This chapter briefly reviews circumstances of use of PB in the PGW, including production and storage of PB, training of personnel with regard to PB use, decisions regarding use, and actual use of PB. (This does not include such circumstances of use as concurrent exposures, which are reviewed elsewhere—see Chapter Nine, “Interactions.”) A review of the circumstances of use was undertaken to ascertain whether any irregularities in these circumstances might pertain to illnesses in PGW veterans and to evaluate ways in which circumstances may be improved in future deployments. This chapter relies heavily on non-peer reviewed sources (government reports and personal communication), because much information regarding circumstances of use is rare in the peer-reviewed literature.

**PRODUCTION**

PB for use in the PGW was produced overseas. No 30 mg PB tablets are manufactured in the United States. Duphar BV in Holland and Roche Products, Ltd., in England produced PB tablets used in Operation Desert Shield and Operation Desert Storm in the PGW (Brake, 1997). Discussion with FDA officials indicates that drugs manufactured overseas for use in the United States are required to meet the same criteria and are subject to the same oversight as drugs manufactured in the United States. PB was distributed in blister packs of 21 30 mg tablets (a one-week supply), each termed a Nerve Agent Pretreatment Pack (NAPP).

**PACKAGING**

The NAPP states the agent and dose (21 tablets PB USP 30 mg). Dutch packaging from 1990 contained the following directions:

1. Commence taking only when ordered by your commander.
2. Take one every eight hours.
3. It is dangerous to exceed the stated dose.

The PB packaged at Duphar in Amsterdam, the Netherlands, included the manufacture date and lot number.

Current packaging (not that used in the Gulf War) on PB packaged at Roche Products Ltd., U.K., states “For Military Combat Use and Evaluation” and contains the following additional warning:

Warning

If you have asthma, are pregnant or are taking medications for high blood pressure or glaucoma, see your unit doctor before taking pyridostigmine.

Pyridostigmine may cause stomach cramps, diarrhea, nausea, frequent urination or headaches.

Seek medical attention if these or other symptoms persist or worsen.

STORAGE

Under Forces Command (FORSCOM) guidelines, following FDA/DSCP directives, PB in NAPP must be stored refrigerated in temperatures ranging from 2° to 8° C (35° to 46° F) to retain potency for the full shelf life. Those that have exceeded their expiration date or have remained unrefrigerated for more than six months are not to be used (FORSCOM, 1990; Field Manual, 1990). According to discussion with some in-theater personnel, PB, once overseas, was not refrigerated, although others report that PB that remained in the hands of the medical/logistics community was reputedly refrigerated (Clawson, 1999); nor was there any indication that PB required refrigeration during what proved to be a short conflict. Discussion with FDA officials indicates that no concerns regarding toxic products were related to a lapse in the refrigeration of PB (FDA, 1997). PB is refrigerated only to ensure efficacy with extended storage. PB given in the PGW was primarily made for the PGW and manufactured shortly prior to it. Other PB was manufactured approximately five years earlier (Clawson, 1999). PB is on a “shelf life extension program” through the FDA. PB from 1985 has continued to undergo testing, and has continued to pass all tests, receiving successive one- to two-year shelf life extensions (Clawson, 1999).

TRAINING AND EDUCATION

As part of granting a waiver of informed consent to DoD for use of PB as a nerve agent pretreatment during the PGW, the FDA required DoD to disseminate information to all military personnel concerning the risks and benefits of PB (Federal Register, 1997; Friedman, 1997).
Efforts were made to train medical personnel in the use of PB and in the recognition and treatment of side effects related to use of PB. According to FORSCOM regulations, unit medical personnel must be trained to recognize the signs and symptoms of PB overdose, allergic reactions, and side effects and to give emergency treatment if necessary (FORCOM, 1990). A “Field Manual” was produced (and has since been updated) that describes the purpose of nerve agent pretreatment; the NAPP Tablet Set; effects of PB; principles of use; administration in an uncontaminated environment; signs and symptoms of overdose, adverse reactions, and contraindications; emergency medical treatment for PB’s adverse side effects, allergic reactions, and overdose; and responsibilities of corps/division/wing commanders, the units, and the unit medical personnel (Field Manual, 1995; Field Manual, 1990).

Evidence suggests there was wide variation in the education of personnel in the combat setting. A survey by DoD, of an unspecified number of military personnel, queried their views on the adequacy of the training and information they received regarding PB (Federal Register, 1997). Of 149 respondents, 43.7 percent responded to the question “Was training about pyridostigmine adequate?” in the negative. Most expressed the desire for more information on side effects, long-term effects, and the drug’s mechanism of action. The following list is a sample of comments from those who felt the training was inadequate, and from those who felt it was adequate but could have been better (Federal Register, 1997):

- “No standard side effects were given.”
- “No training on side effects.”
- “People were worried about the drug’s side effects. Many people avoided taking it. Some people would double dose after missing one.”
- “Combat lifesavers brief it and said it was FDA-approved.”
- “Many soldiers didn’t take the tablets due to the fact that they weren’t FDA approved or thought not.”
- “Didn’t know what it did, what it was for. Disregarded instructions to take it.”
- “Training was not enough in layman’s terms. You would need to know more about nerve agents.”

Veterans made similar remarks regarding the adequacy of the information they received, at hearings before the Senate Committee on Veterans’ Affairs and the Presidential Advisory Committee on Gulf War Veterans’ Illnesses (Federal Register, 1997).
As part of a DoD survey of medical personnel (described in Chapter Three, subsection on “Side Effects”), 15 of 23 medical officers who returned the survey indicated that the information sheet on PB was not distributed to personnel instructed to take the drug. Two respondents said the information was distributed, and one, whose unit was not instructed to commence treatment with PB, indicated that he had the sheet available for distribution (Federal Register, 1997). The FDA has expressed concern about several features of PB training. These include the high rate of dissatisfaction regarding education, the responses indicating that the Army’s educational activities were uneven and possibly not targeted to the education level of all personnel; and the indication that the information sheet on PB was not provided and disseminated to military personnel in the Gulf as conditioned in the commissioner’s letter granting the waiver of informed consent under the interim rule (Federal Register, 1997). (See also Rettig, 1999.)

DECISION REGARDING USE

Under FORSCOM guidelines, the corps or division commander determines whether to begin, continue, or discontinue the NAPP medication with advice from the intelligence officer or chemical officer and the surgeon (FORSCOM, 1990). Unit commanders had discretion on whether and when to order use of PB and could delegate this authority to the lowest level of field command (Federal Register, 1997). Documentation does not exist on how far down the command chain the authority was delegated in each unit (Federal Register, 1997). The decision to use PB was to be reevaluated each three days, and administration beyond 21 days was not recommended without a thorough evaluation of the situation (FORSCOM, 1990). There is no documentation regarding adherence to these directives.

USE

Some unit commanders reportedly advised troops to take more than the stated amount of PB. Veterans’ self-reports of pills taken, based on telephone interviews conducted by the Office of the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses (OSAGWI), range from one tablet daily to five tablets every four to six hours (Brake, 1997). The troops did not necessarily take PB as advised (Federal Register, 1997); monitoring was variable, ranging from strict enforcement, with pills taken while in formation, to use of the honor system (Brake, 1997). Some individuals report having taken more than 60 tablets in total (Zeller, 1997), or in one “Open Letter” on the Internet, 500 tablets over six months (Hamden, 1997).
Although several reports states that “most” or “nearly all” or “a great majority” of U.S. troops received PB (Defense Science Board, 1994; National Institutes of Health, 1994) or that most allied coalition troops and Israeli civilians received PB pretreatment (De Fraites, 1996), the actual usage appears to be substantially less comprehensive. One estimate, in use by the Office of the Special Assistant for Gulf War Illnesses is that 250,000 to 300,000 U.S. personnel received some PB, an estimate based on number of tablets delivered but not returned in the system (Brake, 1997). (This estimate is subject to uncertainty based, among other factors, on uncertainty in average duration of use.) Tablets were taken primarily in January 1991 in preparation for the air war, and again in February 1991 in preparation for the ground war (Brake, 1997). Based on the author’s discussions with Israeli military personnel and leaders, conducted in concert with the OSAGWI, Israeli military but not civilians received PB during the PGW.

There is no documentation on whether or when each unit issued orders to begin taking PB or on who took it (Federal Register, 1997).

**OTHER NATIONS**

PB nerve agent pretreatment was used by the United Kingdom and Canada as well as the United States; perhaps 45,000 U.K. troops received PB (Defense Science Board, 1994). The French evidently dispensed PB to their troops but did not issue the order to use it. However, not all PB was returned, and some French troops took PB. Saudi Arabian and Egyptian troops did not take it.

**PB TIMETABLE IN THE PGW**

The following timetable is adapted primarily from De Fraites (1996) with additional input. (The accuracy of the statements has not in each case been independently verified.)

**Aug. 2, 1990:** Iraq invades Kuwait. At the onset of Operation Desert Shield, the threat of chemical weapons, including exposure to nerve agents is recognized.

**Aug. 7, 1990:** FORSCOM message provides guidance for issue and use of PB, IAW FM 8-285 during Operation Desert Shield. PB tablet to be used when risk of imminent nerve agent exposure is evident, and only on direct order of division or corps commander.

**Oct. 11, 1990:** U.S. Army Medical Research and Development Command identifies the need for FDA waiver for use of PB in Operation Desert Shield. Though PB has been licensed by FDA, it had not been specifically approved for use as NAPP.
Dec. 21, 1990: FDA publishes interim regulation in Federal Register allowing waiver of informed consent for investigational new drugs (IND) for DoD use during Operation Desert Shield. This statement explains FDA position on specific waivers to DoD under circumstances when informed consent is considered unfeasible.

Dec. 28, 1990: Assistant Secretary of Defense (Health Affairs) submits to FDA a specific request for waiver of informed consent for PB pretreatment for Operation Desert Shield.

Jan. 8, 1991: FDA approves the waiver of informed consent for PB for Operation Desert Shield. The FDA’s Informed Consent Waiver Review Group supports the DoD use of PB as the only potentially useful nerve agent pretreatment available. The group “had no specific safety concerns” with the dose of 30 mg each eight hours (only 15 percent of the dose often used to treat myasthenia gravis). The only substantial FDA concern expressed in this memo is that DoD instructional materials (Field Manual 8-285 and Training Manual 90-4) implies that PB pretreatment had been proven effective in human trials. FDA agreed with the text of a supplemental information sheet produced by DoD that stated that PB had been shown effective in animal studies.

Jan. 16–17, 1991: Operation Desert Storm (air war) begins. PB use was ordered on at least two separate occasions in the subsequent 30 days. The soldier information sheet gets very limited distribution.

Feb. 23, 1991: Ground war begins and concludes after 100 hours. Results of a survey involving 40,000 XVIII Corps (Airborne) soldiers conducted shortly after cessation of hostilities indicated that though minor symptoms such as abdominal cramps and frequent urination were quite common, only about 1 percent of people taking PB sought medical care, and fewer than one in 1,000 had to discontinue PB pretreatment.

May 24, 1996: New Drug Application for PB use in NAPP filed with FDA.

SUMMARY

Circumstances of PB use were appropriate in several respects. A waiver of informed consent was obtained from the FDA prior to administration of PB to personnel without informed consent. Conservative strategies for use of PB with the threat of nerve agent exposure were devised, requiring repeated reevaluation of PB use every several days, with decisionmaking regarding use of PB by high-level commanders with medical, chemical, and intelligence consultation. A training manual was devised and training programs were implemented in an effort to ensure that medical and chemical personnel had knowledge regarding
the use and side effects of PB. Agreement in principle was made to educate troops regarding the function and side effects of PB. No irregularities were identified in storage or delivery that would have altered the characteristics of PB to render it unexpectedly deleterious.

The circumstances of PB use were suboptimal in several respects. Training in the use and side effects of PB was not in all cases reflected in practice in the field. The FDA’s requirement of information distribution regarding PB to all military personnel as a condition of the waiver of informed consent was not upheld. Personnel perceived the education they received to be inadequate. Because of these problems, wide variations in de facto use occurred across and within units, with irregularities in orders given regarding dosage in some units and with some personnel electing to alter the dosing schedule or refrain from use of PB. Record-keeping to allow a determination of which units received PB, for how long, and when is not available; neither are records regarding which level of command made the decision regarding the use of PB.

Overall, many circumstances of PB use—including its manufacture, transport, and storage—do not appear to have contributed materially to illnesses in PGW veterans. For instance, there is no evidence that manufacture was flawed and resulted in an inferior or toxic product; or that adverse storage conditions were present and led to toxic substances or byproducts of PB. Whether other types of “circumstances” of PB use—such as coexposure with other PGW exposures—could have been contributory is the subject of subsequent sections (e.g., Chapter Nine, “Interactions Between PB and Other Exposures”).

**SCIENTIFIC RECOMMENDATIONS**

Scientific recommendations for the circumstances of PB use constitute policy recommendations, which are not the primary focus of the present report. However, certain recommendations can readily be made:

- Advance planning and training should be improved regarding education and the consent process.
- Medical personnel should instruct soldiers regarding PB side effects.
- Consistent strategies should be adopted for handling those who “decline” to take PB when ordered.¹

¹The military has held that refusal by personnel to take PB under orders, when the threat of chemical warfare is perceived, potentially compromises the welfare of the whole unit in the event of nerve agent attack and is therefore untenable. This position is made less persuasive by the limited corpus of evidence regarding benefits of PB in the event of nerve agent attack. Evidence of benefit vis-à-vis soman derives from only a few studies in primates: in one study, the effects of atropine and
• Careful planning should be undertaken to ensure accurate generation and coordinated maintenance of records regarding who received which agents, from what lots, in what doses, and when.

• Testing of PB pretreatment for nerve agents other than soman should be performed in primates. The effects of pralidoxime and atropine postexposure treatment should be compared with and without PB pretreatment to ensure that PB pretreatment does not in fact enhance lethality to an important degree.

oxime postexposure treatment were tested with and without PB pretreatment to calculate protective ratios. Of more concern, there is no primate evidence regarding the effect of PB pretreatment in the event of nerve agent attack with other nerve agents. (That is, no studies have evaluated lethality with atropine and pralidoxime, with and without PB pretreatment.) The beneficial effect of PB pretreatment against soman occurs in other mammals but is magnified in primates. It is conceivable that the detrimental effect of PB on death from sarin and VX that is seen in other mammals is also magnified in primates, and there is no primate evidence to preclude this possibility. (Neither is there evidence from close primate relatives to humans that benefit against soman is preserved, though evidence from some other primate species suggests that primates may share similar characteristics related to aging of AChE–nerve agent complexes.) It is also possible, however, that PB provides benefit in primates against all nerve agent threats. Because neither the mechanism of benefit of PB for soman nor the mechanism of “harm” for sarin and VX are fully understood, this determination cannot be made without empirical testing. Thus, the existing state of knowledge is consistent with the possibility that refusal to take PB either compromises or enhances the viability of the unit in the event of nerve agent attack, particularly when the threat includes nonsoman nerve agents. It might be appropriate to consider this element of uncertainty in making judgments about the right of personnel to refuse the pretreatment drug.