Protocol #1

1. A total of _48_ column "E" guinea pigs were utilized in this study.

2. Painful procedure:

Challenge with nerve agent sufficient to produce seizures. Determining toxicity of test oxime compounds. Lethal challenge with nerve agents to test therapeutic efficacy of test compounds.

3. Justification:

Nerve agents are by definition toxic compounds that elicit a variety of toxic responses that are considered distressful. The goal of this protocol is to determine the medical benefit of adding alternative anticholinergic drugs to the standard immediate therapeutic medical countermeasure regimen. Thus, subjecting the animals to levels of nerve agent intoxication that reliably elicit the toxic responses is essential to the goals of this protocol.

4. No federal regulations mandate this procedure.

Protocol #2

1. A total of _8___ column "E" nonhuman primates were utilized in this study.

2. Painful procedure:

Agent exposure

3. Justification:

This protocol requires exposure to potentially lethal doses of chemical agents in unanesthetized nonhuman primates to be able to monitor behavioral performance and physiological parameters. Agent exposure is thought to cause some pain and/or distress because of the intense physiological changes produced by these toxicants. We cannot pre-treat the animals with any medication as this would compromise the results of the study in determining the dose of the chemical agent that leads to behavioral deficits.

4. No federal regulations mandate this procedure.

Protocol #3

1. A total of _6___ column "E" nonhuman primates were utilized in this study.

2. Painful procedure:

Agent Exposure

3. Justification:

This protocol requires exposure to potentially lethal doses of chemical agents in unanesthetized nonhuman primates to evaluate the toxicity of these agents and the efficacy of pretreatment, treatment, decontamination procedures. In addition it allows monitoring of behavioral performance after exposure, pre-treatment, and treatment. Agent exposure is thought to cause some pain and/or distress because of the intense physiological changes produced by these toxicants. We cannot pre-treat the animals with any analgesic medication as this would compromise the results of the study in determining the dose of the chemical agent that leads to behavioral deficits.

4. No federal regulations mandate this procedure.

Protocol #4

1. A total of 10 column "E" pigs were utilized in this study.

2. Painful procedure:

Nerve agent exposure may lead to convulsions followed by potential pain from muscle fasciculations and convulsions. See protocol for more information.

3. Justification:

The use of medical countermeasures (atropine, oxime, and anticonvulsant) increases survival and may reduce pain but is unlikely to completely alleviate all pain. In minipigs a convulsive dose of nerve agent leads to unconsciousness and no pain is thought to be experienced at this time; however, there may be some pain or distress following seizures as a result of the intense physical activity (convulsions). Anesthetics and analgesics have profound effects on brain function that can interact with the drugs of interest (Marshall and Wollman, 1985) and/or the toxicity of the nerve agent (Clement and Copeman, 1984). Anesthetics may have pro-convulsive or anticonvulsive effects which would complicate interpretation of the effects of experimental treatments.

4. No federal regulations mandate this procedure.

Protocol #5

1. A total of 3 column "E" pigs were utilized in this study.

2. Painful procedure:

Exposure to phosgene and the development of pulmonary edema.

3. Justification:

Interfering with the natural progression of phosgene-induced injury would compromise our ability to use the model to assess medical countermeasures and countermeasure strategies. Alleviation of pain via use of analgesics is very likely to influence the same physiological mechanisms as phosgene and any potential therapeutics. Any administration of analgesics or anti-inflammatory drugs to reduce discomfort will confound experimental results and potentially mask the true outcomes of experimental countermeasure strategies. Administration of anesthetics or tranquilizers may also have respiratory depressant effects that would be contraindicated in this model.

4. No federal regulations mandate this procedure.
