations occur include butyrylcholinesterase (Gentry, Bitsko, et al., 1996; Loewenstein-
Lichtenstein, Schwarz et al., 1995; Lotti, 1995) and paraoxonase (Davies, Richter, et al., 1996). Symptoms occurring in some PGW veterans but not in others who experienced similar exposures may have resulted in part from these and other individual differences.

**INTERACTIONS WITH OTHER EXPOSURES: DO INTERACTIONS BETWEEN PB AND OTHER EXPOSURES ENHANCE THE TOXICITY OF EFFECTS?**

PB in interaction with pesticides and insect repellents (permethrin and DEET) may lead to synergistic nervous system toxicity (McCain, 1997; McCain, 1995a; Abou-Donia, 1996a, 1996b, 1996c), which may contribute to symptoms seen in PGW veterans. Interactions with other drug and chemical exposures may be germane, and a “toxic cocktail” of many exposures may possibly have contributed to illnesses in PGW veterans. A possible PB interaction with nicotine use in tobacco merits evaluation.

**BROMISM: DOES ACCUMULATION OF THE BROMIDE FROM PB PRODUCE BROMISM?**

Excessive use of PB may lead to symptoms of bromism from accumulation of bromide in the body. Bromide intoxication may cause various combinations of a host of neurological and psychiatric symptoms, including confusion, irritability, tremor, memory loss, concentration difficulties, incoordination, vision changes, and psychotic behavior. An acne-like eruption of the face and hands (“bromoderma”), or other rash may also occur. Some of these symptoms were seen in PGW veterans who received PB.

**MULTIPLE CHEMICAL SENSITIVITY (MCS): DOES PB LEAD TO MCS?**

PB, together with other chemical exposures, may contribute to the condition termed “multiple chemical sensitivity syndrome,” or “toxicant-induced loss of tolerance” (Miller and Hitzel, 1995; Miller, 1996a, 1997; Miller, Ashford, et al., 1997). Some evidence suggests that symptoms in some PGW veterans are compatible with this “syndrome.”

**NEUROMUSCULAR JUNCTION EFFECTS: DOES PB PRODUCE NEUROMUSCULAR JUNCTION CHANGES?**

PB, as with other AChE inhibitors, may lead to motor endplate degradation (Gebbers, Lotscher, et al., 1986; Glickson, Achiron, et al., 1991). Changes can be detected in the signaling cell side (“presynaptic”), as well as at the side of the
receiving muscle cell ("postsynaptic"). Gross changes in the muscle are seen under a microscope and with testing of synaptic function, and these changes may contribute to symptoms in PGW veterans.

NEUROTRANSMITTER DYSREGULATION: DOES PB ALTER REGULATION OF NEUROTRANSMITTERS, PARTICULARLY ACETYLCHOLINE?

Heightened ACh activity from PB use may lead to changes in regulation of the cholinergic system, such as "desensitization" of cholinergic receptors, reduced release of ACh, and other strategies of "adaptation" to high levels of ACh. Regulatory effects may persist after cessation of PB, producing subsequent symptoms of low ACh. Such symptoms might be expected to include fatigue, memory loss, and sleep difficulties—symptoms prominent in PGW veterans.

CHRONIC EFFECTS

It has been questioned whether PB, in conjunction with other AChE inhibitor exposures (Gordon, Inns, et al., 1983), could lead to delayed and/or chronic neuropsychiatric effects, perhaps through mechanisms described in other chapters. This chapter reviews the plausibility and evidence regarding long-term neuropsychiatric effects following PB and other AChE administration.

OTHER CONSIDERATIONS

An assortment of other topics possibly relating PB to symptoms and complaints in PGW veterans are briefly reviewed. These include

- Fertility
- Hormone effects (PB has been shown to lead to effects on growth hormone, thyroid-related hormone, and ACTH that vary by sex, age, circadian timing, presence of dementia, or cognitive, affective, or anxiety disorder (Giustina, Brescian, et al., 1994; O’Keane, Abel, et al., 1994; Murialdo, Fonzi, et al., 1993; Llorente, Lizcano, et al., 1996; Lucey, Butcher, et al., 1993)
- Sleep (regulated by ACh and serotonin)
- Violent death (especially from unintentional injury)
- Teratogenicity (effects on fetal development)
COMMENT ON PB DOSES

In subsequent chapters, when doses of PB are given in mg/kg, they will be translated to the corresponding number of PGW doses, calculated assuming a 30 mg dose was given to a 70 kg (154 lb) man, for 0.43 mg/kg. (This assumes that the equivalent mg/kg dose is the physiologically equivalent dose, which unfortunately need not be the case, as discussed below.) It is important to note that the mg per kilogram dose given to a 45 kg (100 pound) serviceperson (of which there were some)—is a full 54 percent higher (0.66 mg/kg). The same per kilogram dose will be a smaller multiple of the small-person-PGW dose: the stated number of PGW doses will overstate the small-person multiple by 54 percent (multiply by $0.43/0.66$, or 0.65 to get the number of small-person PGW doses). (Although the stated number of PGW doses will understate the large-person PGW multiple, this is less relevant to concerns about amplified risk in some individuals.)

This correction may deviate from the "true" dose equivalent particularly when a mode of administration other than oral is used, resulting in a higher dose to the blood with than when PB is given orally. Because of widely different estimates of the multiplier, an adjustment for route of administration will not be calculated into the PGW dose. For a more accurate presentation, the stated PGW multiple may need to be further multiplied by a factor in the range of two to 30, and the reader is invited to bear this in mind. For instance, as stated earlier, PB manufacturer Roche Products, Ltd., has recommended that one-thirtieth of the oral dose should be used when giving PB intramuscularly or intravenously; whereas one study based on eight humans reported that an average of 16 percent of the oral dose was absorbed (16 percent ± 4 percent, range 10–22 percent in that sample) (Moylan Jones, Parkes, et al., 1979), suggesting a multiplier of five or six.

Although some animal studies that find PB to be toxic use many times the PGW mg/kg dose, some animal studies on which efficacy of PB is based also do so. The dose of PB in animals that is “equivalent” to that in people cannot simply be determined by administering the same number of mg of PB per weight. Just as the same mg/kg dose leads to different levels of AChE inhibition from one person to another, so there are differences from one species to another in the amount of AChE inhibition conferred, on average, by a given mg/kg dose of PB. Since the “benefit” of PB is presumed to result from the AChE inhibition produced by PB, the percentage of AChE inhibition rather than the PB dose may be used to determine a “pharmacologically equivalent dose.” In short, producing the same average percentage of AChE inhibition in a different species may require a different PB dose. (Unfortunately, what is pharmacologically equivalent for therapy may not be identical to what is pharmacologically
equivalent for adverse effects, unless these effects are also predicted exclusively by AChE inhibition.)

As an example, in studies showing PB to be effective for soman pretreatment in primates, the “equivalent” dose has often been chosen to be the dose of PB that produces a degree of inhibition of AChE comparable to that sought in humans (e.g., approximately 30 percent), rather than the same mg/kg dose given to humans (1.2 mg/kg/day, for a “typical” person). The consequence is that higher doses of PB are administered per weight in monkeys compared to man—three times as high (Hayward, Wall, et al., 1990), 10 times as high (4.13 mg/kg PB intragastric single dose “to produce” blood ChE carbamylation of 30 percent, comparable to that expected with 30 mg/man) (Dirnhuber and French, 1978; Dirnhuber, French, et al., 1977), or even an individualized 21–50 times as high a mg/kg dose in monkeys (25–60 mg/kg/d (Dirnhuber, French, et al., 1977) versus 1.2 mg/kg/d in people) to achieve an AChE inhibition range of 20 percent to 50 percent, similar to the AChE inhibition range seen in humans on the designated pretreatment dose of 30 mg three times a day (Moylan-Jones, Parkes, et al., 1979, 1984).

Analogously, while the dose of atropine given to the “typical” human is 2 mg, a dose four times higher (on a per weight basis) of atropine is administered to primates to produce the “equivalent” dose in testing the protective effect of post-nerve-agent atropine, on the grounds that they are less “sensitive” to the effects of atropine. Much higher doses of atropine—e.g., 17 mg/kg—have been used in other animal models, such as guinea pigs (Gordon, Maidment, and Leadbeater, 1974).

Therefore, if higher doses per kg of PB are used in animals and considered pharmacologically equivalent when showing the benefits of PB (an assumption that is optimistic in extrapolating benefit to humans with lower doses), they should surely also be considered clinically equivalent in evaluating toxicity (the conservative and therefore prudent assumption which supposes that comparable AChE inhibition in primates—as reflected in a higher dose—is required to fairly show possible toxicity).