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PRINCIPAL INVESTIGATOR: Mary R. Cook, Ph.D.

CONTRACTING ORGANIZATION: Midwest Research Institute
Kansas City, Missouri 64110

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Mary R. Cook, Ph.D.

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
Midwest Research Institute
Kansas City, Missouri 64110

E-Mail: mcook@mriresearch.org

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We conducted two double-blind studies designed to test the following specific hypotheses about pyridostigmine bromide (PB): (a) under well-controlled conditions, AChE and/or BuChE inhibition will be related to alterations in the performance of complex tasks, heart rate variability (HRV), and peripherally mediated measures of physiological and sensorimotor functions; (b) individual differences can be differentiated from pharmacokinetic variability by use of a dose-response design, and (c) PB will produce more centrally-mediated effects under heat stress. Both studies were double-blind, placebo-controlled, crossover design. Volunteers were 18-35 yrs of age. In Study 1, physiological, sensorimotor, and cognitive measures were collected. In addition, plasma and urinary PB and 3-hydroxy-*N*-methylpyridinium bromide (THMP, the major metabolite of PB), as well as AChE and BuChE, were measured. These endpoints were measured, time-locked to time of intake of the pills and time of the test battery. Significant PB effects on heart rate and heart rate variability were observed. In study 2, volunteers were exposed to heat prior to and during testing; on the other day, they were tested at normal room temperature. Study 1 findings on side effects, heart rate and heart rate variability were replicated.

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# Final Report

# Individual Differences in Neurobehavioral Effects of Pyridostigmine Bromide

## Investigators:

**Principal Investigator:**

Mary R. Cook, Ph.D. (Company Signatory)
Principal Advisor
Midwest Research Institute
425 Volker Boulevard
Kansas City, Mo. 64110

**Co-Principal Investigator:**

Antonio Sastre, Ph.D.
Senior Advisor
Midwest Research Institute
425 Volker Boulevard
Kansas City, Mo. 64110

## Organization:

Midwest Research Institute
425 Volker Boulevard
Kansas City, Mo 64110

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| **Point of Contact** | Ronald E. Clawson, Ph.D.<br>Pharmaceutical Systems<br>U.S. Army Medical Materiel<br>Development Activity (USAMMDA)<br>Attn: MCMR-UMP<br>622 Neiman St.<br>Ft. Detrick, MD 21702-5009<br>Phone (301) 619-2051,<br>Fax (301) 619-2304 |
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| **Principal Investigator:** | Mary R. Cook, Ph.D. (Company Signatory)<br>Senior Advisor<br>Midwest Research Institute<br>425 Volker Boulevard<br>Kansas City, Mo. 64110<br>Tel: (816) 753-7600 (extension 1157)<br>Fax: (816) 753-7380 |
| **Medical Monitor:** | Dr. Mary Centner Brothers<br>Midwest Occupational Medicine<br>Union Hill Commons<br>3037 Main Street, Suite 201<br>Kansas City, MO 64108-3323 |

This study was performed in compliance with Good Clinical Practices (GCP) procedures, including the archiving of essential documents.

**Date of Report:** May 2, 2001

Mary R. Cook, Ph.D. (Company Signatory)
Principal Investigator
Principal Advisor
Midwest Research Institute

5/5/01
Date

Richard D. Brown
Director, Life Sciences Division
Midwest Research Institute

5/2/01
Date

James E. Dworak, Ph.D.
Quality Assurance Officer
Midwest Research Institute

5/2/01
Date

# SYNOPSIS

Previous studies of the effects of pyridostigmine bromide (PB) on healthy volunteers have provided valuable information, but many questions remain. Of particular interest are the contribution of PB, if any, to Gulf War Veterans' illnesses, and the military relevance of individual differences in the reported symptoms and inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) induced by PB. MRI has conducted two double-blind studies designed to test the following specific hypotheses: (a) under well-controlled conditions, the amount of AChE and/or BuChE inhibition observed will be related to alterations in the performance of complex tasks, heart rate variability, and peripherally mediated measures of physiological and sensorimotor functions; (b) individual differences can be differentiated from pharmacokinetic variability by use of a dose-response design, and (c) under heat stress, PB will produce more centrally-mediated effects than it does without heat stress.

Study 1 is relevant to hypotheses (a) and (b). This study used a double-blind, crossover design. Young men (N = 36) and women (N = 31) aged 18 to 35 yr participated. Each phase (PB or PL) of the study consisted of one week, with one week separating phases; order of phases was randomly assigned. Approximately half of each gender group was randomly assigned to each dose group (30 mg or 60 mg every 8-hr for 13 doses). In this study, two test batteries that included physiological, sensorimotor, and cognitive measures were performed. The first battery consisted of seven tasks: Orthostatic Stress with electrocardiogram (ECG) and Blood Pressure measurements; Pattern Reversal Visual Event-related Potential (VEP); Brain Stem Auditory Evoked Potential (BAEP); Critical Flicker Fusion (CFF); OPTEC visual function; Hand Steadiness and Grip Strength; and subjective report of workload and fatigue. The tasks for the second battery were selected from the Neurobehavioral Evaluation System 2 (NES2) and the Automated Neuropsychological Assessment Metrics (ANAM); four tasks from the NES2 and nine tasks from the ANAM were included. The primary focus was on measures of higher-order cognitive abilities (memory, attention, complex processing, time sense, pattern recognition, mathematical processing, visual/motor integration, and reasoning). In addition, plasma and urinary PB and 3-hydroxy-*N*-methylpyridinium bromide (THMP, the major metabolite of PB), as well as AChE and BuChE, were the measured biochemical endpoints. These endpoints were measured from blood samples that were taken time-locked to time of intake of the pills and also to the time of the test battery. The results indicated that PB was well-tolerated, even at twice (60 mg every 8 hr) the military doctrinal dose; there were no serious adverse events. Side-effects were few and mild, not related to plasma PB levels, and the best predictor for side-effects during the PB week were side-effects during the placebo week. Significant PB effects on heart rate and heart rate varability were observed.

Study 2 is relevant to hypotheses (a) and (c). Study 2 used a double-blind, cross-over design. Thirteen men and 11 women were randomly assigned to two groups. Each volunteer took 13, 30 mg doses of PB at 8-hr intervals. Each subject also took 13 doses of placebo. One group was administered PB during the first testing week and placebo during the second testing week. The other group received pills in the reverse

order (i.e., order of administration of PB and placebo were counterbalanced). Testing took place on days 4 and 5 of each drug regimen. On one test day of each phase, the volunteers were exposed to heat prior to and during testing; on the other day, they were tested at normal room temperature. Testing was counterbalanced so that half the volunteers were tested first in the heat, and half were tested first at ambient temperature. The test battery included physiological, sensorimotor, and cognitive measures. Tasks were included in the battery if they showed drug effects in Study 1, or showed promise of clarifying unresolved questions raised by the first study. On test days, blood was drawn to quantitate AChE, BuChE, PB, and THMP. No analysis of urinary PB or THMP was performed, as the results of Study 1 indicated that they added no useful information beyond the information provided by the plasma levels.

In Study 2, dose in mg/kg was the best predictor of plasma PB. Plasma PB was the best predictor of AChE. The effects of PB on heart rate and on heart rate variability replicated the findings of Study 1, except that in Study 2, the predictors of change in heart rate variability were somewhat different. PB also enhanced the inhibition of the eye blink startle response by a pre-startle stimulus. There was a trend for PB to be associated with decreases in performance of the tracking task at elevated environmental temperature. As in Study 1, side effects were infrequent and mild, and the best predictor of side effects during the PB week was the individual's side effects during the PL week.

The two studies have provided important information for evaluating the military consequences of using PB as a prophylactic drug to aid survival in the event of a chemical warfare attack.

## 3. TABLE OF CONTENTS


1. TITLE PAGE ..... i

2. SYNOPSIS ..... iv

3. TABLE OF CONTENTS ..... vi

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS ..... viii

5. ETHICS ..... 1
   - 5.1 Ethics ..... 1
   - 5.2 Ethical Conduct of the Study ..... 1
   - 5.3 Patient Information and Consent ..... 1

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE ..... 1

7. INTRODUCTION ..... 3

8. STUDY OBJECTIVES ..... 4

9. INVESTIGATIONAL PLAN ..... 5
   - 9.1 Description of Overall Study Design and Plan ..... 5
   - 9.2 Discussion of Study Design ..... 13
   - 9.3 Selection of Study Population ..... 13
   - 9.4 Treatments ..... 15
   - 9.5 Methods ..... 16
   - 9.6 Data Quality Assurance ..... 25
   - 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size ..... 26
   - 9.8 Changes in the Conduct of the Study or Planned Analyses ..... 26

10. STUDY PATIENTS ..... 27
    - 10.1 Disposition of Patients ..... 27
    - 10.2 Protocol Deviations ..... 27

11. EFFICACY EVALUATION ..... 28

12. SAFETY EVALUATION ..... 28
    - 12.1 Extent of Exposure ..... 28
    - 12.2 Adverse Events ..... 28
    - 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events ..... 30
    - 12.4 Results, Study 1 ..... 30
    - 12.5 Results, Study 2 ..... 47

13. DISCUSSION AND OVERALL CONCLUSIONS ..... 55

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT ..... 59
    14.1 Demographic Data Summary Figures and Tables ..... 59
    14.2 Efficacy Data Summary Figures and Tables ..... 61
    14.3 Safety Data Summary Figures and Tables ..... 61

15. REFERENCE LIST ..... 62

Volume 2—Appendix 16
Section 16.1.1

Volume 3—Appendix 16
Section 16.1.2 to 16.2.8

## 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACD ..... acidified citrate dextrose
AChE ..... acetylcholinesterase
ANAM ..... Automated Neuropsychological Assessment Metrics
ANOVA ..... analysis of variance
BAEP ..... brain stem auditory evoked potential
BBB ..... blood-brain barrier
BMDP ..... BioMeDical Package
BuChE ..... butyrylcholinesterase
CFF ..... critical flicker fusion
ChE ..... cholinesterase
CNS ..... central nervous system
DR ..... doctrinal regimen
ECG ..... electrocardiogram
EDTA ..... ethylenediaminetetracetic acid
EEG ..... electroencephalogram
HCG ..... human chorionic gonadotropin
HF ..... high frequency
HPLC ..... high pressure liquid chromatography
HR ..... heart rate
HRV ..... heart rate variability
HSRRB ..... Human Subjects Research Review Board
IRB ..... Institutional Review Board
LF ..... low frequency
MRI ..... Midwest Research Institute
NES2 ..... Neurobehavioral Evaluation System 2
OP ..... organophosphate
PB ..... Pyridostigmine Bromide
PBSES ..... Pyridostigmine Bromide Side Effects Scale
PI ..... Principal Investigator
PL ..... placebo
PPI ..... pre-pulse inhibition
QAU ..... quality assurance unit
QC ..... quality control
RBC ..... red blood cell
S ..... subject
SD ..... Sprague-Dawley
THMP ..... 3-hydroxy-*N*-methylpyridinium bromide
USAMMDA ..... United States Army Medical Materiel Development Activity
UV ..... ultra-violet
VEP ..... visual event-related potential
WKY ..... Wistar-Kyoto

# 5. ETHICS

## 5.1 Ethics

The protocol, protocol amendments, and consent form for this study were reviewed by the Midwest Research Institute (MRI) Institutional Review Board for Human Studies (IRB), and by the U. S. Army Human Subjects Research Review Board (HSRRB).

## 5.2 Ethical Conduct of the Study

The study was conducted in accordance with the ethical principles of both MRI and the sponsor, which have their origins in the Declaration of Helsinki.

## 5.3 Patient Information and Consent

The procedures, risks, and benefits of participation were explained over the telephone. Individuals who indicated interest in participating were asked to come to MRI, where the procedures, risks and benefits were again explained, and written consent obtained (see Appendix 16.1.3). A copy of the consent form was given to the volunteer. Volunteers then received a physical examination and, if deemed suitable by the project physician, were assigned a subject number that allocated them to the 30 v 60 mg groups (for study 1; 30 mg only for study 2), and to the order of administration of placebo (PL) and PB.

# 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Figure 6.1 summarizes the administrative structure of the study within the context of MRI's administrative structure. The MRI IRB reports directly to the President and Chief Executive Officer. The Quality Assurance Unit (QAU) reports to the Senior Vice President. The Project Physician and Medical Monitor are shown as reporting to the Principal Investigator (PI); it should be noted, however, that they functioned independently in determining whether a volunteer was suitable for the study, whether an adverse event implied that the volunteer should be withdrawn from the study, and whether an adverse event was attributable to PB. Appendix 16.1.4 includes a list of the investigators and other persons who participated in analysis of study data. Resumes are also included in Appendix 16.1.4.

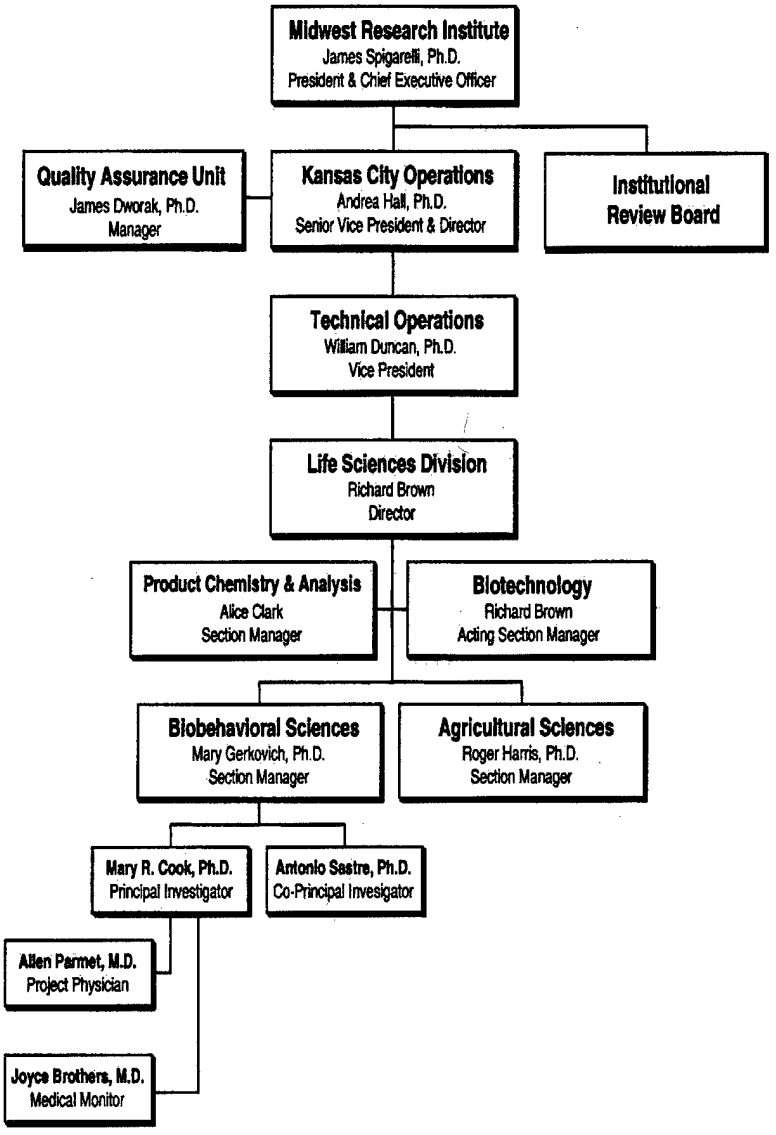


**Figure 6.1. Organizational Structure**

# 7. INTRODUCTION

Pyridostigmine bromide (PB) is used worldwide for the long-term treatment of myasthenia gravis at doses of 360 mg/day to more than 1,400 mg/day (Bryer-Pfaff et al., 1985; Drachman, 1998). More recently, low-dose regimens (30 mg every 8 hr: doctrinal regimen [DR]) have become an important part of the U.S. Armed Forces prophylactic defense against exposure to organophosphate (OP) chemical warfare agents such as soman. Field use of low-dose PB is based on studies of efficacy in animals, and on studies of safety in humans (Dirnhuber et al., 1979; Gall, 1981). Most human laboratory studies report few (if any) decrements in performance or adverse effects associated with DR of PB. However, questions have recently been raised and hypotheses have been formulated about a possible role of PB, singly or in combination with insecticides and/or other chemical, immunological or stress factors, in the etiology of Gulf War Veterans' illnesses (Golomb, 1999). This collection of illnesses has recently been reported as having central nervous system (CNS) origins. Among several hypotheses, a pharmacologically questionable mechanism has been proposed whereby the Gulf War Syndrome results from an OP-induced delayed neuropathy caused by PB in combination with insecticides (Haley, Kirk & Horn, 1997).

Several pivotal questions in the evaluation of some of these hypotheses are whether there are CNS effects of the ostensibly peripheral drug PB, and how those effects, if any, could persist long after discontinuation of the drug. The current belief is that the ionic nature of PB prevents its passage across the blood-brain barrier (BBB). However, some of the reported functional alterations resulting from PB (e.g., flicker fusion frequency (Borland et al., 1985) or vigilance (Graham and Cook, 1984)) are CNS processes. While there is little doubt that under nonstressful laboratory conditions and low doses, penetration of PB across the BBB into the CNS is minimal, the data are much weaker or non-existent for ranges of environmentally relevant temperature and stress conditions. The Medical Corps of the Israel Defense Forces has reported that mice subjected to a stressful 4-min forced swim exhibited a temporary breakdown of the BBB (Friedman et al., 1996). This breakdown allowed PB to enter the brain and inhibit brain AChE with the same effectiveness as the centrally-acting inhibitor physostigmine. Other large molecules normally excluded from the brain by the BBB (e.g., an Evan's Blue-albumin complex) also penetrated the brain under these conditions. These findings are based on, and consistent with, earlier work in rodents indicating that cold stress or mild heat stress can *reversibly* increase the BBB permeability. However, subsequent research attempting to replicate this work has been equivocal. If the original observations were applicable to humans, plausible scenarios exist whereby effects of such transient breakdowns of the BBB might lead to persistent effects. It is not possible to evaluate carefully this or other hypotheses, however, with the existing data on humans.

Previous functional human CNS studies have, by and large, failed to examine appropriate, sensitive measures with adequate sample sizes at a range of environmentally relevant temperatures and conditions. Their experimental designs have also failed to account for known absorptional variability and pharmacokinetic complexities of PB.

This has resulted in studies with large individual variations in plasma PB, as large as would be expected in a deliberate dose-response study, without the controls inherent in such a study design. The net result is a collection of studies that, due to lack of statistical power and to other methodological issues, would have likely failed to detect a central response to PB even if one exists. Study 1 was designed to take these factors into account. The results indicated that PB was well-tolerated, even at twice (60 mg every 8 hr) the military doctrinal dose; there were no serious adverse events. Side-effects were few and mild, not related to plasma PB levels, and the best predictor for side-effects during the PB week were side-effects during the placebo week. Significant PB effects on heart rate and heart rate variability were observed.

Study 1 has helped to determine whether there are functional CNS consequences of PB use. As expected, the responses observed were subtle and required sensitive measures and robust experimental designs to detect. Second, it evaluated whether the large, individual differences in AChE and BuChE inhibition and PB levels were reflected in physiological and performance measures (whether central or peripheral) and whether such differences might have military significance. Study 2 tested the replicability of the Study 1 findings, and evaluated the extent to which heat exposure increased the effects of PB.

In Study 2, dose in mg/kg was the best predictor of plasma PB. Plasma PB was the best predictor of both AChE and BuChE . The effects of PB on heart rate and on heart rate variability replicated the findings of Study 1, except that in Study 2, the predictors of change in heart rate variability were somewhat different. PB also enhanced the inhibition of the eye blink startle response by a pre-startle stimulus. There was a trend for PB to be associated with decreases in performance of the tracking task at elevated environmental temperature. As in Study 1, side effects were infrequent and mild, and the best predictor of side effects during the PB week was the individual's side effects during the PL week.

The two studies provide the U.S. Army with a more complete body of knowledge for optimal use of PB as a prophylactic OP-defense agent if a future large-scale deployment is needed.

## 8. STUDY OBJECTIVES

The following major questions were addressed by Study 1.

1. Is there a relationship between PB ingestion, ChE inhibition, and functional responses? Previous data did not allow multivariate correlation between plasma PB levels, degree of AChE and/or BuChE inhibition, and functional responses. Different conclusions have been drawn about the relationship between inhibition and response. We have clarified the reasons for the reported discrepancies by simultaneous measurement of plasma and urinary PB and AChE and BuChE inhibition, and by relating

the values obtained to functional responses in dose-response studies under well-controlled conditions.

2. Can true individual differences in responses to PB be distinguished from pharmacokinetic variability? While individual differences in responses to PB are known, as are the ranges of PB pharmacokinetic variations, *in vitro* measures have failed to predict *in vivo* individual differences. We distinguished pharmacokinetic variation from true individual differences by using a two-point dose-response study with simultaneous functional and biochemical measures.

The following major objectives were addressed by Study 2.

1. Determine whether the effects observed in Study 1 can be replicated in a similar sample of volunteers.

2. Determine whether exposure to heat alters the metabolism of PB, or the relationship between plasma PB, inhibition, and functional response.

## 9. INVESTIGATIONAL PLAN

### 9.1 Description of Overall Study Design and Plan

Both studies used a double-blind cross-over design. Figure 9.1 shows the design for Study 1; Figure 9.2 shows the sequence of study periods. In Study 1, volunteers were randomly assigned to one of two PB dose levels (30 and 60 mg); within each level, they were randomly assigned to receive either PB or PL during the first dosing week, and the other pill during the second dosing week. Pills were given at 8 hr intervals for 13 doses. A given subject received only one dose level. Prior to entering the drug intake part of the experiment, each volunteer was given a complete physical examination, and spent up to 10 hr becoming familiar with the tasks to be performed in the physiological and performance task batteries and the subjective measures. Table 9.1 lists the measures obtained in each of the batteries. During this time, two blood samples for baseline determination of BuChE and AChE were obtained between 1100 and 1130 hr. After training and baseline procedures had been completed, the volunteer subject (S) began Phase 1 of the experiment. Dosing began on Monday morning. Because field data indicated that some military personnel had adverse effects of PB after only one dose, Ss returned approximately 3.5 hr later for testing. Half of the Ss in each dose/order group were tested on the physiological battery on Monday; the other half were tested on the performance battery. Testing was repeated on Thursday and Friday. On Friday subjects were tested on the battery that was administered on Monday; on Thursday they were tested on the other battery. After testing on Friday, subjects were released for the weekend. A blood sample was obtained the following Monday, after which the volunteer was free for a week. On the next Monday, they returned to the laboratory and repeated the entire process. A blood test for pregnancy was performed for all women volunteers as part of the entrance examination, and just prior to Phases 1 and 2. When both phases

had been completed for a given S, he/she received another physical examination and was released from the study. Subjects who completed the study were paid $600; pay for those who did not was pro-rated.

Figure 9.3 shows the design and Figure 9.4 shows the sequence of study periods for Study 2. Table 9.2 shows the measures obtained. Dosing procedures were the same as Study 1, except that only one dose level (30 mg) was used. Subjects were randomly assigned to one of two PB/PL orders and within order, to the order of hot and control temperature conditions. No "wash-out" week was included in Study 2, as Study 1 had demonstrated that, by the Monday following the last PB dose, no detectable plasma PB was found. Testing was conducted in the Thermoelectric Laboratory at MRI. Half the subjects were tested in the heat on Thursday for two consecutive weeks (95°F, 30% relative humidity) and under control (75°F, 30%) conditions on Friday. The other half was tested in the reverse environmental order. Testing took place about 3.5 hr after the morning pill. At the conclusion of both phases, volunteers received another physical examination, and were released from the study. Those who completed the study were reimbursed $600.

No interim analyses were conducted. Monitoring of data quality and of safety occurred continuously, and both were discussed at project meetings held at least once each month.

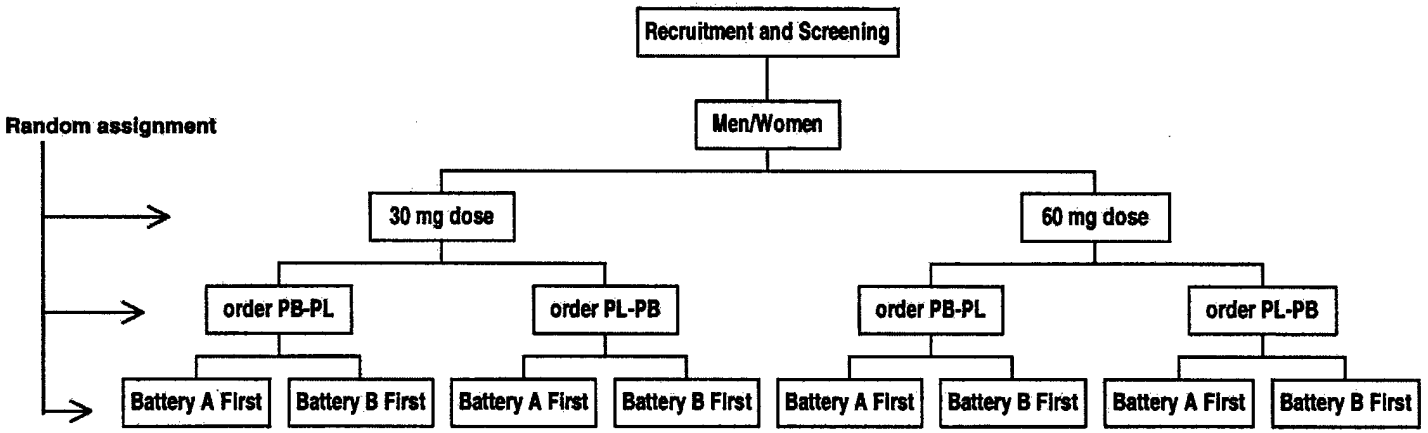


**Figure 9.1. Design of Study 1**

| Training Schedule: WEEK 1 | | Mon | Tues | Wed | Thur | Fri | Sat | Sun |
|---|---|---|---|---|---|---|---|---|
| ACTION | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Battery A Training | | | | Bty A | | | | |
| Battery B Training | | Btry B | Bty B | | | Bty B | | |
| Dosing Training | | | | Dose | | | | |
| Baseline Urine | | | | U | | | | |
| Baseline Blood | | | | Bld | | | | |
| Blood for Pregnancy Test—♀ only | | | | Prg Bld | | | | |
| Begin Food Diary | | | | | | | | Fd Diary |
| **Phase I and Phase II Schedule: WEEKS 2 and 4** | | **Mon** | **Tues** | **Wed** | **Thur** | **Fri** | **Sat** | **Sun** |
| **TIME** | **ACTION** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| 8:00 | Pill, Breakfast | P,Bk | P,Bk | P,Bk | P,Bk | P,Bk | | |
| 11:25 | Urine | | | | U | U | | |
| 11:30 | Blood | Bld | | | Bld | Bld | | |
| 11:35 | Lunch | L | | | L | L | | |
| 11:45 | Battery | Bty | | | Bty | Bty | | |
| 16:00 | Pill | P | P | P | P | P | | |
| 24:00 | Pill | P | P | P | P | P | | |

**Total Urine Collections = 5 Total Blood Draws = 9 (men), 10 (women) Total Doses = 26**

**Figure 9.2. Study 1, Training and Phase Schedule**

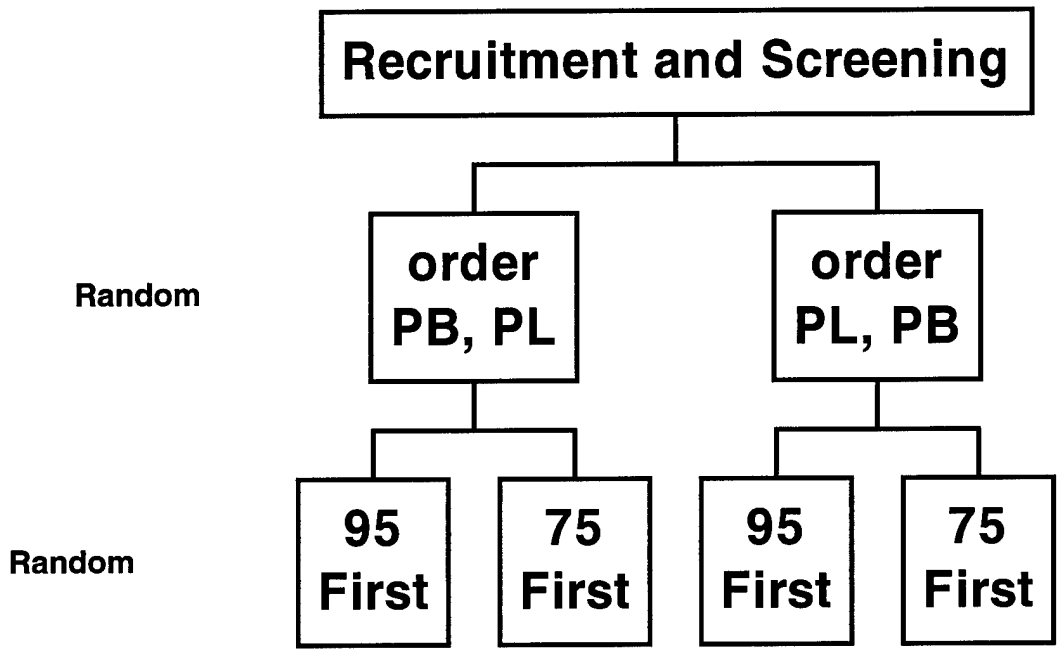


**Figure 9.3. Design of Study 2**

| Training Schedule: WEEK 1 | | Mon | Tues | Wed | Thur | Fri | Sat | Sun |
|---|---|---|---|---|---|---|---|---|
| ACTION | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Battery Training | | | Phys. | | Perf. | Perf. | | |
| Dosing Training | | | | Dose | | | | |
| Baseline Blood | | | | Bld | | | | |
| Blood for Pregnancy Test—♀ only | | | | Prg Bld | | | | |
| Begin Food Diary | | | | | | | | Fd Diary |
| **Phase I & II Schedule: WEEKS 2 & 3** | | **Mon** | **Tues** | **Wed** | **Thur** | **Fri** | **Sat** | **Sun** |
| **TIME** | **ACTION** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| 7:30 | Phase I, Day 1 blood draw | Bld | | | | | | |
| 8:00 | Pill, Breakfast | P,Bk | P,Bk | P,Bk | P,Bk | P,Bk | | |
| 11:30 | Blood | | | | Bld | Bld | | |
| 11:35 | Lunch | | | | L | L | | |
| 11:45 | Battery | | | | Bty | Bty | | |
| 16:00 | Pill | P | P | P | P | | | |
| 24:00 | Pill | P | P | P | P | | | |

**Total Blood Draws = 8 Total Doses = 26**

**Figure 9.4. Study 2, Training and Phase Schedule**

## Table 9.1. List of Measures, Study 1

Chemistry:
- Plasma PB
- Plasma THMP
- Urinary PB
- Urinary THMP

Biochemistry:
- AChE
- BuChE
- Ex-vivo affinity for carbomates

Physiology
- Heart Rate
- Heart Rate Variability
- Systolic and Diastolic Blood Pressure
- Pattern Reversal Visual Event-related Potential (VEP)
- Brain Stem Auditory Evoked Potential (BAEP)
- Critical Flicker Fusion (CFF)
- OPTEC visual function tests

Performance
- Hand Steadiness
- Grip Strength and subjective report of workload and fatigue.
- Simple reaction time
- Running memory
- Unstable tracking
- Sternberg memory task, set size 4
- Sternberg memory task, set size 6
- 2 choice reaction time
- Dual task: tracking/Sternberg set-size 4
- Math processing
- Dual task: tracking/Sternberg set-size 6
- Pattern memory
- Symbol digit substitution
- Switched attention
- Grammatical reasoning

Subjective
- Fatigue
- Workload
- Perceived Exertion Scale
- PB Side Effects Scale
- Daily Log
- Double-blind rating form

## Table 9.2. List of Measures, Study 2

Chemistry:
- Plasma PB
- Plasma THMP

Biochemistry:
- AChE

Physiology
- Heart Rate
- Heart Rate Variability
- Prepulse Inhibition

Performance
- Hand Steadiness
- Running memory
- Unstable tracking
- Sternberg memory task, set size 6
- Dual task: tracking/Sternberg set size 6
- Switched attention task
- Stroop color-word task

Subjective
- Fatigue
- Workload
- Perceived Exertion Scale
- PB Side Effects Scale
- Daily Log
- Double-blind rating form

## 9.2 Discussion of Study Design

A double-blind cross-over design was used for both studies. Performing the study under a double blind design helps to control for expectation about the effects of the drug on the part of either the volunteer or the experimenter. The cross-over design increases statistical power and reduces error variance because each volunteer serves as his/her own control. Since only healthy participants were used, and the order of PB and PL was counterbalanced, random events were unlikely to affect the results. In Study 1, carry-over effects were dealt with by allowing a one-week period between dosing weeks. In Study 2, this week was eliminated, as data from Study 1 indicated that PB had become nondetectable 72 hr after the last dose.

## 9.3 Selection of Study Population

### 9.3.1 Inclusion Criteria

- at least 18 years of age
- weigh between 121 lbs and 231 lbs (upper limit for study 2 only)
- no chronic disease or disorder
- not pregnant and not planning to become pregnant
- willing to come to MRI for training, dosing, and testing sessions
- willing to abstain from alcohol, illicit drugs, and over-the-counter drugs other than vitamins during the drug administration and testing phases of the program
- able to speak, read, and write English
- normal (corrected) vision and hearing
- ability to see all colors (for study 2 only)

### 9.3.2 Exclusion Criteria

An appointment was made with the project physician for a physical examination, plasma dibucaine test, and urine test for drug use. In addition to the routine physical examination (blood chemistries, electrocardiogram, etc.) the project physician excluded potential volunteers who show evidence of:

- latent myasthenia gravis
- asthma
- bronco-constrictive disease
- cardiac dysrhythmias

- hypo- or hypertension
- prostatitis
- urinary obstruction
- gastric ulcers
- pregnancy (plasma hCG test)
- GI obstructions
- weight less than 120 lbs
- seizure disorders
- homozygotes for the atypical BuChE mutation using each volunteer's plasma dibucaine number; excluded if below 40
- chronic disease or disorder
- taking prescription medications (other than birth control) that could interfere with any of the measures

9.3.3 Removal of Volunteers from Assessment

In accordance with guidelines for protection of human subjects, volunteers could discontinue participation at any time. Table 9.3 lists the disposition of Ss For Study 1, and Table 9.4 lists the disposition for Study 2.

**Table 9.3. Disposition Of Subjects For Study 1**

| |
|---|
| 432 calls received |
| 231 subjects refused participation |
| 112 rejected at pre-screen or entrance medical exam |
| 22 dropped from study after enrolling (5 after dosing began) |
| 67 completed study |

**Table 9.4. Disposition Of Subjects For Study 2**

| |
|---|
| 95 calls received |
| 32 refused participation |
| 36 rejected at pre-screen or entrance medical exam |
| 2 dropped from study after dosing began |
| 25 completed study—1 dropped from analyses due to technical error |

## 9.4 Treatments

### 9.4.1 Treatments Administered

Study 1: PB, 30 mg or 60 mg; Placebo. Study 2: PB, 30 mg; Placebo.

### 9.4.2 Identity of Investigational Products

Pyridostigmine bromide, manufacturer's (Hoffman-LaRoche, HLR) code Lot # 325035, bottle number BN96947 (Study 1), manufacturer's code C191538-01, bottle number BN97293 (Study 2) and placebo manufacturer's (HLR) code C191538-01, bottle number BN97293 (Study 1 and Study 2) were supplied to MRI by USAMDDA. Dosing schedule, packaging, labeling, and storage of both PB and PL were conducted by MRI staff members who had no other connection with the study or its results. Each dose was packaged in a blister pack and labeled with the S's identification number, pill number, and phase. Only the medical monitor, the project physician, and the individual in charge of the dose repository (Dr. Dora Arneson) had access to the dose schedule. Prepared doses of PB and PL were kept in a locked lab under Dr. Arneson's supervision. When project staff members checked out doses, they signed for the doses they took, and were responsible for returning unused pills, if any, to the repository.

### 9.4.3 Assignment of Volunteers to Study Groups

The PI used a random number table to assign men and women Ss for Study 1 to dose level, order of PB and PL, and testing order. The resulting schedule was given to Dr. Arneson, who rotated the schedule so that the PI no longer had access to information about any particular S's assignment. The same procedure was followed for Study 2, except that only one dose level was used. Copies of the schedules are shown in Appendix 16.1.7.

### 9.4.4 Selection of Doses in the Study

Because 30 mg PB every 8 hr is the regimen used by the military for protection against OP agents, both studies used a 30 mg dose. In study 1, approximately half the Ss received a 60 mg dose every 8 hr to provide dose-response information, while staying well below the therapeutic range levels used in the treatment of myasthenia gravis.

### 9.4.5 Selection and Timing of Doses for Each Volunteer

All Ss received doses of PB and PL every 8 hr for 13 consecutive doses. Half the subjects received PB during the first week of dosing and half received PL during the first week of dosing (cross-over design).

### 9.4.6 Blinding

Only the project physician, medical monitor, and Dr. Arneson had access to the dose level and order of dosing information for the Ss. All other personnel were kept blind. The double-blind code was not broken until all data decisions had been made, and the initial statistical analyses were complete.

### 9.4.7 Prior and Concomitant Therapy: Not applicable

### 9.4.8 Treatment Compliance

Doses of PB and PL were administered at MRI, except that because of scheduling problems, some Ss were allowed to take one of the daily doses elsewhere. They were required to call a project staff member when they took the dose; if a S failed to call within 20 min of the scheduled time, the staff member contacted the S to remind him/her to take the dose. During the first study, 238 of the 1,742 scheduled doses were taken > 20 min past the scheduled dose time. Two hundred two of these were AM doses, of which only 19 were taken > 40 min past the scheduled dose time. Dr. Sastre determined that these late doses did not affect the plasma levels significantly. During Study 1, eight doses were missed. No subject missed more than one dose; these missed doses also did not significantly alter plasma PB levels on test days. For Study 2, the AM dosing sessions were scheduled 15 min before the actual dose time to prevent late doses. Nine doses were taken > 20 min past the scheduled dose time (AM, 16:00, and 24:00) and four doses were missed (two of which were Subject 52, who was dropped from the study for non-compliance and replaced). One battery session was missed by Subject 55, and she was dropped from the study for non-compliance and replaced.

## 9.5 Methods

### 9.5.1 Dosing, Monitoring, and Sample Collection

When Ss arrived at the laboratory for the morning dose, vital signs were measured, the food diary the S had maintained for the past 24 hr was reviewed, and the volunteer completed a Daily Log Form and a symptoms questionnaire (PB Side Effects Scale; PBSES). Specific definitions of symptoms that might indicate an adverse effect were developed with the project physician. The investigator examined the PBSES and, if criteria for an adverse event were met, the S was referred to the medical monitor and took the dose packet to the medical monitor. If continuation was approved, the medical monitor administered the dose; if not, the monitor returned the pill to MRI. If there was no indication of an adverse event, the S ate breakfast and took the morning dose. The time for the next appointment was confirmed, and the S released. Afternoon and evening doses were administered without completion of additional forms or vital signs unless the S complained of feeling ill. On the Monday following each dosing week, the S completed a questionnaire about whether the S thought he/she had taken PB or PL during the previous week, how confident the S was of the judgment, and what the S had based

the judgment on. When the S arrived at the laboratory for testing (approximately 3.5 hr after the morning dose), a blood sample was obtained. Urine samples were also collected on Thursday and Friday testing sessions in Study 1. Sample processing is described in Section 9.5.4. Immediately after testing in Study 2, Ss completed a PBSES for the time they were in the temperature chamber.

### 9.5.2 Chemistry

Methods were developed for the concomitant determination of PB and its metabolite (3-hydroxy-*N*-methylpyridinium bromide; THMP) in either human plasma or human urine. The same high pressure liquid chromatography (HPLC) system is used to separate and quantify PB and THMP. The HPLC system and parameters that are used for both plasma and urine are an isocratic pump equipped with a programmable UV detector, autosampler with a refrigerated tray (~ 6°C) and a data system. The column used is a Silica LUNA column from Phenomenex, 5 µm, 250 x 4.6 mm I.D. with a Security Guard Silica column, also from Phenomenex. In addition, a saturation column packed with silica gel (250 x 4.6 mm I.D.) is installed between the pump and autosampler. The run time is 30 min using a flow rate of 1.0 mL/min with a mobile phase that is 50:50 (v/v) acetonitrile:water (0.04% w/v tetramethyl ammonium chloride, 5 mM ammonium acetate). Typical retention times are ~ 11 min for THMP and ~ 21 to 25 min for pyridostigmine bromide. Detection is by UV at 324 nm for the initial ~ 16 min, then changed to 270 nm until ~ 30 min. For plasma, standard curves are constructed by spiking control plasma to contain ~ 5, ~ 10, ~ 50, or ~ 100 ng/mL of both PB and THMP. Samples, standards, and quality control solutions are extracted by adding 2 mL of acetonitrile incrementally to the 1 mL of sample. The solutions are vortexed after each addition. The entire solution is centrifuged for 10 min at 1,430 xg to separate. The supernatant is decanted and blown to dryness with $N_2$ at ~ 40°C. The residue is reconstituted in 200 µL of water and then filtered (0.2 µm, Nylon) into autosampler vials for analysis. Aliquots (100 µL) of each spiked Standard Curve Solution are injected onto the HPLC system. The area response is examined with weighted linear regression against the theoretical concentration (based on the amount of PB and THMP that was added in the spiking procedure) to obtain the correlation coefficient, slope and intercept of the best fit line for each analyte. A similar injection of the control is used to confirm that there are no interfering peaks. Aliquots of study samples are injected onto the HPLC system and the area response of each is used to calculate the concentration based on the linear regression equation for each analyte. Essentially the same procedure is used for urine samples, except that the acetonitrile extraction is replaced by an ethanol precipitation step.

The methods for the analysis of PB/THMP in both plasma and urine incorporate the following sequence of HPLC system/method suitability verifications:

- System Suitability-Precision (from six injections, ≤ 10%), peak tailing (≤ 3.0), and theoretical plates (≥ 2,000).

- Standard Curve-Linearity (≥ 0.98)
- QC Samples-Calculated using standard curve to show suitable recovery/stability (± 25%).
- Matrix Blank—Verifies suitability of reagents (≤ 20% of lowest standard)
- Matrix Standard—Spaced throughout samples to verify system integrity (± 25%)

As is evident from Tables 9.5 and 9.6, the accuracy and precision observed with this method are excellent for both plasma and urine:

**Table 9.5. Accuracy and Precision of Analysis for THMP and Pyridostigmine in Plasma**

| THMP (n=6) | | | |
|---|---|---|---|
| Actual ng/mL | Determined ng/mL | % RSD | % Recovery |
| – | 102.0 | 2.3 | 104 |
| 48.88 | 46.39 | 6.0 | 94.9 |
| 9.78 | 11.13 | 5.3 | 114 |
| Pyridostigmine (n=6) | | | |
| Actual ng/mL | Determined ng/mL | % RSD | % Recovery |
| 102.5 | 104.3 | 3.7 | 102 |
| 51.26 | 48.05 | 5.0 | 93.1 |
| 10.25 | 11.47 | 6.8 | 112 |

**Table 9.6. Accuracy and Precision of Analysis of THMP and Pyridostigmine in Urine**

| THMP (n=6) | | | |
|---|---|---|---|
| Actual ng/mL | Determined ng/mL | % RSD | % Recovery |
| 19.73 | 19.7 | 3 | 100 |
| 9.86 | 9.3 | 1 | 95 |
| 1.97 | 2.3 | 4 | 115 |
| Pyridostigmine (N=6) | | | |
| 19.74 | 19.7 | 3 | 100 |
| 9.87 | 9.5 | 1 | 97 |
| 1.97 | 2.3 | 4 | 117 |

We observed no interfering peaks co-eluting with PB. There was, however, an interfering peak in some of the plasma and urine samples that co-eluted with THMP. We

ascertained that the interfering peak is present only in individuals who are coffee drinkers; the peak is markedly reduced or absent if subjects abstain from drinking coffee for 18 to 24 hours, and reappears after coffee intake resumes. In one subject, the peak was detectable after intake of a single cup of coffee. The interfering peak is not caffeine since it is not present in plasma from individuals who drink caffeinated beverages but do not drink coffee; it is also not present in people who drink only herbal or regular tea.

### 9.5.3 Biochemistry

We have quantified red cell (AChE) and plasma (BuChE) with a radioisotopic assay based upon the quantitation of [$^3$H]acetate produced by hydrolysis of labeled [$^3$H]acetylcholine. The sensitive radiometric method of Johnson and Russell (1975) as modified by Nostrandt et al. (1993) was implemented in our lab with minor modifications to increase the extraction efficiency of the $^3$H-labeled acetate into the fluor and reduce sample variation. The key to the assay is separation of [$^3$H]acetate from unhydrolyzed [$^3$H]acetylcholine substrate. This is accomplished quickly and inexpensively by adding the entire reaction mixture, after stopping enzymatic activity, into a scintillation cocktail chosen for its inability to form an emulsion or incorporate aqueous solutions. Acetylcholine is hydrophilic and is therefore trapped into the aqueous reaction mixture. The unhydrolyzed [$^3$H]acetylcholine thus has no access to the fluorophores in the organic-based scintillation cocktail. In contrast, [$^3$H]acetate is liphophilic and preferentially partitions into the fluorophore-containing organic phase. We have used InstaFluor®, supplemented with 15% Isopentyl Alcohol to further enhance the extraction of [$^3$H]acetate into the organic phase.

One unit of AChE activity is generally defined as 1 μmol acetylcholine hydrolyzed per min at 37°C at pH 8.0. This assay is run at 26°C; therefore, AChE activity is 1/2 to 2/3 of the activity seen at 37°C. BuChE activity is determined indirectly (using acetylcholine instead of butyrylcholine as the substrate) in plasma. One unit of BuChE activity is defined as 1 μmol butyrylcholine hydrolyzed per min at 37°C at pH 8.0. When acetylcholine is used as the substrate, approximately 0.4 μmol of acetylcholine is hydrolyzed per min at 37°C at pH 8.0 when incubated with one unit of the enzyme. This assay is run at 26°C; therefore, BuChE activity is 1/2 to 2/3 of the activity seen at 37°C. Our standard substrate is unlabelled acetylcholine iodide (0.015 M) with tracer [acetyl-H$^3$] acetylcholine iodide (0.00023 M).

Since our protocol called for nine separate samples each for plasma and red blood cells (RBC) per subject, all nine plasmas and RBCs from a given subject were assayed on the same day to eliminate day-to-day variation. The assay was run in a block without interruption. Assays were run in triplicate for each specimen. A substrate blank was run in triplicate at least every hr once the incubations began to determine the amount of spontaneous hydrolysis of the acetylcholine. Our internal controls were Bio-Rad Lyphocheck® Assayed Controls-Level 1 and 2, which were run in triplicate once daily. Prior to assay, the samples were allowed to thaw in a refrigerator. The blanks, internal controls, and experimental samples were set up and assayed at 26 ± 1°C during a 30-sec incubation to minimize dissociation of PB from the enzymes. Total assay volume was 100 μL. Enzymatic activity was stopped by addition of 100 μL of a chloracetic acid

buffer at pH 2.5. After thorough mixing, 4 mL InstaFluor® cocktail with 15% isopentyl alcohol were added to each vial, and the contents shaken vigorously to extract [$^3$H]acetate into the organic fluor-containing phase.

The vials were allowed to sit undisturbed in the dark for at least 30 min before counting in a liquid scintillation counter. After the samples had been counted, three plasma and three RBC samples from each subject were spiked with ~ 25,000 dpms of a calibrated [$^3$H] hexadecane or [$^3$H] toluene internal standard. This permitted determination of percent efficiency on an absolute basis without assumptions inherent in quench curve or external standard methods.

A validation SOP consistent with GCP criteria was developed and used to validate the cholinesterase assays. We initially used commercially available cholinesterase from electric eel (Sigma Chemical Co.) as an internal standard during the validation process. Due to inconsistencies in the eel acetylcholinesterase that we received from Sigma, Bio-Rad Lyphocheck® Assayed controls were used as the internal controls in all subject assays. Linearity was documented for 5 to 15 microliters of plasma, or 5 to 15 microliters of a 1:1 dilution of packed red cells, and for times of 15 sec to up to 3 min. However, the best results with lower coefficients of variation and least amount of substrate depletion were obtained with 30-sec incubations and volumes of plasma or red cells less than 10 microliters.

We examined the stability of the red cell and plasma enzymes. Both activities were stable to storage at ~ –20° and ~ –80°C for several weeks. However, in order to create conditions similar to those observed *in vivo*, we treated plasma and red cells with $3 \times 10^{-7}$ M PB for 1 hr at 26°C. This produced a 30% to 40% inhibition of the plasma enzyme, and about a 20% to 30% inhibition of the red cell enzyme. At this point aliquots of plasma and red cells were stored at ~ –20° and ~ –80°C. Subsequent assay indicated that the plasma ChE-pyridostigmine complex appears stable at ~ –80°C for 27 days (when the test was terminated) and under ~ –20°C for up to 63 days of storage. All assay values were within 15% from the values obtained at day "0" (i.e., before freezing and storing), and most assay values were within ± 10% of the day zero results.

Our initial tests indicated that the red cell AChE-pyridostigmine complex was not stable at either ~ –20 ° or ~ –80 °C, with a return of enzyme activity of about 10% after 1 day and about 30% after 5 days and even 100% after 7 days. We examined a number of potential variables, and explored a number of buffers for collection and/or storage of the samples, in an effort to find conditions that would permit storage without breakdown of the red cell AChE-pyridostigmine complex. We examined permutations of blood collection in EDTA and ACD tubes, undiluted samples, red-cell dilution buffers of 0.1 M and 0.2 M Na-phosphate (pH = 8.0), a citrate-phosphate (0.1 M, pH = 8.0), presence and absence of 4% Triton X-100 in the dilution buffer, and/or quick-freezing aliquots in liquid nitrogen prior to storage at ~ –80°C. After the first series of tests we narrowed down the possibilities to two candidate sets of conditions: (1) red cells collected in EDTA, diluted in citrate-phosphate buffer with Triton and stored at ~ –80°C; and (2) red cells collected in ACD, diluted in citrate-phosphate buffer with Triton and stored at ~ -80°C. Under these two conditions, all assay values were within ± 20% from the values

obtained at day "0" (i.e., before freezing and storing), and most assay values were within ± 10% of the day zero results for up to 36 days of storage.

Since both of these conditions appeared satisfactory in our battery of tests, we opted for beginning the performance of Study 1, storing and assaying the blood samples from the first four volunteers under both conditions, and making a final decision based on the results obtained from the pilot studies and the samples of the first four volunteers. After examination of all of the data, it became evident that both storage conditions gave different units of enzyme activity, but essentially identical percent inhibition by pyridostigmine. In addition, virtually all samples assayed in triplicate under both conditions had CVs of less than 10%. We decided to use red cells collected in ACD, diluted in citrate-phosphate buffer with Triton and stored at ~ –80°C for the remainder of the study.

9.5.4 Blood Processing

Due to the rapid breakdown of the pyridostigmine-enzyme complex at body and room temperatures, we developed a protocol that minimizes any breakdown by rapidly chilling blood and maintaining it chilled throughout all processing procedures until it is stored under frozen conditions. ACD and EDTA Vacutainer® tubes are pre-chilled in a refrigerator (2° to 8°C). After blood samples are collected from volunteers by venipuncture, the ACD and EDTA tubes are placed into an ice-water slurry. The tubes are centrifuged for ~ 20 min at ~ 2,800 g forces (~ 3,500 rpm) at ~ 5°C.

For plasma BuChE determinations, plasma from EDTA tubes is aliquoted in 0.5 mL volumes into cryovials and stored at ~ –20°C. For red cell AChE determinations, erythrocytes from ACD tubes are diluted with equal volume of RBC buffer (0.1 M citrate phosphate buffer w/ 4% Triton X-100, pH of 6.0 ± 0.1). This RBC/buffer mixture is then aliquoted in ~ 500-µL volumes into four cryovials and stored at ~ –80°C.

For plasma PB and THMP determinations, plasma is aliquoted in 1.0-mL volumes from ACD tubes into three appropriately labeled 1-dram vials and stored at ~ -80°C. For lymphocytes and erythrocytes that will be shipped to another laboratory, either the buffy coat layer or an aliquot of erythrocytes are removed, placed into a cryovial, and stored at ~ –80°C.

Urine samples are stored refrigerated (2° to 8°C) until the sample is aliquoted, which is performed within 3 hr of collection. For PB and THMP determinations, urine is aliquoted in ~ 200-µL volumes in 1-dram vials and stored at ~ –80°C. Additional samples are aliquoted in ~ 500-µL volumes and stored at ~ –20°C for urinary creatinine determinations.

### 9.5.5 Physiological and Performance Measures

#### 9.5.5.1 Study 1, Battery A

Battery A for Study 1 consisted of seven tasks: Orthostatic Stress with electrocardiogram (ECG); and Blood Pressure measurements; Pattern Reversal Visual Event-related Potential (VEP); Brain Stem Auditory Evoked Potential (BAEP); Critical Flicker Fusion (CFF); OPTEC visual function; Hand Steadiness and Grip Strength; and subjective report of workload and fatigue. All volunteers completed a physiology training session consisting of the above measures before beginning Phase 1 of the study. The purpose of the training session was to familiarize the volunteer with the various tasks and procedures that would be performed during the dosing phases.

During the experimental phases, half the volunteers performed Battery A on Days 1 and 5 and half performed Battery A on Day 4 of each phase. The battery was conducted after the blood and urine samples were collected and the volunteer had eaten lunch.

ECG was obtained using a standard 3-Lead configuration. Red Dot sensors (3M Health Care, Ontario, Canada) were placed on the right clavicle, left clavicle (ground), and lower left rib. A 16-min ECG was recorded electronically using a Colin Tonometry 9200 unit. Each collection consisted of eight min supine, rising to a standing position, and eight min standing. A blood pressure cuff was attached to the volunteer's right arm and the Colin unit automatically recorded blood pressure every 2 min during the ECG collection.

Electroencephalogram (EEG) was recorded during the VEP and BAEP tasks using 10 mm Gold Cup electrodes at Cz, Oz, Fp (ground), and left and right mastoids (International 10 to 20 placement system). Oz was referenced to linked mastoids for the VEP collection. Left and right mastoids were unlinked and referenced to Cz for the BAEP collection. Sensors were filled with Grass EC2 Electrode Cream as the contact medium. Impedance was tested with a Checktrode Model 1089 MKII electrode tester (UFI, Morro Bay, CA) using $\leq$ 3 kOhm as the criterion value. EEG recordings were collected in a sound-attenuated electrically shielded chamber using the Neuroscan SynAmp System (Neurosoft, Inc. Sterling, VA). For the VEP task, the S viewed a rapidly reversing checkerboard pattern presented on a computer monitor; the EEG to 200 reversals of each of two checkerboard sizes was sampled at 500 Hz and averaged to obtain the VEP. BAEP consisted of recording EEG while the volunteer listened to a series of brief auditory clicks (10/sec) presented to the ear at intensities 70 db above threshold. The clicks were presented in the left ear and white noise in the right ear. EEG activity to each click was recorded from the midline, sampled at 20,000 Hz, and averaged to produce the BAEP waveform.

Critical Flicker Fusion (CFF), the point at which a flickering light is perceived as a steady light, was measured using a Grass Photo Stimulator, model PS22C (Grass Medical Instruments, Quincy, MA). After two practice trials, three ascending and three descending frequency trials were averaged to obtain the CFF threshold, in hertz. All measurements were conducted with the flash lamp intensity set at low and located at a distance of 72.5 cm from the S's nasion.

Depth perception, near and far acuity, and near and far lateral and vertical phoria were measured using the Optec 2000 Vision Tester (Stereo Optical Co., Chicago, IL). Standard Optec scoring procedures were used for each test.

Hand steadiness was measured using a Model 32011 Steadiness Tester (Lafayette Instruments, Lafayette, IN). The S held the stylus in the dominant hand, with only the front of the elbow resting on the table, and attempted to hold a metal stylus in a small hole in the metal plate for 10 sec without allowing the stylus to touch the edges of the hole. Five holes of decreasing diameter were used (0.156 to 0.078 in). A logic box connected to the apparatus measured the amount of time (msec) the stylus was in contact with the apparatus.

A Lafayette Instrument 100 KG Hand Dynamometer (Lafayette Instrument, Lafayette, IN) and Perceived Exertion Scale (Borg, 1990) were used to measure grip strength of the dominant and non-dominant hands, along with the volunteer's perceived exertion. The volunteer held the hand dynamometer in one hand with the arm hanging down at the side. Instructions were to squeeze as hard as possible, release, and to give a number (1 to 20) from the perceived exertion scale that represented their level of exertion during the task. This was repeated three times alternating between the dominant and non-dominant hands, with a 10 sec pause between trials.

#### 9.5.5.2 Study 1, Battery B, Cognitive and Performance Measures

Tasks for Study 1 were selected from the Neurobehavioral Evaluation System 2 (NES2; Letz, 1990) and the Automated Neuropsychological Assessment Metrics (ANAM; Reeves, et al. 1989). The performance battery (Battery B) consisted of four tasks from the NES2 and nine tasks from the ANAM, with a primary focus on measures of higher-order cognitive abilities (memory, attention, complex processing, time sense, pattern recognition, mathematical processing, visual/motor integration, and reasoning.)

During the week prior to dosing volunteers participated in three training sessions in which they performed several trials of each task. The number of trials and performance criteria are shown in Table 9.7. Volunteers worked exclusively on NES2 or ANAM tasks in training sessions one and two. Volunteers performed only one trial of each task from each group in the third training session. The experimenter reviewed the scores with the volunteer after each training session to determine if criteria had been met. If the criteria were not met, the volunteer was allowed up to three additional practice trials. If the volunteer still failed to meet the training criteria, he/she was dismissed and the performance measurement supervisor reviewed the scores. Additional practice trials ($\leq 3$) were allowed and scores were reviewed again. Volunteers who did not meet criteria for a particular task were still admitted into the study if their performance was consistent (e.g. unstable tracking error between 30 to 40 consistently.)

All Ss received doses of PB and PL every 8 hr for 13 consecutive doses. Half the subjects received PB during the first week of dosing and half received PL during the first week of dosing (cross-over design). Half the volunteers in each dose-order group were

tested on Battery B on Day 4 and Battery A on Day 5; the other half were tested in reverse order. On Day 1 of each phase, the volunteers were tested on the battery that was administered on Day 5. During experimental phases of the study, the performance battery was administered after the volunteer provided a blood sample and had eaten lunch. One trial of each task from each group was performed and the experimenter did not review scores.

**Table 9.7. Study 1 Performance Tasks Used to Assess the Effects of Pyridostigmine Bromide**

| ANAM TASKS | | |
|---|---|---|
| **TASK** | **TRIALS** | **TRAINING CRITERIA** |
| RUNNING MEMORY | 4 | Twice w/mean RT ≤ 800 ms, accuracy ≥ 90% |
| SIMPLE REACTION TIME | 4 | Twice w/mean RT ≤ 400 ms, accuracy ≥ 90% |
| UNSTABLE TRACKING | 5 | Twice **in a row** w/overall RMS tracking error ≤ 20, control losses ≤ 3 |
| STERNBERG MEMORY SET SIZE 4 | 4 | Twice w/mean RT correct ≤ 700 ms, errors ≤ 4 |
| STERNBERG MEMORY SET SIZE 6 | 4 | Twice **in a row** w/mean RT correct ≤ 900 ms, errors ≤ 5 |
| 2 CHOICE REACTION TIME | 4 | Twice w/mean RT correct ≤ 500 ms, % correct ≥ 90% |
| DUAL TRACKING/ STERNBERG SET SIZE 4 | 5 | Twice **in a row** % correct ≥ 80%, mean RT correct ≤ 1,000, control losses ≤ 6, RMS error ≤ 25 |
| MATH PROCESSING | 4 | Twice w/mean RT correct ≤ 3,500 ms, % correct ≥ 80% |
| DUAL TRACKING/STERNBERG SET-SIZE 6 | 5 | Twice **in a row** % correct ≥ 80%, mean RT correct ≤ 1,300 ms, control losses ≥ 6, RMS error ≤ 25 |
| **NES2 TASKS** | | |
| **TASK** | **TRIALS** | **TRAINING CRITERIA** |
| PATTERN MEMORY | 3 | Twice w/ ≤ 3 errors, mean RT ≤ 7 sec |
| SYMBOL DIGIT SUBSTITUTION | 4 | Twice w/ ≤ 5 errors, mean RT ≤ 4 sec |
| SWITCHED ATTENTION | 4 | Twice w/# of errors in 3rd "switching" block ≤ 5, mean RT ≤ 800 ms |
| GRAMMATICAL REASONING | 4 | Twice w/ ≤ 8 errors, mean RT ≤ 5 sec |

Tasks for Study 2 (Table 9.8) included those that appeared to be affected in Study 1, plus two new tasks designed to further evaluate PB effects on the central nervous system: the Stroop Color Word Task, and measures of the auditory startle response and its inhibition by pre-startle stimuli. Half the Ss, assigned at random, received doses of PB every 8 hr for 13 consecutive doses, followed by 13 consecutive, 8-hr doses of PL. The other half received PL first, followed by PB. Testing occurred on days 4 and 5 of each dosing phase; on one test day, the chamber temperature was maintained at 95°F, and on the other at 75°F. Humidity was kept at 30% on both test days. The battery was administered after the subject provided a blood sample, and had

eaten lunch. One trial of each task was performed and the experimenter did not review scores.

**Table 9.8. Study 2 Performance Tasks Used to Assess the Effects of Pyridostigmine Bromide**

| NES2 TASKS | | |
|---|---|---|
| **TASK** | **TRIALS** | **TRAINING CRITERIA** |
| RUNNING MEMORY | 4 | Twice w/mean RT ≤ 650 ms, accuracy ≥ 90% |
| UNSTABLE TRACKING | 5 | Twice **in a row** w/overall RMS tracking error ≤ 20, controls losses ≤ 3 |
| STERNBERG MEMORY SET SIZE 6 | 4 | Twice **in a row** w/mean RT correct ≤ 900 ms, errors ≤ 5 |
| DUAL TRACKING/ STERNBERG SET SIZE 6 | 5 | Twice **in a row** % correct ≥ 80%, mean RT correct ≤ 1,300 ms, control losses ≤ 6, RMS error ≤ 25 |
| **OTHER TASKS** | | |
| SWITCHED ATTENTION | 4 | Twice w/# of errors in 3rd "switching" block ≤ 5, mean RT ≤ 800 ms |
| STROOP | 2 | Perform twice |

## 9.6 Data Quality Assurance

Rigorous quality assurance procedures are included in all studies performed in our laboratory. The procedures vary between studies only as a function of the specific tasks and measures used and the level of regulatory oversight required. The studies described here were performed under Good Clinical Practice guidelines. All hardware and software development for computerized data collection and control of task presentation were documented and verified. A log was kept of equipment calibration records, decisions with regard to specific experiments and protocols, and deviations from protocol. All data were uniquely coded for study, S, session, and events within the session. Data that were keyed into the computer database were entered independently by two staff members, and computer verified; nonclerical disagreements are resolved by the PI. Databases were created using Microsoft Access for Windows and were networked for access by authorized members of the project team. The databases were backed up daily.

All data originally collected in electronic format were byte-by-byte verified to be identical from the data capture computer to files in the MRI LAN and in two sets of CD-ROMs. These data, together with the Access databases, were backed up in the MRI servers and also in CD-ROMs. The CD-ROMs and the daily, weekly and monthly backups of the MRI servers provide highly redundant archival storage of the electronic data, and in the case of the CD-ROMs unalterable backup as well.

## 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical and Analytical Plans

All statistical analyses were conducted using standard packages such as BMDP-Dynamic and Systat V 8.0; both of these programs are fully compatible with Microsoft Access. The primary method of analysis was multivariate analysis of variance (ANOVA) for repeated measures (i.e., BMDP-4V). Each study contains a large number of endpoints to be analyzed. Multivariate groupings of these variables primarily used a systems approach; endpoints that have inherent interdependencies were analyzed together. In addition, preliminary correlation matrices were computed to identify additional groupings that should be treated multivariately. The Huynh-Feldt epsilon correction for lack of sphericity was used when appropriate. Appropriate simple effects analyses were conducted to clarify significant interactions.

Multivariate linear regression of continuous variables was conducted using a general linear model (Systat, V 8.0). Automatic stepwise entry and removal were used for the more complex models, and at all times residuals were saved and examined for trends and non-random clusterings. The adjusted squared multiple R was used as the figure of merit, since several models included more than one independent variable.

### 9.7.2 Determination of Sample Size

Selection of the appropriate sample size is critical. When sample size is too large, resources are wasted; when it is too small, statistical tests do not have the power to detect an effect even if it does exist, and negative results can not be interpreted with confidence. Power analysis (Cohen, 1977) of our previous PB study (N = 24, one dose group) on measures similar to those used here indicated that a sample size of 24 per dose group would be adequate for the function with the lowest effect size. Since both men and women were to be included in the study, and since little is known about variance in these measures in women taking pyridostigmine, we selected a sample size of 36 (18 men and 18 women) per dose group for Study 1. Due to scheduling problems, and to local press coverage of purported adverse effects of PB which affected recruitment, the final sample consisted of 67 individuals (36 men, 31 women). Power analysis for Study 2 was based on the results of Study 1. Since gender comparisons were not planned, we selected a sample size of 24, with the restriction that at least 10 of each gender must be included in the final sample. Fourteen men and 11 women completed the study. One man's data was dropped because of technical problems during the testing session.

## 9.8 Changes in the Conduct of the Study or Planned Analyses

Not applicable.

# 10. STUDY PATIENTS

## 10.1 Disposition of Patients

See Tables 9.3 (Study 1) and 9.4 (Study 2).

## 10.2 Protocol Deviations

Several deviations in which a S did not receive a dose within 20 min of the scheduled dose time occurred during data collection for Studies 1 and 2. All of these events were properly documented with the MRI IRB and the Army HSRRB. It was determined that these deviations did not affect the data significantly.

During Study 1, Subject No. 54 was admitted into the study while taking Prozac. Data were not significantly affected and S did not experience any adverse reactions during dosing or during the 12-month follow-up period. Subject No. 21 took one PB dose and dropped out of the study due to schedule conflicts. This subject was mistakenly not scheduled for an exit examination with the study physician. At 3-month follow-up, S did not report any adverse reactions.

During Study 2, problems occurred within the test chamber and the humidity was not maintained at 30% ± 3 for Subject No. 2, Phase 1. During Phase 2, EEG and PPI data were not usable. Consequently, data for Subject No. 2 were replaced. Minor equipment problems necessitated the replacement of a mouse and a keyboard in the testing facility. The mouse was replaced on 10/20/00 and the keyboard on 10/27/00. No significant changes in performance occurred for the remaining Ss in the study.

All above deviations were properly documented in PI files, with MRI IRB, and with the Army HSRRB.

## 11. EFFICACY EVALUATION

Not applicable.

## 12. SAFETY EVALUATION

### 12.1 Extent of Exposure

As described above, approximately half the volunteers in Study 1 took 30 mg PB every 8 hr for 13 doses, and approximately half took 60 mg PB every 8 hr for 13 doses. In Study 2, all volunteers took 30 mg PB every 8 hr for 13 doses. In both studies, volunteers took 13 doses of placebo every 8 hr during the placebo phase of the study.

### 12.2 Adverse Events

No serious adverse events occurred during either study. However, twelve subjects were referred to the medical monitor either during dosing or after study participation had ended. Six of these referrals were because of symptoms/side effects reported by the subject or vital signs that were outside baseline. Four were referred after study participation had been completed because the S reported symptoms that he/she perceived to be "unusual" at follow-up. There were three referrals due to skin rashes, all occurring from 2 weeks to 6 months after the volunteers had concluded their participation in the study. The medical monitor determined in all three cases that the rashes were unrelated to participation in the study. The medical monitor considered the possibility of a PB-induced "bromide rash," but rejected that possibility due to the fact that bromide-induced rashes are prompt in onset, pruritic, cover most of the skin, and quickly resolve upon discontinuation of exposure to bromide. None of the three volunteers who developed rashes fit this pattern. One was referred during dosing due to an irregular EKG. All events were determined to be unrelated to study participation and Ss who were dosing were approved to continue study participation. Table 12.1 lists the adverse events by subject identification number for both studies.

## Table 12.1. Table of Adverse Events

| Sbjid | Date | Event Description | Outcome |
|---|---|---|---|
| **STUDY 1** | | | |
| 05 | 09/01/98 | Low pulse, referred to medical monitor | Approved to continue in study. |
| 31 | 04/13/99 | Checked "blurred/double vision" on symptom questionnaire. Referred to medical monitor. | Approved to continue in study. |
| 51 | 09/16/98 | Subject complained of heartburn and diarrhea over several days. Referred to medical monitor | Approved to continue in study. |
| 34 | 06/09/99 | Checked "dark/bloody urine" on symptom questionnaire. Referred to medical monitor. | Approved to continue in study by medical monitor, but dropped by PI. |
| 03 | 07/30/99 | S called after study participation had ended and wanted to see the medical monitor for an unexplained rash. | Determined by the medical monitor to not be related to study participation. |
| 92 | 10/04/99 | S complained of "flushing" during dosing week. Also mention that she had Raynaud's disease (information not initially given in screening or physical). Referred to medical monitor. | Approved to continue in study. |
| 95 | 10/28/99 | Irregularities in EKG alerted PI to refer S to medical monitor. | Approved to continue in study. |
| 06 | 11/04/99 | During 12-month follow up, S mentioned "chest pains" and was referred to medical monitor. | Determined by the medical monitor to not be related to study participation. |
| 46 | 03/21/00 | During 6-month follow-up, S mentioned "joint/muscle pain" and was referred to medical monitor. | Determined by the medical monitor to not be related to study participation. |
| 32 | 01/17/00 | During 6-month follow-up, S mentioned "rash" and was referred to medical monitor. | Determined by the medical monitor to not be related to study participation. |
| **STUDY 2** | | | |
| 55 | 08/02/00 | Checked "vomiting, nausea, and chest pain" on symptom questionnaire. Referred to medical monitor. | Approved to continue in study. |
| 53 | 10/31/00 | Developed rash 2 weeks post-participation. Reported to Study Coordinator on 1-9-01. S saw own dermatologist and medical monitor. | Determined by medical monitor that rash was not associated with study. Dermatologist investigating allergies. |

## 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths or serious adverse events during either study.

## 12.4 Results, Study 1

### 12.4.1 Plasma and Urinary Levels of PB and THMP.

Descriptive Statistics: Table 12.4.1 shows the plasma and urinary levels of PB and THMP, stratified by dose (30 or 60 mg), for each testing point. As noted in the methods (Section 9.5.2 Chemistry), values for THMP are meaningful only for those volunteers who were not coffee drinkers, and only those are included in averages. This is reflected in the number of subjects listed for each entry in the table. Tables 16.2.8 in Appendix 16.2 show the raw data for each subject.

Regression analyses: Tables 12.4.2 and 12.4.3 show the correlation matrices, with means and standard deviations, for both predictor and dependent variables that were used to predict plasma PB on Day 1, Day 4, and Day 5. Table 12.4.2 shows all subjects but not the THMP measures, while Table 12.4.3 shows all variables but with the subjects restricted to non-coffee drinkers, so that the THMP values are meaningful. A series of regression analyses was conducted to determine the best predictors of plasma PB. Preliminary analyses indicted that Body Mass Index did not increase the amount of the variance that could be explained, and it was deleted from further analyses. Regressions were done separately for Day 4 and Day 5. The initial model used to predict plasma PB was:

plasma PB = constant + dose (mg/kg) + normalized urinary THMP + normalized urinary PB.

For Day 4 (Table 12.4.4), the adjusted $r^2$ was .42, the coefficient for normalized dose was 11.5 (95% CI 0.06 to 22.9), and the coefficient for urinary PB was 0.51 (95% CI .008 to 1.009); urinary THMP did not enter the model.

For Day 5 (Table 12.4.5), the adjusted $r^2$ was .55, the coefficient for normalized dose was 13.2 (95% CI 2.1 to 24.2) and the coefficient for urinary PB was .95 (95% CI 0.44-1.460). Urinary THMP was deleted, and regressions performed again.

## Table 12.4.1. Descriptive Statistics for Plasma and Urinary PB and THMP in Study 1

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N = 34 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| Plasma PB Day 1 (ng/mL) | 10.46 ± 1.08 | 18.43 ± 1.20 |
| Plasma PB Day 4 (ng/mL) | 18.33 ± 1.17 | 30.97 ± 1.59 |
| Plasma PB Day 5 (ng/mL) | 18.17 ± 1.21 | 30.73 ± 2.11 |
| Plasma PB Day 8 (ng/mL) | 0.00 ± 0.00 | 0.00 ± 0.00 |

| | 30 mg Dose Group N = 22 | 60 mg Dose Group N = 29 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| Plasma THMP Day 1 (ng/mL) | 8.36 ± 1.32 | 15.01 ± 0.97 |
| Plasma THMP Day 4 (ng/mL) | 13.26 ± 1.34 | 21.32 ± 1.11 |
| Plasma THMP Day 5 (ng/mL) | 17.24 ± 3.48 | 21.17 ± 1.23 |
| Plasma THMP Day 8 (ng/mL) | 0.26 ± 0.26 | 0.49 ± 0.49 |

Note: Values shown are for non-coffee drinkers only

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N = 34 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| Urinary PB Day 4 (μg/mg) | 10.51 ± 0.88 | 19.38 ± 1.11 |
| Urinary PB Day 5 (μg/mg) | 11.16 ± 0.96 | 19.34 ± 1.42 |

Note: Urinary PB values are normalized by creatinine

| | 30 mg Dose Group N = 22 | 60 mg Dose Group N = 29 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| Urinary THMP Day 4 (μg/mg) | 4.56 ± 0.55 | 6.96 ± 0.53 |
| Urinary THMP Day 5 (μg/mg) | 4.90 ± 0.53 | 7.07 ± 0.56 |

Note 1: Urinary THMP values are normalized by creatinine
Note 2: Values shown are for non-coffee drinkers only

## Table 12.4.2. Study 1—Correlation Matrices
## Pyridostigmine Phase, Day 1

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Dose | BMI |
|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 66 | 72.55 | 11.87 | 1.00 | | | | |
| % BuChE Activity | 66 | 92.54 | 11.17 | 0.22 | 1.00 | | | |
| Plasma PB (ng/mL) | 66 | 14.54 | 7.74 | –0.79 | –0.25 | 1.00 | | |
| Dose (mg/kg) | 66 | 0.60 | 0.25 | –0.58 | –0.08 | 0.46 | 1.00 | |
| BMI ($kg/m^2$) | 66 | 26.09 | 4.42 | 0.16 | 0.18 | –0.13 | –0.48 | 1.00 |

## Pyridostigmine Phase, Day 4

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Urinary PB | Dose | BMI |
|---|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 65 | 60.57 | 10.80 | 1.00 | | | | | |
| % BuChE Activity | 65 | 87.25 | 8.67 | 0.17 | 1.00 | | | | |
| Plasma PB (ng/mL) | 65 | 24.47 | 10.20 | –0.74 | –0.22 | 1.00 | | | |
| Urinary PB (µg/mg)[1] | 65 | 15.04 | 7.40 | –0.61 | –0.11 | 0.65 | 1.00 | | |
| Dose (mg/kg) | 65 | 0.61 | 0.25 | –0.66 | –0.09 | 0.59 | 0.61 | 1.00 | |
| BMI ($kg/m^2$) | 65 | 26.06 | 4.44 | 0.07 | –0.06 | –0.06 | –0.06 | –0.48 | 1.00 |

## Pyridostigmine Phase, Day 5

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Urinary PB | Dose | BMI |
|---|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 63 | 60.17 | 9.96 | 1.00 | | | | | |
| % BuChE Activity | 63 | 86.77 | 10.39 | 0.46 | 1.00 | | | | |
| Plasma PB (ng/mL) | 63 | 25.01 | 11.87 | –0.81 | –0.47 | 1.00 | | | |
| Urinary PB (µg/mg)[1] | 63 | 15.65 | 8.22 | –0.73 | –0.38 | 0.75 | 1.00 | | |
| Dose (mg/kg) | 63 | 0.61 | 0.25 | –0.72 | –0.32 | 0.61 | 0.58 | 1.00 | |
| BMI ($kg/m^2$) | 63 | 26.17 | 4.49 | 0.30 | 0.21 | –0.29 | –0.23 | –0.50 | 1.00 |

[1] Normalized to creatinine.

## Table 12.4.3. Study 1—Correlation Matrices for Non-Coffee Drinkers

### Pyridostigmine Phase, Day 1

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Plasma THMP | Dose | BMI |
|---|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 50 | 71.12 | 11.86 | 1.00 | | | | | |
| % BuChE Activity | 50 | 91.68 | 10.81 | 0.14 | 1.00 | | | | |
| Plasma PB (ng/mL) | 50 | 14.70 | 8.30 | –0.84 | –0.24 | 1.00 | | | |
| Plasma THMP (ng/mL) | 50 | 12.17 | 6.57 | –0.78 | –0.20 | 0.83 | 1.00 | | |
| Dose (mg/kg) | 50 | 0.62 | 0.24 | –0.59 | –0.01 | 0.49 | 0.50 | 1.00 | |
| BMI ($kg/m^2$) | 50 | 26.18 | 4.32 | 0.18 | 0.15 | –0.15 | –0.14 | –0.46 | 1.00 |

### Pyridostigmine Phase, Day 4

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Urinary PB | Plasma THMP | Urinary THMP | Dose | BMI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 50 | 59.69 | 10.99 | 1.00 | | | | | | | |
| % BuChE Activity | 50 | 88.04 | 8.03 | 0.29 | 1.00 | | | | | | |
| Plasma PB (ng/mL | 50 | 24.88 | 10.28 | –0.73 | –0.33 | 1.00 | | | | | |
| Urinary PB (µg/mg)[1] | 50 | 15.66 | 7.80 | –0.59 | –0.13 | 0.63 | 1.00 | | | | |
| Plasma THMP (ng/mL) | 50 | 17.76 | 7.31 | –0.67 | –0.41 | 0.78 | 0.50 | 1.00 | | | |
| Urinary THMP (µg/mg)[1] | 50 | 5.91 | 2.99 | –0.41 | –0.21 | 0.52 | 0.76 | 0.61 | 1.00 | | |
| Dose (mg/kg) | 50 | 0.62 | 0.24 | –0.65 | –0.09 | 0.54 | 0.57 | 0.49 | 0.40 | 1.00 | |
| BMI ($kg/m^2$) | 50 | 26.18 | 4.32 | 0.03 | –0.10 | 0.01 | 0.01 | –0.05 | 0.04 | –0.46 | 1.00 |

### Pyridostigmine Phase, Day 5

| | N | Mean | S.D. | % AChE Activity | % BuChE Activity | Plasma PB | Urinary PB | Plasma THMP | Urinary THMP | Dose | BMI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 49 | 58.92 | 9.73 | 1.00 | | | | | | | |
| % BuChE Activity | 49 | 86.42 | 8.73 | 0.48 | 1.00 | | | | | | |
| Plasma PB (ng/mL) | 49 | 25.58 | 11.73 | –0.81 | –0.55 | 1.00 | | | | | |
| Urinary PB (µg/mg)[1] | 49 | 16.13 | 8.32 | –0.66 | –0.36 | 0.71 | 1.00 | | | | |
| Plasma THMP (ng/mL) | 49 | 19.58 | 12.04 | –0.36 | –0.12 | 0.36 | 0.29 | 1.00 | | | |
| Urinary THMP (mg/mg)[1] | 49 | 6.23 | 2.98 | –0.54 | –0.25 | 0.56 | 0.82 | 0.34 | 1.00 | | |
| Dose (mg/kg) | 49 | 0.63 | 0.24 | –0.70 | –0.32 | 0.56 | 0.50 | 0.15 | 0.44 | 1.00 | |
| BMI ($kg/m^2$) | 49 | 26.20 | 4.36 | 0.25 | 0.25 | –0.25 | –0.14 | –0.01 | –0.12 | –0.47 | 1.00 |

[1] Normalized to creatinine.

For Day 4, the remaining predictor variables were significant. The adjusted $r^2$ was .47. The adjusted $r^2$ for Day 5 was 0.61. Finally, we predicted plasma PB from constant + dose in mg/kg. Table 12.4.6 shows the results for Day 4 and Table 12.4.7 shows the results for Day 5. For both days, plasma PB was significantly predicted by the constant and the dose in mg/kg. While the weight-normalized dose was the best predictor for plasma PB, we also found that urinary measures could be used to predict plasma PB if normalized dose information was not available.

### 12.4.2 Cholinesterases

An analysis was conducted to determine the best baseline to use for quantifying activity of plasma and red blood cell cholinesterase. For plasma BuChE, a significant session (predose, sham days 1, 4, 5 and 8) difference was found ($F = 3.20$, df 4, 236, $p = .015$). The differences, however were quite small (means of 2.06 to 2.15). There was also a significant gender by session interaction ($F = 2.85$, df 4, 236, $p = .026$). For men, the highest value was on Sham Day 4, while for women the highest value was on Sham Day 8. Since there did not appear to be any biological significance to these differences, we decided to use the mean of all five sessions for each individual as the baseline value for plasma BuChE. No significant session, gender, or interaction effects were found for AChE, and the mean of all five sessions was used as the baseline for each individual subject.

Tables 16.2.8 and 16.3.6 in Appendix 16.2 show the AChE and BuChE values for each volunteer at each testing point, together with information about dose level and other important characteristics.

Table 12.4.8 shows descriptive statistics for AChE and BuChE activity in both absolute units and normalized as percent remaining activity when compared to baseline.

To predict BuChE activity, we tested the model:

BuChE percent remaining activity = constant + dose (mg/kg) + plasma PB.

BuChE remaining activity was predicted only by the constant for Day 4 (multiple $r = .23$, adjusted $r^2 = .02$). For Day 5, the model fit the data, but dose did not contribute significantly to the prediction. Dose was dropped from the model; the resulting adjusted $r^2$ was .17, the coefficient for plasma PB was –.38 (95% CI –.58 to –.18).

To predict AChE activity we tested the model:

AChE percent remaining activity = constant + dose (mg/kg) + plasma PB.

**Table 12.4.4. MODEL PB Day 4 = CONSTANT + DOSE (mg/kg) + Normalized Urinary THMP Day 4 + Normalized Urinary PB Day 4**

Multiple R: 0.671 Squared multiple R: 0.450
Adjusted squared multiple R: 0.415 Standard error of estimate: 7.862

| Effect | Coefficient | Std Error | Std Coef | Tolerance | T | P (2 Tail) | Lower <95%> | Upper <95%> |
|---|---|---|---|---|---|---|---|---|
| CONSTANT | 7.347 | 3.315 | 0.000 | | 2.216 | 0.032 | 0.674 | 14.020 |
| DOSE (mg/kg) | 11.470 | 5.670 | 0.270 | 0.670 | 2.023 | 0.049 | 0.057 | 22.882 |
| Urin THMP | 0.408 | 0.579 | 0.119 | 0.420 | 0.704 | 0.485 | –0.758 | 1.574 |
| Urin PB | 0.509 | 0.248 | 0.386 | 0.336 | 2.047 | 0.046 | 0.008 | 1.009 |

Analysis of Variance

| Source | Sum-of-Squares | df | Mean-Square | F-ratio | P |
|---|---|---|---|---|---|
| Regression | 2330.264 | 3 | 776.755 | 12.568 | 0.000 |
| Residual | 2842.987 | 46 | 61.804 | | |

**Table 12.4.5. MODEL PB Day 5 = CONSTANT + DOSE (mg/kg) + Normalized Urinary THMP Day 5 + Normalized Urinary PB Day 5**

Multiple R: 0.760 Squared multiple R: 0.577
Adjusted squared multiple R: 0.549 Standard error of estimate: 7.947

| Effect | Coefficient | Std Error | Std Coef | Tolerance | T | P (2 Tail) | Lower <95%> | Upper <95%> |
|---|---|---|---|---|---|---|---|---|
| CONSTANT | 4.592 | 3.339 | 0.000 | | 1.375 | 0.176 | –2.130 | 11.313 |
| DOSE (mg/kg) | 13.166 | 5.488 | 0.269 | 0.731 | 2.399 | 0.021 | 2.119 | 24.213 |
| Urin THMP | –0.429 | 0.678 | –0.109 | 0.313 | –0.634 | 0.530 | –1.794 | 0.935 |
| Urin PB | 0.949 | 0.252 | 0.673 | 0.289 | 3.772 | 0.000 | 0.443 | 1.456 |

Analysis of Variance

| Source | Sum-of-Squares | f | Mean-Square | F-ratio | P |
|---|---|---|---|---|---|
| Regression | 3961.661 | 3 | 1320.554 | 20.908 | 0.000 |
| Residual | 2905.382 | 46 | 63.160 | | |

## Table 12.4.6. MODEL PB Day 4 = CONSTANT + DOSE (mg/kg)

Multiple R: 0.594 Squared multiple R: 0.353
Adjusted squared multiple R: 0.343 Standard error of estimate: 8.269

| Effect | Coefficient | Std Error | Std Coef | Tolerance | t | P (2 Tail) | Lower <95%> | Upper <95%> |
|---|---|---|---|---|---|---|---|---|
| CONSTANT | 9.779 | 2.705 | 0.000 | | 3.615 | 0.001 | 4.373 | 15.185 |
| DOSE (mg/kg) | 24.158 | 4.118 | 0.594 | 1.000 | 5.867 | 0.000 | 15.930 | 32.387 |

## Table 12.4.7. MODEL PB Day 5 = CONSTANT + DOSE (mg/kg)

Multiple R: 0.623 Squared multiple R: 0.388
Adjusted squared multiple R: 0.378 Standard error of estimate: 9.362

| Effect | Coefficient | Std Error | Std Coef | Tolerance | t | P (2 Tail) | Lower <95%> | Upper <95%> |
|---|---|---|---|---|---|---|---|---|
| CONSTANT | 6.725 | 3.024 | 0.000 | | 2.224 | 0.030 | 0.685 | 12.766 |
| DOSE (mg/kg) | 29.452 | 4.627 | 0.623 | 1.000 | 6.365 | 0.000 | 20.209 | 38.696 |

## Table 12.4.8. Descriptive Statistics for AChE and BuChE Activity in Study 1

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N = 34 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| BuChE Day 1 (U/mL) | 2.03 ± 0.09 | 1.84 ± 0.08 |
| BuChE Day 4 (U/mL) | 1.91 ± 0.08 | 1.76 ± 0.09 |
| BuChE Day 5 (U/mL) | 1.94 ± 0.09 | 1.69 ± 0.08 |
| BuChE Day 8 (U/mL) | 2.16 ± 0.10 | 2.03 ± 0.09 |

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N= 34 |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| % BuChE Activity Day 1 | 93.37 ± 2.16 | 91.75 ± 1.67 |
| % BuChE Activity Day 4 | 88.09 ± 1.60 | 87.01 ± 1.42 |
| % BuChE Activity Day 5 | 89.01 ± 2.08 | 84.13 ± 1.40 |
| % BuChE Activity Day 8 | 98.83 ± 2.18 | 101.37 ± 1.62 |

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N = 33, N = 34* |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| AChE Day 1 (U/mL) | 3.44 ± 0.12 | 2.72 ± 0.09 |
| AChE Day 4 (U/mL) | 2.94 ± 0.10 | 2.21 ± 0.08 |
| AChE Day 5 (U/mL) | 2.88 ± 0.12 | 2.25 ± 0.09 |
| AChE Day 8 (U/mL) | 4.29 ± 0.15 | 4.11 ± 0.11 |

* N = 33 for Days 1, 4, and 5; N = 34 for Day 8

| | 30 mg Dose Group N = 33 | 60 mg Dose Group N = 33, N = 34* |
|---|---|---|
| | Mean ± SEM | Mean ± SEM |
| % AChE Activity Day 1 | 79.84 ± 1.69 | 65.26 ± 1.58 |
| % AChE Activity Day 4 | 68.07 ± 1.45 | 52.91 ± 1.18 |
| % AChE Activity Day 5 | 66.85 ± 2.27 | 53.79 ± 1.35 |
| % AChE Activity Day 8 | 99.05 ± 2.02 | 98.75 ± 0.94 |

* N = 33 for Days 1, 4, and 5; N = 34 for Day 8

For day 4, the model fit the data (multiple r = 0.78, adjusted $r^2$ = 0.60), the coefficient for normalized dose = –14.7 (95% CI –23.1 to –6.3) and the coefficient for plasma PB = -0.56 (95% CI –0.77 to –0.36). For day 5 the model also fit the data, (multiple r = 0.79, adjusted $r^2$ = 0.61), the coefficient for normalized dose = -13.1 (95% CI –21.1 to –5.1), and the coefficient for plasma PB = –.47 (95% CI –.64 to –0.3).

Genetics: The 1999 Rand Pyridostigmine report (Golomb, 1999), which was released while our studies were in progress, had suggested that individuals who were carriers of BuChE mutations that do not hydrolize succinylcholine or other choline esters effectively may be more suspectible to adverse effects upon ingestion of PB. As a secondary analysis, we examined the genotype of the 67 volunteers who participated in Study 1. Genotyping was performed at the University of Nebraska by the method of Altamirano, Bartels and Lockridge (2000). Descriptive statistics and univariate analyses were used to relate genotype with side effects scores. Analyses that included genotype indicated that carriers of the U/K (n = 22), K/K (n = 1), U/AK (n =3) and K/AK (n = 1) genotypes did not differ in reported side effects from those with the usual U/U (n = 40) genotype.

### 12.4.3 Physiological Measures

If PB affects physiology or performance, we would expect to see a significant Phase (PB, PL) effect, or a significant interaction between Phase and Dose, such that there is no difference between the groups receiving the 30 and 60 mg doses during the PL phase, and a significant difference during the PB phase. Because volunteers were randomly assigned to dose level, and to order (PB/PL, PL/PB), individual pre-dosing differences in physiology or performance may result in significant effects that are, in fact, spurious. Because testing took two sessions, half the subjects received Battery A on Monday and Friday of each dosing week, and half received Battery B. Tests were made after one dose of PB or PL (Monday), and after 10 doses (Thursday, half the subjects) or 13 (Friday, half the subjects). The statistical power of the tests carried out on Monday data is therefore less than for the main tests carried out on Thursday and Friday data.

Event-related Brain Potentials: The primary outcome variable for the VEP is the latency difference between N70, a negative potential approximately 70 ms after the stimulus, and P100, a positive potential approximately 100 ms after the stimulus. After one dose, the latency between N70 and P100 was longer for the 30 mg dose group than for the 60 mg dose group (F = 6.66, df 1,25, p = .016; 34.3 v 30.2 msec). Of greater interest was an interaction between phase, dose, and gender (F = 6.89, df 1,25, p = .015). For men who took 60 mg, there was little difference in latency between the PL phase and the PB phase (29.3 v 29.8 msec). For men who took 30 mg, latency was longer in the PL phase than in the PB phase (36.2 v 34.2 msec). For women, the 60 mg dose resulted in longer latency in the placebo phase (32.3 v 29.7 msec), while the 30 mg dose resulted in longer latency in the PB Phase (34.5 v 32 msec). N70 and P100 latency were also analyzed separately to aid in interpretation. No significant effects were found for N70. Latency of P100 was longer for the 30 mg than the 60 mg group (F = 8.06, df 1,25, p =

.009; 101.8 v 98.3 msec). After multiple doses, latency between N70 and P100 was again longer for the 30 mg group than for the 60 mg group ($F = 4.84$, df 1,59, $p = .032$; 31.6 v 29.3 msec). This appears to be a function of individual differences in VEP latency, since there were no phase-related significant differences for either the 30 mg or the 60 mg group.

The major outcome measures for the BAEP are the latency differences between waves 1, 3, and 5. The results were similar to those for the VEP. After one dose, no effects attributable to PB were found. After multiple doses, the latency between Wave 5 and Wave 3 was longer during the PB than the PL phase ($F = 4.01$, df 1, 58, $p = .05$). A trend for a Dose by Phase interaction ($F = 3.76$, df 1, 58, $p = .057$) was also observed for Wave 5 minus Wave 3. Under the 60 mg dose, latency during the PB phase was longer than during the PL phase; under the 30 mg dose there was essentially no difference between the PB and PL phases. When each dose group was analyzed separately, a significant phase effect was found for the 60 mg dose group only ($F = 9.55$, df 1, 30, $p = .004$). The fact that the phase effect was seen in only one of the dose groups and the small magnitude of the difference (1.79 v 1.87 msec) suggests that this is more likely due to individual differences than a true effect of PB.

Visual Function: CFF measures the temporal acuity of the visual system. After one dose of PB or PL, fusion frequency for those volunteers taking the 60 mg dose was longer during the PL phase than during the PB phase (35.9 v 33.6 Hz), while for those subjects taking the 30 mg dose, there was little difference between phases (29.6 v 30 Hz). The interaction effect was significant ($F = 5.02$, df 1,25, $p = .034$), but analysis of each dose separately revealed a trend for a phase difference in the 60 mg dose group only. After multiple doses, no significant effects attributable to PB were found.

We further tested multiple visual functions using the Optec Vision Tester. After one dose, no effects attributable to pyridostigmine were found for depth perception or acuity. There was a phase by far/near by vertical/lateral interaction ($F = 12.94$, df 1, 25, $p < .002$) for phoria that was due to a high near/lateral phoria score under PB compared to PL. After multiple doses, no effects were found for depth perception. Near acuity was better than far acuity ($F = 78.6$, df 1, 58, $p < .0001$). There was also a significant phase by dose by gender interaction ($F= 5.22$, df 1, 58, $p < .03$), and a significant practice effect ($F = 7.30$, df 1, 58, $p < .01$). Regardless of dose, phoria was greater in the PB phase than in the PL phase ($F = 9.40$, df 1, 57, $p < .01$). Lateral phoria was greater than vertical phoria ($F = 152.42$, df 1, 57, $p < .0001$). In the PB phase, but not in the PL phase, near phoria was greater than far phoria ($F = 8.02$, df 1, 57, $p < .01$). As seen after one dose, there was also a phase by far/near by vertical/lateral interaction ($F = 9.35$, df 1, 57, $p < .003$). Again, this was due to a high near/lateral phoria score under PB compared to PL.

Cardiovascular effects: Both systolic ($F = 20.53$, df 1, 24 $p = .0001$) and diastolic blood pressure ($F = 7.73$, df 1, 24, $p = .01$) were higher for men than for women, but there was no evidence that blood pressure was altered by one dose of pyridostigmine or by multiple doses. The expected effects of orthostatic stress were observed in both

analyses. After one dose of PB, heart rate (HR) was faster in women than in men ($F = 4.74$, df 1, 24, $p = .04$), and when volunteers were standing ($F = 243.94$, df 1, 24, $p = .0001$). As expected because of the known effects of PB on the heart, HR was faster during the PL phase than during the PB phase ($F = 5.89$, df 1, 24, $p = .02$) after one dose of PB or PL. After multiple doses, HR was higher during the PL than the PB phase ($F = 11.83$, df 1, 57, $p = .001$; 76 v 72.5), and this effect was greatest for men who took the 60 mg dose and for women who took the 30 mg dose (Phase by Dose by Gender interaction $F = 7.91$, df 1. 57, $p = .007$). The results are summarized in Figure 12.1. There was also a Phase by Dose by Drug Order interaction ($F = 4.39$, df 1, 57, $p = .041$), which appears to be the result of individual differences in HR in the randomly assigned groups that received the PL phase before the PB phase, versus those who received the PB phase first. As expected, HR increased significantly when subjects stood up, but this phenomenon was not affected by PB.

Heart rate variability: Beat-to-beat heart rate variability (HRV) is a noninvasive indicator of sympathetic and vagal cardiovascular control. It has a number of periodic and nonlinear components. Spectral or autoregressive methods yield two main components of HRV: a low-frequency (LF; 0.04-0.15 Hz) periodic component that reflects sympathetic baroreceptor and thermoregulatory influences combined with some parasympathetic effects, and a high-frequency (HF; 0.15-0.40 Hz) periodic component that reflects primarily parasympathetic tone. Reductions in HRV are recognized as predictive indices of long-term cardiac morbidity and mortality in a number of different populations. Statistical analysis focused on the results obtained after multiple doses.

Table 12.2 shows the amplitudes (square root of the power) in the supine LF and HF HRV bands, expressed both in absolute units (ms) and as percent of total power. Quantitative analysis of HRV was conducted by ANOVA for repeated measures from continuous EKG recordings after at least 3 days of dosing, when a steady-state in plasma PB levels had been achieved. The two dose groups did not differ during their placebo weeks (Absolute LF: $F = 2.80$, df 1, 63, $p = .10$; Absolute HF: $F = .54$, df 1, 63, $p = .46$; Percent LF: $F = .44$, df 1, 63, $p = .51$; Percent HF: $F = .11$, df 1, 63, $p = .74$). Analysis also showed highly significant *reductions* in HF HRV power as a main effect during the PB compared to the PL week, whether the reduction was expressed in absolute units ($F = 34.62$, df 1, 57, $p < .0001$; 23.7 v 30.1) or as percent of total power ($F = 34.03$, df 1, 57, $p < .0001$; 32.0 v 35.9). The reduction in HF power during the PB compared to the PL phase was especially strong under supine conditions (26.7 v 37.5) and less noticeable under standing conditions (20.7 v 22.7; interaction $F = 18.72$, df 1, 57, $p = .0001$). The effects of PB on HF as a percent of total power were greater in the group that received 60 mg every 8 hr than in the group that received 30 mg every 8 hr ($F = 6.39$, df 1, 57, $p < .01$). There were effects on LF power as well. Percent LF was increased by PB ($F=15.60$, df 1, 57, $p < .0002$), but a phase effect was not evident when LF was examined in absolute units.

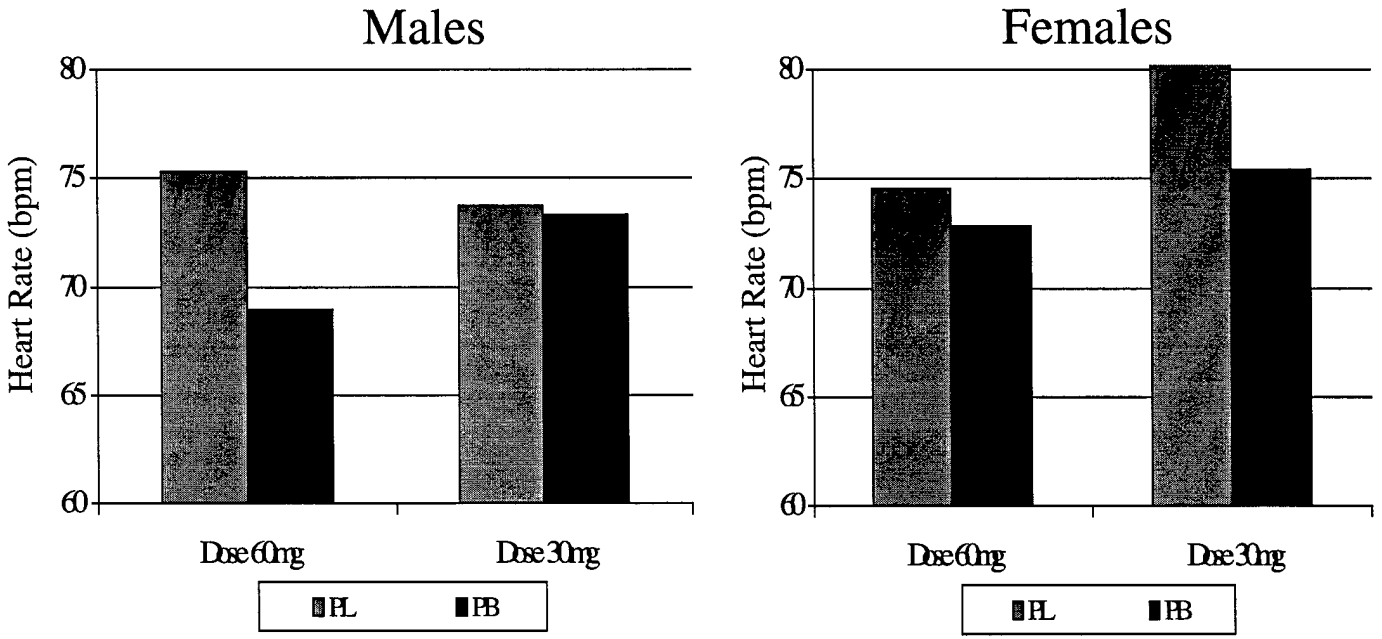


**Figure 12.1. Mean Heart Rate During PL and PB**

**Table 12.2. Absolute and Relative Amplitude of HRV Bands**

| | Absolute low mean ± SEM | Percent low mean ± SEM | Absolute high mean ± SEM | Percent high mean ± SEM |
|---|---|---|---|---|
| PL (30 mg) | 28.36 ± 2.02 | 34.94 ± 1.55 | 39.80 ± 4.10 | 45.86 ± 2.00 |
| PB (30 mg) | 25.24 ± 1.82 | 36.22 ± 1.26 | 31.11± 3.17 | 42.53 ± 1.75 |
| PL (60 mg) | 24.06 ± 1.61 | 33.63 ± 1.17 | 35.03 ± 3.62 | 46.17 ± 1.98 |
| PB (60 mg) | 23.09 ± 2.08 | 39.15 ± 1.09 | 22.17 ± 2.41 | 37.31 ±1.59 |

The magnitude of the difference between PL and PB HF HRV for each subject was predicted by cholinesterase inhibition. We examined the following regression model:

Change in HF HRV = constant + plasma PB + dose (mg/kg) + percent remaining AChE + percent remaining BuChE

The regression was highly significant ($p = 0.003$), with the significant predictors being percent remaining AChE (coefficient = –0.63 [95% CI –1.19 to –0.07]) and percent remaining BuChE (coefficient = –0.47 [95% CI –0.84 to –0.11]). This was the case when including the full range of cholinesterase inhibition obtained from both the 30 mg and the 60 mg dose groups. When each dose group was analyzed individually, the percent inhibition ranges were too narrow to obtain significance in the regression.

In addition to these major findings, percent LF power was increased more by PB in women than in men ($F = 4.11$, df 1, 57, $p = .05$). The increase in percent LF power as a function of PB was more pronounced for those who took the 60 mg dose, and was greater when the volunteers were supine than when they were standing ($F = 13.86$, df 1, 57, $p = .0005$). Results of the analysis of percent HF power showed that the reduction in power was greater for volunteers who took the 60 mg dose, and was more pronounced when the volunteers were supine than when they were standing ($F = 4.55$, df 1, 57, $p = .04$).

### 12.4.4 Performance Measures

Reaction time data for running memory, simple reaction time, two-choice reaction time, math processing, pattern memory, symbol-digit substitution, switched attention, and grammatical reasoning were submitted to multivariate ANOVA. After one dose of PB or PL, there was a trend for a multivariate phase effect and a significant phase by dose level effect, indicating that pyridostigmine improved reaction time. Univariate analyses revealed that reaction time on the math processing task was faster during the PB phase than during the PL phase ($F = 8.25$, df 1, 25, $p = .01$). Volunteers taking the 60 mg dose performed better than those taking the 30 mg dose on 2-choice reaction time ($F = 12.30$, df 1, 25, $p < .01$). The multivariate F for the Phase x Order interaction was also significant; this suggests that subjects should have had more practice on the following tasks prior to dosing: running memory, 2-choice reaction time, math processing, and grammatical reasoning. Significant gender differences were found for running memory, with trends for 2-choice reaction time and pattern memory. There were several other

significant interactions, but they are not directly relevant to pyridostigmine effects. After multiple doses, multivariate analysis revealed that reaction time was faster in the PB phase than in the PL phase. Significant univariate improvements in performance were found for running memory ($F = 9.89$, df 1, 58, $p < .01$) and switched attention ($F = 6.02$, df 1, 58, $p = .02$).

The Sternberg Memory Test was performed alone, and together with a tracking task. After one dose, no effects on reaction time attributable to pyridostigmine were found. There was a trend for error on the tracking task to be affected by both phase and dose ($F = 3.92$ df 1, 25, $p = .06$). Error scores for those in the 60 mg dose group improved during the PB phase compared to the PL phase (12.4 v 15.6); there was essentially no difference in error scores for those in the 30 mg dose group (10.9 v 11.0).

After multiple doses, there was no indication that pyridostigmine altered reaction time on the Sternberg Memory Task. The task did work as designed, however, with the expected highly significant task and set size effects. As expected, tracking error after multiple doses of PB or PL was higher when the task was performed simultaneously with the Sternberg Memory Task, ($F = 14.83$, df 1,58, $p < .0001$). As shown in Figure 12.2, tracking error scores were affected by drug phase, task, and dose level ($F = 3.39$, df 2, 116, $p = .04$). Examination of the data indicated that follow-up analysis should compare error scores under single and dual task conditions with Sternberg, set size 6. In general, tracking error was lower during the PB phase. Under single task conditions, this was equally true for both dose groups. Under dual task conditions, however, the 60 mg dose group showed an exaggerated improvement in tracking error that appears to be due, in large part, to unusually high tracking error during the PL phase. Women showed more tracking error than men ($F = 6.75$, df 1, 58, $p = .01$), but this difference was not affected by drug phase. It appears that, while reaction time to the Sternberg Memory task was not altered by pyridostigmine, performance on the tracking task was.

### 12.4.5 Subjective Measures

Training included repeated practice on the PBSES. The PBSES was created for this study, and was made up of 13 symptoms previously shown to be side effects of PB (weakness, nausea, belching, blurred/double vision, urination problems, bloating, vomiting, heartburn, diarrhea, flatulence, hand tremor, abdominal pain, and fatigue; Graham & Cook, 1984; PDR, 2000). Each side effect was rated from 0 (did not occur) to 6 (extremely bothersome). The 13 items were embedded in a 45-item list of commonly experienced physical and psychological symptoms. Appendix 16.3.7 shows the data on the 13 items for the PL and PB dosing weeks for each volunteer.

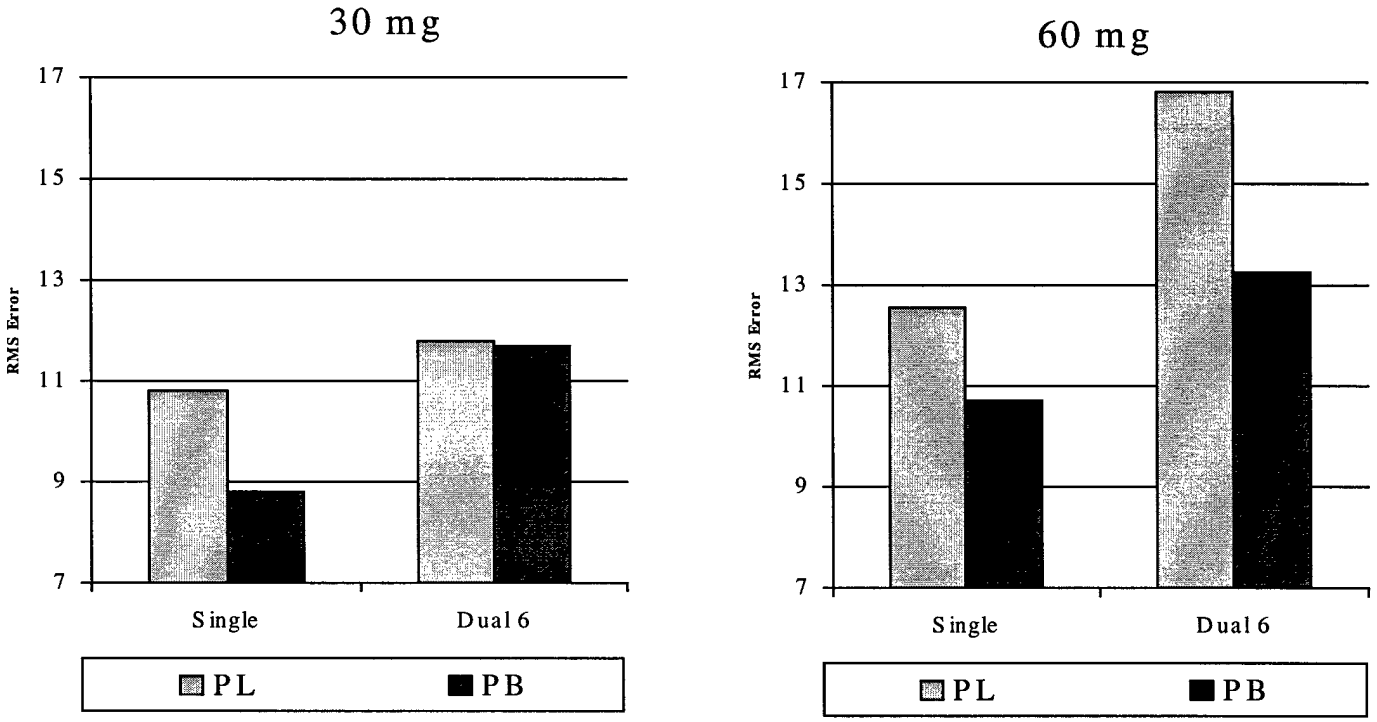


**Figure 12.2. RMS Error During Tracking Task**

A daily score was computed for each administration of the PBSES based on the 0-6 rating made by the subject for each of the 13 side effects. The scores were summed over all five administrations for the PB week and for the PL week, and evaluated by ANOVA. In general, side effects were more likely to be reported during the PB phase, and women were more likely to report side effects. At the 30 mg dose, the percent of volunteers reporting one or more side effects was similar for the PB and PL weeks and for men and women. At the 60 mg dose, however, side effects were more likely to be reported during the PB phase (76%) compared to the PL phase (24%), and women were more likely to report side effects than were men (75% v 50%). The mean PBSES score was not different from the score for the two dose groups. ANOVA revealed that women had higher PBSES scores than men (6.0 v 3.5, $F = 5.03$, df 1, 57, $p < .03$), and PBSES scores were greater during the PB week than during the PL week (6.0 v 3.2, $F=12.65$, df 1, 57, $p < .001$). The most frequently reported symptom was flatulence (28% of volunteers), followed by nausea (19%) and abdominal pain (15%). None of the participants reported vomiting while taking pills.

Some veterans who took PB during the Persian Gulf War reported that they had immediate, intense symptoms after taking the first few pills (Keeler et al., 1991). To determine the frequency of such effects in this laboratory study, we tabulated the reported intensity of each of the PBSES items after the volunteers took the first three doses of PB at eight hr intervals. Most participants reported few, if any, side effects after one day of dosing. Only one volunteer rated any of the symptoms more than "somewhat bothersome" and this occurred only for the symptom "abdominal pain."

Multiple regression analysis was used to test two related models. One model used side effects during the PB week as the dependent variable, and side effects during the PL week, percent AChE activity, percent BuChE activity, dose in mg/kg, drug order and plasma PB level as the predictors. The model provided a significant fit that explained 26% of the variance ($p = .006$). However, only the PBSES score during the PL week contributed significantly to the prediction of side effects during the PB week; this single variable explained 21% of the variance (standardized regression coefficient = 0.51).

The purpose of the second model was to evaluate whether, when the difference between PBSES scores during the PB week and during the PL week was used as the dependent variable, other important predictors might be identified. This further analysis was felt to be important, since PBSES score during the PL week explained much more of the variance than any other predictor. The full model explained 12% of the variance. The single significant predictor was the order of administration of PB and PL, and it explained only 5% of the variance.

When volunteers judged whether they had taken PB or PL during the previous week, they were accurate 66% of the time, and this accuracy was greater for those who received 60 mg doses (72%) than for those who received 30 mg doses (59%). Conditional Logistic Analysis indicated that phase of study (PB, PL) was the only variable that predicted the volunteers' judgements; gender, dose level, and order of administration of PB and PL did not enter the model. For those subjects who correctly

reported that they were taking PB (N = 43), confidence in the judgment was not related to dose level. There was a trend for order of PB/PL administration to be a significant predictor of confidence (PL/PB = 65% highly confident; PB/PL = 22% highly confident; p = .054). There was also a trend for women to be more confident of the accuracy of their judgments than men (p =.07). As expected, those individuals who had higher levels of confidence in their judgements when they correctly judged that they were taking PB also reported more side effects.

In this laboratory-based study of the effects of PB on healthy young men and women, side effects occurred infrequently and were generally mild. Even at the same dose level, however, some volunteers reported more side effects than others when taking both PB and PL. PBSES scores during the PL week were the best predictor of side effects during the PB week. Furthermore, side effects occurred more frequently and the PBSES score was higher when volunteers took the 60 mg dose than when they took the 30 mg dose. The absolute difference in PBSES scores between the dose groups was small, and there was no indication that the 60 mg regimen interfered with the daily lives of the volunteers. Women had higher PBSES scores than men, but gender was not a significant predictor of side effects during the PB week. The presence of side effects was a major determinant of the volunteers' ability to accurately judge whether, during the previous week, they had taken PB or PL.

## 12.5 Results, Study 2

### 12.5.1 Plasma Levels of PB

Descriptive Statistics: Table 12.5.1 shows the plasma levels of PB and THMP for each testing point. As noted in the methods, values for THMP are meaningful only for those volunteers who were not coffee drinkers, and only those are included in averages. This is reflected in the number of subjects listed for each entry in the table. Tables 16.2.8 in Appendix 16 show the raw data for each subject.

Regression analyses: Tables 12.5.2 and 12.5.3 show the correlation matrices, with means and standard deviations, for both predictor and dependent variables that were used to predict plasma PB on Day 4, and Day 5. Table 12.5.2 shows all subjects but not the THMP measures, while Table 12.5.3 shows all variables but with the subjects restricted to non-coffee drinkers, so that the THMP values are meaningful. A series of regression analyses was conducted to determine the best predictors of plasma PB. Preliminary analyses indicted that Body Mass Index did not increase the amount of the variance that could be explained, and it was deleted from further analyses. Regressions were done separately for Day 4 and Day 5. The initial model used to predict plasma PB was:

plasma PB = constant + dose (mg/kg) + BMI

The model did not lead to a significant regression. As in Study 1, a single dose level was insufficient to provide a large enough dose range to predict plasma PB.

## Table 12.5.1. Descriptive Statistics for Plasma PB and THMP in Study 2

| | 30 mg Dose N = 24 |
|---|---|
| | Mean ± SEM |
| Plasma Pyrido Day 4 (ng/mL) | 15.82 ± 1.62 |
| Plasma Pyrido Day 5 (ng/mL) | 17.53 ± 1.24 |
| Plasma Pyrido Day 8 (ng/mL) | 0.00 ± 0.00 |

| | 30 mg Dose N = 16 |
|---|---|
| | Mean ± SEM |
| Plasma THMP Day 4 (ng/mL) | 16.98 ± 1.43 |
| Plasma THMP Day 5 (ng/mL) | 17.69 ± 1.58 |
| Plasma THMP Day 8 (ng/mL) | 0.00 ± 0.00 |

Note: Values shown are for non-coffee drinkers only

## Table 12.5.2.
## Study 2—Correlation Matrix for Pyridostigmine Phase, Day 4

| | N | Mean | S.D. | % AChE Activity | Plasma PB | Dose | BMI |
|---|---|---|---|---|---|---|---|
| % AChE Activity | 24 | 61.43 | 11.83 | 1.00 | | | |
| Plasma PB (ng/mL) | 24 | 15.82 | 7.94 | –0.72 | 1.00 | | |
| Dose (mg/kg) | 24 | 0.40 | 0.08 | –0.08 | 0.08 | 1.00 | |
| BMI (kg/m2) | 24 | 25.94 | 4.73 | 0.12 | –0.02 | –0.83 | 1.00 |

## Study 2—Correlation Matrix for Pyridostigmine Phase, Day 5

| | N | Mean | S.D. | % AChE Activity | Plasma PB | Dose | BMI |
|---|---|---|---|---|---|---|---|
| % AChE Activity | 24 | 58.57 | 8.37 | 1.00 | | | |
| Plasma PB (ng/mL) | 24 | 17.53 | 6.06 | –0.68 | 1.00 | | |
| Dose (mg/kg) | 24 | 0.40 | 0.08 | –0.09 | –0.01 | 1.00 | |
| BMI (kg/m2) | 24 | 25.94 | 4.73 | 0.18 | –0.14 | –0.83 | 1.00 |

## Table 12.5.3.
## Study 2—Correlation Matrix for Non-Coffee Drinkers Pyridostigmine Phase, Day 4

| | N | Mean | S.D. | % AchE Activity | Plasma PB | Plasma THMP | Dose | BMI |
|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 16 | 60.24 | 13.12 | 1.00 | | | | |
| Plasma PB (ng/mL) | 16 | 16.44 | 8.00 | –0.76 | 1.00 | | | |
| Plasma THMP (ng/mL) | 16 | 16.98 | 5.73 | –0.57 | 0.36 | 1.00 | | |
| Dose (mg/kg) | 16 | 0.42 | 0.09 | 0.02 | 0.12 | 0.10 | 1.00 | |
| BMI (kg/m2) | 16 | 24.71 | 4.67 | 0.11 | –0.16 | –0.16 | –0.81 | 1.00 |

## Study 2—Correlation Matrix for Non-Coffee Drinkers Pyridostigmine Phase, Day 5

| | N | Mean | S.D. | % AchE Activity | Plasma PB | Plasma THMP | Dose | BMI |
|---|---|---|---|---|---|---|---|---|
| % AChE Activity | 16 | 60.06 | 8.85 | 1.00 | | | | |
| Plasma PB (ng/mL) | 16 | 18.20 | 6.06 | –0.72 | 1.00 | | | |
| Plasma THMP (ng/mL) | 16 | 17.69 | 6.30 | –0.38 | 0.65 | 1.00 | | |
| Dose (mg/kg) | 16 | 0.42 | 0.09 | –0.26 | –0.18 | –0.01 | 1.00 | |
| BMI (kg/m2) | 16 | 24.71 | 4.67 | 0.48 | –0.12 | –0.22 | –0.81 | 1.00 |

12.5.2 Cholinesterases

Tables 16.2.8 in Appendix 16.2 show the AChE values for each volunteer at each testing point, together with information about dose level and other important characteristics. BuChE was not measured in Study 2 since it was found in Study 1 to offer minimal predictive value for physiological parameters.

Table 12.5.4 shows descriptive statistics for AChE activity in both absolute units and normalized as percent remaining activity when compared to baseline.

To predict AChE activity we tested the model:

AChE percent remaining activity = constant + dose (mg/kg) + BMI + plasma PB.

For each of the two days of data, the regressions were highly significant ($p = .005$). Stepwise regression indicated that the only significant term was the plasma PB value.

**Table 12.5.4. Descriptive Statistics for AChE activity in Study 2**

| | 30 mg Dose N = 24 |
|---|---|
| | Mean ± SEM |
| AChE Day 4 (U/mL) | 2.01 ± 0.09 |
| AChE Day 5 (U/mL) | 1.92 ± 0.08 |
| AChE Day 8 (U/mL) | 3.30 ± 0.09 |

| | 30 mg Dose N = 24 |
|---|---|
| | Mean ± SEM |
| % AChE Activity Day 4 | 61.43 ± 2.42 |
| % AChE Activity Day 5 | 58.57 ± 1.71 |
| % AChE Activity Day 8 | 100.79 ± 1.47 |

12.5.3 Physiological Measures

Heart Rate: As expected, and shown in Table 12.5.5, HR was higher at 95°F than at 75°F (92.2 v 76.8 bpm, F = 130.73, df 1, 21, p = .0001), and also higher when standing than when lying down (98.1 v 70.9 bpm, F = 153.62, df 1, 21, p = .0001). There was a trend for HR to be lower when the volunteer was taking PB than when taking PL (83.3 v 85.7 bpm, F = 4.05, df 1, 21, p < .06). The difference between standing and supine HR was greater in the heat (33.2 bpm) than at normal room temperature (21.2 bpm) (F = 101.2, df 1, 21, p = .0001). This effect was greater for volunteers who participated in the order PB/PL than those who participated in the order PL/PB (F = 5.72, df 1, 21, p < .03), although the general pattern was the same for the two groups. The difference in HR between 75° and 95° was greater during week 1 than during week 2, indicating that the temperature effect may decline over time (F = 7.70, df 1, 21, p = .01).

**Table 12.5.5. Mean (SEM) of Heart Rate in Study 2**

| | Placebo phase | | Pyrido phase | |
|---|---|---|---|---|
| BPM | 75° | 95° | 75° | 95° |
| Supine | 67.02 ± 0.96 | 76.47 ± 1.20 | 65.34 ± 0.97 | 74.73 ± 1.29 |
| Standing | 89.19 ± 1.43 | 110.08 ± 1.58 | 85.62 ± 1.27 | 107.56 ± 1.79 |

Heart Rate Variability:

Absolute Total Power: There was a trend for total power to be less when volunteers were taking PB (F = 3.53, df 1,21, p < .08). Total power was reduced by heat (F = 6.12, df 1, 21, p < .03), and was lower when the volunteer was lying down than when the volunteer was standing (F = 30.43, df 1, 21, p < .0001). The difference between supine and standing was greater in the first week, regardless of whether PB or PL was being administered (F = 5.08, df 1, 21, p < .04).

Absolute Power: LF power was increased by standing (F = 60.69, df 1, 21, p = .0001), and there was a trend for this effect to be greater in the first week than the second (F = 4.10, df 1, 21, p < .06). HF power was reduced by PB (F = 19.55, df 1, 21, p < .0002), and by temperature (F = 25.58, df 1, 21, p = .0001), and there was a trend for it to be reduced by standing as well (F = 4.06, df 1, 21, p < .06). The decrease in HF power as a function of standing was reduced by PB compared to PL (1.8 v 4.4; F = 6.23, df 1, 21, p = .02). This effect was especially true for those volunteers who took PB in the first week; no HF power response to standing was seen for them (F = 8.11, df 1, 21, p < .01). The reduction in supine HF power replicates the paradoxical reduction with PB observed in Study 1.

Percent Power: Percent LF power was increased by heat (F = 20.16, df 1, 21, p = .0002) and increased by standing (F = 70.70, df 1, 21, p < .0001). Percent HF was decreased by PB (F = 15.25, df 1, 21, p < .001), decreased by heat (F = 38.91, df 1, 21,

p = .0001), and decreased by standing (F = 107.74, df 1, 21, p = .0001). No significant interaction effects were observed for percent power measures. Like the results with absolute power, the reduction in percent HF supine power replicates the paradoxical reduction with PB observed in Study 1.

We attempted to predict the magnitude of the effect by the regression:

Change in HF HRV = constant + plasma PB + dose (mg/kg) + percent remaining AChE

As noted in Study 1, when one group was analyzed individually, the percent inhibition ranges were too narrow to obtain significance in the regression. This was also observed in Study 2, which only had a 30 mg dose group.

Pre-Pulse Inhibition (PPI): Some individuals do not show a startle response, and for additional individuals, the startle response habituates very quickly. As shown in Table 12.5.6, a significant interaction between Phase (PB v PL), temperature, and order of administration of PB and PL was observed (F = 4.32, df 1, 20, p = .05) for the difference between startle and prepulse EMG amplitude as a percent of startle EMG amplitude (PPI). The greater the inhibition, the lower the resulting PPI index. These results could be due to individual differences between the individuals who made up the two order groups, or to differential effects on rate of habituation. To clarify this, we first tested each order group separately; no significant effects were found for either order group. We then examined the response to the first prepulse EMG amplitude as a percent of the preceding startle response. Inhibition was greater under PB than under PL (F = 5.87, df 1, 12, p = 0.03), suggesting that PB initially enhanced prepulse inhibition; this effect was not altered by temperature. We also examined the first startle response as a percent of the third startle response to estimate rate of habituation, and found that startle declined at a faster rate under PB than under PL (F = 6.31, df 1, 21, p < .02). Again, temperature did not alter this effect.

**Table 12.5.6. PPI as % of Startle Response**

| Order PB/PL | PB Phase | PL Phase |
|---|---|---|
| 95° | 80.9 | 89.0 |
| 75° | 90.6 | 79.4 |
| Order PL/PB | | |
| 95° | 66.6 | 64.7 |
| 75° | 76.7 | 80.6 |

12.5.4 Performance Measures

No effects attributable to PB were observed for Running Memory, Switched Attention, or Hand Steadiness tasks. For the Stroop Color-Word Task, there was a significant interaction between phase (PB v PL) and testing temperature ($F = 8.24$, df 1, 22, $p < .01$). When volunteers were taking PB, reaction time on the Stroop was faster at 75 (642 msec) than at 95°F (663 msec); when they were taking PL, reaction time was faster in the heat (629 msec) than at normal room temperature (660 msec). In other words, at 75°, PB improved reaction time performance on the Stroop Color Word Task, while at 95° performance was impaired. A significant interaction between phase (PB vs. PL), temperature, order of drug administration, and stage of task was observed ($F = 7.25$, df 1, 21, $p < .02$) for the number of errors on the Stroop Color Word Task. When the stages were analyzed separately, no significant effects were found for the easy stage of the task. For the more difficult stage of the task, a phase by temperature by order interaction was found ($p = .02$). This effect was due entirely to those Ss who were given PL first. Thus, for this group, more errors were made during PL dosing at 75°F, and more errors were made at 95°F during PB dosing.

As expected, reaction time was much faster for the Sternberg Memory Task when it was performed alone than when it was performed with the tracking task ($F = 77.50$, df 1, 21, $p = .0001$). There was a significant Phase (PB v PL) by Temperature by Task Type interaction ($F = 4.51$, df 1, 22, $p < .05$). When the Sternberg Memory Task was performed alone, reaction time was not affected by PB ($F = .03$, df 1, 21, ns). When it was performed with the tracking task, however, reaction time was improved during the PB phase compared to the PL phase at regular temperature (749 v 763 msec), and was slowed during the PB phase compared to the PL phase under heat conditions (777 v 720 msec). There was a trend ($F = 3.51$, df 1, 20, $p < .08$) for RMS error on the tracking task to be greater during the PB phase (22.3) than during the PL phase (19.7). A trend was also observed for an interaction between phase and temperature ($F = 3.56$, df 1, 20, $p < .08$). During the PB phase, higher temperature increased error (24.4 v 20.3) while during the PL phase, no temperature effect was seen (20.2 v 19.2). In other words, tracking error was not affected by PB under regular temperature conditions; tracking error was increased during the PB phase under heat conditions.

Overall, performance was either unaltered or improved by PB at 75° F. At 95°F, however, reaction time performance on the Stroop Color Word and Sternberg memory tasks was impaired, as was the accuracy of tracking. There was some indication that errors on tracking when performed as a dual task and errors on the Stroop task were also impaired by the combination of PB and heat, although the error results are more ambiguous than the reaction time results.

12.5.5 Subjective Measures

ANOVA of the PBSES completed Tuesday through Friday mornings, with drug order as the between subjects variable, and phase (PB v PL) as the within subjects variables, did not result in any significant effects.

We then predicted PBSES score for the PB phase as follows:

PBSES(PB) = constant + PBSES(PL) + drug order + dose (mg/kg) + AChE activity + plasma PB.

Subjects 53 and 56 were deleted because they were outliers. The model did not fit. Based on Study 1 results, we then tested the simple model:

PBSES(PB) = constant + PBSES(PL).

The multiple r was .51, adjusted $r^2$ = .22, PBSES coefficient .37 (95% CI .09 to .66). Again, as in Study 1, the best predictor of reported side effects when taking PB was reported side effects when taking PL.

When the PBSES was completed immediately after testing, the symptom score was greater when the testing occurred at 95°F than at 75°F ($F = 9.22$, df 1, 22, $p < .01$). There was also an interaction between temperature and phase ($F = 4.24$, df 1, 22, $p = .05$). When Ss were taking PB, symptom scores were higher after heat exposure (0.2 v 1.7); when they were taking PL, the difference (0.7 v 1.1) was minor. Regressions were performed to determine the extent to which the post-testing PBSES score was predicted by plasma PB and AChE; PB and AChE were highly correlated. Plasma PB predicted PBSES score significantly only when the S was tested at 75°F.

When volunteers were asked whether they had taken PB or PL during the previous week, they were not able to judge more accurately than at chance levels (33% accuracy during the PB phase, and 50% accuracy during the PB phase).

12.5.6 Safety Conclusions

Not applicable.

# 13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 Relationship between plasma and urinary PB, plasma and urinary THMP, and cholinergic activity: Previous studies had suggested that PB exhibited complicated absorption and distribution kinetics that made it difficult or impossible to use plasma PB levels or AChE or BuChE inhibition levels as predictive of individual variation in functional responses. Several important parameters which had not been previously controlled were accounted for in our studies. Absorption of PB is dependent on the gastric status of the subject, with peak plasma levels obtained at 1.7 or 3.2 hr after ingestion in fasting or non-fasting subjects, respectively (Aquilonius et al., 1980). We fixed the time from pill ingestion to blood sampling and collection of physiologic measures to control for this variable, as well as having complete documentation of the volunteers' eating habits.

Previous studies and the RAND Pyridostigmine report (Golomb, 1999) indicated that there was large inter- and intra-subject variability in PB plasma levels and degree of ChE inhibition for a given dose of PB; for a given study this variation (three- to seven fold) is larger than the range in bioavailability (typically 1.5-fold) and not accounted for by individual height, weight, or surface area (Kornfeld et al., 1971). We did not find this to be the case. We observed that normalized dose (i.e., mg PB ingested per kg body weight) was a useful predictor of plasma PB, and that plasma PB was in turn a robust predictor of percent remaining red cell AChE. At steady-state, the plasma PB values and degree of inhibition of AChE and BuChE were tight within each dose group, with standard errors typically less than 5% of the mean. For the most striking physiologic response obtained in this study, the reduction in HF HRV, percent remaining red cell AChE predicted the magnitude of the decrease in HRV. Urinary clearance and volume of distribution were not examined in comparable detail, but it was evident that the majority of the ingested PB appeared in urine either unchanged or as the primary metabolite THMP. As an incidental finding, we observed that the urinary parameters did not serve to explain a greater fraction of the variance than could be explained by the plasma and enzyme measures. Nonetheless, in the absence of plasma measures, the urinary values gave reasonable predictions for the red cell enzyme inhibition.

We introduced a number of technical controls and refinements. We insured that our collection, storage and assay conditions of plasma and red cells gave the same values for plasma PB and enzyme inhibition for freshly drawn blood and for blood components that had been frozen for over 30 days. We developed and validated a new, reproducible and rugged HPLC assay for plasma and urinary PB and THMP. We also used an extremely rapid and sensitive radiometric assay for AChE and BuChE that demanded little sample dilution; these conditions are required for accurate determination of inhibition due to carbamate inhibitors like PB. As a result of these improvements over previous studies, we had consistent values and excellent quantitative agreement between the results obtained in Study 1 and Study 2 for 30 mg dose groups for both plasma PB and remaining AChE activity, and were able to establish significant correlations between enzyme inhibition and physiological responses.

13.2 Side effects: In both Study 1 and Study 2, the side effects of PB were minimal. Side effect scores were not greater with higher blood levels of PB, or with greater inhibition of either AChE or BuChE activity. Sharabi et al. (1991) also reported a lack of relationship between side effects and BuChE inhibition. The only reliable predictor of the PBSES score during the PB week was the PBSES score during the PL week. This finding implies that individual style in the noticing and/or reporting of symptoms was the most important predictor of those symptoms. To the extent that a situation is ambiguous, factors that influence the perception and reporting of elements in the situation become more important. Since the side effects reported in this study were infrequent and generally mild, the volunteers may have been presented with the type of ambiguous situation that magnifies these effects. When the PBSES was completed immediately after testing, the PBSES score was higher when Ss were taking PB and also exposed to heat.

The present results are in good agreement with those from other laboratory studies of the side effects of PB (Arad et al., 1992; Cook et al., 1992; Gawron et al., 1990). They differ, however, from studies conducted under battlefield conditions (e.g., Izaraeli et al., 1990; Keeler et al., 1991; Sharabi et al., 1991). The observation that, in field studies, side effects are experienced more frequently and are more severe than during laboratory studies implies that symptoms may be exacerbated by the unavoidable physiological and psychological stresses of war. Hotopf et al. (2000) came to a similar conclusion with regard to vaccinations and the stress of deployment as contributors to Gulf War Illnesses. Since none of the battlefield studies of PB included a larger dose of PB than the accepted military regimen, no information is available as to whether the side effects of higher doses are also exacerbated by stress. It will be important to examine this issue, as higher doses of PB may cause greater AChE inhibition at the relevant target tissues, and hence provide greater protection against the consequences of organophosphate agents.

In general, performance on a variety of tasks was either unaltered or improved by PB compared to PL in Study 1. Study 2 included exposure to heat during testing, to examine whether heat altered the response to PB. There was some evidence that heat combined with PB slowed reaction time on the Sternberg Memory Task when it was performed together with the tracking task, and there was a trend for heat and PB together to increase error on the tracking task. It is not clear whether this can be attributed entirely to peripheral effects, or has some CNS component. The Stroop Color Word Task was included in Study 2 specifically to address CNS issues. When volunteers were taking PB, heat increased reaction time on the task; when they were taking PL, heat improved reaction time. While reaction time was previously shown to be improved by PB in other tasks in our first study, heat appears to reverse this effect. There was some indication that errors on the Stroop Test might be increased by the combination of PB and heat; since this occurred only in Ss who received PL first, it should be interpreted very cautiously.

All three of the physiological domains tested in Study 2 showed significant effects of PB. In our Study 2, with PPI as an endpoint, we observed an interaction between Phase (PB or PL), temperature, and order of administration of PB and PL. When each order group was analyzed separately, however, no significant effects were found, indicating that the finding was spurious. We did, however, find that initial PPI was

enhanced by PB, and that startle habituated more quickly under PB than under PL. One possible way to rationalize these findings comes from animal experiments. Since BuChE could serve as a "scavenger" of PB, lower BuChE activity as a function of either genetics or stress may enhance the effects of PB. Servatius et al., (1998) tested this hypothesis using Sprague-Dawley (SD) and Wistar-Kyoto (WKY) rats. The WKY rats have lower baseline BuChE than the SD rats. PB decreased BuChE activity as a percent of baseline for both strains. The WKY rats, but not the SD rats, had exaggerated startle response, but this effect was not significant until Day 22, 14 days after the last dose of PB. The effect was dose-related. The authors attributed the effect to enhanced sensitivity to startle, rather than to reduced habituation. These observations should be extended by comparing volunteers who have different polymorphisms of the BuChE gene.

HR and HRV results in Study 2 essentially replicated the findings of Study 1: HR was decreased by PB, and HRV in the high frequency band, which reflects parasympathetic activity, was also decreased. While the effect on HR was expected, the effect on HF HRV was completely unexpected.

Peripheral AChE inhibition is known to enhance tonic and phasic vagal action at the SA node, which results in a decreased mean heart rate and an increase in HRV (Taylor, 1996). The observed reduction in mean heart rate is in the direction that would be expected from peripheral AChE inhibition at the cholinergic synapse between the preganglionic sympathetic fibers and the postganglionic neurons. However, we observed a strong, highly-significant, paradoxical decrease in HF HRV. The magnitude of the reduction (21% in absolute units for the 30 mg dose group) was comparable to the values reported in the prospective epidemiologic studies that have shown increases in morbidity with reduced HRV (Tsuji et al., 1996; Liao et al., 1997; Dekker et al., 1997; Dekker et al., 2000).

The effects of PB on HF HRV observed in our study are not consistent with a purely peripheral action of PB. Central cholinergic antagonists (e.g., atropine, scopolamine) are well-known to have biphasic effects on animals and humans as a function of dose (Epstein et al., 1990; Alkalay et al., 1992; Bigger, 1995). At very low doses, these antagonists produce a centrally-mediated increase in vagal firing and a consequent vagally-mediated decrease in mean heart rate. At higher doses, their ability to block the M2 muscarinic receptors in the SA node produces their classic vagolytic effect, resulting in a biphasic dose-response curve (e.g., Alkalay et al, 1992). These pharmacologic data serve as indirect evidence that the medullary centers that control vagal activity (e.g., the *nucleus tractus solitarius* and the *nucleus ambiguus*) are partially under the influence of cholinergic neurons, a view supported by histochemical and iontophoretic studies (Hoover et al, 1985; Loewy and Spyer, 1990; Tsukamoto et al, 1994; Goodwin et al, 1995).

It should be noted that there is empirical support in the literature for the phenomenon reported here, although investigators have failed to make the decisive PL vs. PB comparisons, and have interpreted their findings in purely peripheral terms. In an earlier report examining modulation of atropine effects by PB, Izraeli et al., (1990) incidentally noted that PB attenuated the increase in HF power caused by low-dose

atropine, but they failed to examine the effects of PB alone. Similarly, Douchet et al., (1999) examined myasthenic patients taking therapeutic PB doses and normal controls, and found a reduction in both time-domain and spectral measures of HF in the myasthenics; however, their controls did not take PB, and these authors interpreted these findings as an effect of the disease process.

The effects reported here on HF HRV are consistent with a central action of PB in healthy volunteers. It is not necessary to postulate a disruption of the blood-brain barrier (BBB) for these actions since the medullary *area postrema*, an area of the brain which has strong reciprocal innervation with the control centers of the vagus, is outside of the BBB (Kooy and Koda, 1983; Ferguson, 1990). Kooy and Koda (1983) had suggested that the *area postrema* may serve as a relay station to transfer blood-borne information that cannot cross the BBB to other brain regions. Given their potential health implications, these findings should be followed up.

In conclusion, we attained our original objectives. We established analytical and experimental conditions that let us establish the relationship between PB ingestion, AChE inhibition, and functional responses. We conducted simultaneous measurement of plasma and urinary PB and AChE and BuChE inhibition, and related the values obtained to functional responses in dose-response studies under well-controlled conditions. We also distinguished pharmacokinetic variation from true individual differences by using a two-point dose-response study with simultaneous functional and biochemical measures. We established that dose normalized to body weight was a significant predictor of plasma PB values. Plasma PB values were in turn significant predictors of remaining AChE activity and remaining AChE activity was a significant predictor of physiological responses. This was accomplished using only a very narrow range of doses (30 or 60 mg every 8 hrs). We also provided some insights into the variables that appear best correlated with reported side effects. Finally, we identified one highly-significant, reproducible and paradoxical dose-related response to PB (decreased HF HRV) that deserves further examination.

# 14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

## 14.1 Demographic Data Summary Figures and Tables

**Table 14.1. Study 1, Demographics**

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 1 | 31 | M | white |
| 3 | 22 | M | black |
| 4 | 30 | M | white |
| 5 | 29 | M | white |
| 6 | 26 | M | white |
| 7 | 28 | M | white |
| 8 | 27 | M | white |
| 9 | 34 | M | white |
| 10 | 29 | M | white |
| 11 | 32 | M | white |
| 12 | 21 | M | white |
| 13 | 18 | M | black |
| 17 | 35 | M | white |
| 20 | 28 | M | white |
| 22 | 19 | M | white |
| 23 | 18 | M | white |
| 24 | 22 | M | white |
| 25 | 19 | M | white |
| 26 | 21 | M | white |
| 28 | 30 | M | white |
| 30 | 24 | M | black |
| 31 | 18 | M | hispanic |
| 32 | 19 | M | asian |
| 33 | 19 | M | white |
| 35 | 24 | M | black |
| 36 | 24 | M | white |
| 38 | 23 | M | hispanic |
| 39 | 27 | M | white |
| 40 | 21 | M | white |
| 41 | 19 | M | asian |
| 43 | 25 | M | white |
| 44 | 21 | M | white |
| 45 | 19 | M | white |
| 46 | 23 | M | white |
| 47 | 25 | M | white |
| 48 | 19 | M | asian |
| 51 | 28 | F | white |
| 52 | 32 | F | white |
| 53 | 28 | F | white |
| 54 | 24 | F | white |
| 55 | 19 | F | white |
| 56 | 19 | F | white |
| 60 | 21 | F | white |
| 61 | 35 | F | white |
| 63 | 23 | F | white |
| 64 | 19 | F | black |

## Table 14.1. Study 1, Demographics (Continued)

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 65 | 21 | F | black |
| 66 | 24 | F | white |
| 67 | 18 | F | white |
| 68 | 26 | F | white |
| 69 | 27 | F | black |
| 70 | 23 | F | asian |
| 71 | 18 | F | white |
| 74 | 22 | F | white |
| 75 | 24 | F | white |
| 76 | 28 | F | black |
| 80 | 28 | F | white |
| 83 | 20 | F | white |
| 85 | 18 | F | white |
| 88 | 24 | F | white |
| 89 | 20 | F | white |
| 90 | 18 | F | white |
| 91 | 24 | F | white |
| 92 | 21 | F | white |
| 95 | 22 | F | white |
| 97 | 24 | F | white |
| 99 | 23 | F | white |

## Table 14.2. Study 2, Demographics

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 1 | 32 | M | white |
| 3 | 24 | M | asian |
| 4 | 19 | M | white |
| 5 | 25 | M | white |
| 6 | 19 | M | asian |
| 7 | 19 | M | asian |
| 8 | 31 | M | white |
| 9 | 29 | M | white |
| 10 | 21 | M | asian |
| 11 | 19 | M | white |
| 12 | 22 | M | white |
| 82 | 23 | M | white |
| 84 | 21 | M | white |
| 51 | 19 | F | white |
| 53 | 26 | F | white |
| 54 | 19 | F | white |
| 56 | 32 | F | white |
| 57 | 32 | F | white |
| 58 | 25 | F | white |
| 59 | 21 | F | white |
| 60 | 19 | F | white |
| 61 | 18 | F | black |
| 62 | 19 | F | white |
| 80 | 19 | F | white |

## 14.2 Efficacy Data Summary Figures and Tables

Not applicable.

## 14.3 Safety Data Summary Figures and Tables

See Table 12-1.

## 15. REFERENCE LIST


Alcalay, M., Izraeli, S., Wallach-Kapon, R., et al. (1992). Paradoxical pharmacodynamic effect of atropine on parasympathetic control: A study by spectral analysis of heart rate fluctuations. *Clin. Pharmacol. Ther.*, 52, 518-527.

Arad, M., Varssano, D., Moran, D., Arnon, R., Vazina, A., Epstein, Y. (1992). Effects of heat-exercise stress, NBC clothing, and pyridostigmine treatment on psychomotor and subjective measures of performance. *Mil. Med.*, 157(4), 210-214.

Bigger, J.T., Jr. (1995). Spectral analysis of R-R variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans. In: Zipes, D.P., Jalife, J., eds. *Cardiac Electrophysiology, From Cell to Bedside.* Philadelphia: W. B. Saunders, 1151-1170.

Borg, G. (1990). Perceived exertion as an indicator of somatic stress. *Scand. J. Rehabil. Med.*, 2-3, 92-98.

Breyer-Pfaff, U., Maier, U., Brinkmann, A.M., Schumm, F. (1985). Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin. Pharmacol. Ther.*, 37(5), 495-501.

Cohen, J. (1977). *Statistical Power Analysis for the Behavioral Sciences.* New York: Academic Press.

Cook, J.E., Kolka, M.A., Wenger, C.B. (1992). Chronic pyridostigmine bromide administration: side effects among soldiers working in a desert environment. *Mil. Med.* 157(5):250-254.

Dalrymple-Alford, E.C., Budayer, B. (1966). Examination of some aspects of the Stroop Color-Word Test. *Percept. Mot. Skills*, Dec, 23(3), 1211-4.

Dekker, J.M., Crow, R.S., Folsom, A.R., et al. (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk in Communities. *Circulation*, 102, 1239-1244.

Dekker, J.M., Schouten, E.G., Klootwijk, P., et al. (1997). Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: The Zutphen Study. *Am. J. Epidemiol.*, 145, 899-908.

Dirnhuber, P., French, M.C., Green, D.M., Leadbeater, L., Stratton, J.A. (1979). The protection of primates against soman poisoning by pretreatment with pyridostigmine. *J. Phar. Pharmacol.* 31(5), 295-299.

Douchet, M.-P., Quiring, E., Bronner, F., et al. (1999). Diminution paradoxale des paramètres parasympathiques chez les patients myasthéniques. *Arch. Mal. Coeur Vaiss.* 92, 711-717.

Drachman, D.B. (1998). Myasthenia gravis and other diseases of the neuromuscular junction. In: *Harrison's Principles of Internal Medicine.* Fauci, A.S., Braunwald, E., Isselbacher, K.J., et al., eds. New York: McGraw-Hill, 2469-2472.

Epstein, A.E., Hirschowitz, B.I., Kirklin, J.K., et al. (1990). Evidence for a central site of action to explain the negative chronotropic effect of atropine: Studies on the human transplanted heart. *J. Am. Coll. Cardiol.*, 15, 1610-1617.

Ferguson, A.V. (1990). The area postrema: A cardiovascular control centre at the blood-brain interface? *Can. J. Physiol. Pharmacol.*, 69, 1026-1034.

Friedman, A., Kaufer, D., Shemer, J., Hendler, I., Soreq, H., Tur-Kaspa, I. (1996). Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response. *Nat. Med.* 2(12), 1382-5.

Gall, D. (1981). The use of therapeutic mixtures in the treatment of cholinesterase inhibition. *Fundam. Appl. Toxicol.*, 1, 214-216.

Gawron, V.J., Schiflett, S.G., Miller, J.C., Slater, T., Ball, J.F. (1990). Effects of pyridostigmine bromide on in-flight aircrew performance. *Hum. Factors*, 32(1), 79-94.

Golomb, A. (1999). A review of the scientific literature on Persian Gulf War Illnesses. Available from http://www.gulflink.osd.mil/library/randrep/stress/GFI.

Goodwin, B., Anderson, G., Barraco, R. (1995). Characterization of muscarinic receptors in the rat nucleus tractus solitarius. *Neurosci. Lett.*, 191, 131-135.

Graham C., Cook M.R. (1984). Biochemical tests, Aircrew stress: Effects of Pyrodostigmine on psychomotor and visual performance. USAF Aerospace Medical Research Laboratory (AFSC). Contract F33615-80-C-0606. Final Report.

Hoover, D., Hancock, J., DePorter, T. (1985). Effect of vagotomy on cholinergic parameters in nuclei of rat medulla oblongata. *Brain Res. Bull.,* 15, 5-11.

Hotopf, M., David, A., Hull, L., Ismail, K., Unwin, C., Wessely, S. (2000). Role of vaccinations as risk factors for ill health in veterans of the Gulf War: Cross-sectional study, *Br. Med. J.* 320, 1363-1367.

Izraeli, S., Alcalay, M., Benjamini, Y., et al. (1990). Modulation of the dose-dependent effects of atropine by low-dose pyridostigmine: Quantification by spectral analysis of heart rate fluctuations in healthy human beings. *Pharmacol. Biochem. Behav.*, 39, 613-617.

Keeler, J.R., Hurst, C.G., Dunn, M.A. (1991). Pyridostigmine used as a nerve agent pretreatment under wartime conditions, *JAMA* 266(5), 693-695.

Johnson, C.D., Russell, R.L. (1975). A rapid, simple radiometric assay for cholinesterase, suitable for multiple determinations. *Anal. Biochem.*, 64, 229-238.

Kooy, D., Koda, L.Y. (1983). Organization of the projections of a circumventricular organ: The area postrema in the rat. *J. Comp. Neurol.*, 219, 328-338.

Letz, R. (1990). The Neurobehavioral Evaluation System (NES): An international effort. Johnson, B.L. Anger, W.L., Durao, A., Xintaras, C., eds. In: *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health,* Chelsea, Michigan: Lewis Publishers (NES2, version 4.73, 1994).

Liao, D., Cai, J., Rosamond, W.D., Barnes, R.W., Hutchinson, R.G., Whitsel, E.A., Rautaharju, P., Heiss, G. (1998). Cardiac autonomic function and incident coronary heart disease: A population-based case-cohort study: the ARIC Study. Atherosclerosis Risk in Communities Study. *Am. J. Epidemiol.*, 145(8), 696-706.

Loewy, A.D., Spyer, K.M. (1990). Vagal preganglionic neurons. In: *Central Regulation of Autonomic Functions*, Loewy, A.D., Spyer, K.M., eds. New York and Oxford: Oxford University Press.

Nostrandt, A.C., Duncan, J.A., Padilla, S. (1993). A modified spectrophotometric method appropriate for measuring cholinesterase activity in tissue from carbaryl-treated animals. *Fundam. Appl. Toxicol.*, 21, 196-203.

*Physicians' Desk Reference.* (2000). Medical Economics Co., Inc., Montvale, N.J.

Reeves, D.L., Thorne, D.R., Winter, S.L., Hegge, F.W. (1989). *The Unified Tri-Services Performance Assessment Battery (UTCPAB): II Hardware/Software design and specifications* (Report No. SR 89-1). Pensacola: Naval Aerospace Medical Research Laboratory (ANAM, versions 3.0 and 3.1).

Servatius, R.J., Ottenweller, J.E., Beldowicz, D., Guo, W., Zhu, G., Natelson, B.H. (1998). Persistently exaggerated startle responses in rats treated with pyridostigmine bromide. *J. Pharmacol.* Exp. *T her.*, 287, 1020-1028.

Sharabi, Y., Danon, Y.L., Berkenstadt, H., et al. (1991). Survey of symptoms following intake of pyridostigmine during the Persian Gulf War. *Isr. J. Med. Sci., J.* 27, 656-658.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643-662.

Task Force (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Special report, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*, 1043-1065.

Taylor, P. (1996). Anticholinesterase Agents. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., et al., eds. In: *The Pharmacological Basis of Therapeutics.* New York: McGraw-Hill, 161-176.

Tsuji, H., Martin, G., Larson, M.G., et al. Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study. *Circulation*, 94, 2850-2855.

Tsukamoto, K., Yin, M., Sved, A.F. (1994). Effect of atropine injected into the nucleus tractus solitarius on the regulation of blood pressure. *Brain Res.*, 648:9-15.

MRI

# Individual Differences in Neurobehavioral Effects of Pyridostigmine Bromide

## Final Report

## Volume 2—Appendix 16
## Section 16.1.1

MRI Project No. 104863.1.004.03

May 2, 2001

Midwest Research Institute

425 Volker Boulevard
Kansas City, Missouri
64110-2299
(816) 753-7600

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## 16. APPENDICES

### 16.1 Study Information

16.1.1 Protocol and protocol amendments, Study 1 and Study 2

16.1.2 Sample case report form (unique pages only), Study 1 and Study 2

16.1.3 List of IEC's or IRB's (plus the name of the committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms.

16.1.3.1 Study 1 consent form
16.1.3.2 Study 2 consent form

16.1.4 List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study.

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.

16.1.6 N/A, Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.

16.1.7 Randomization schemes

16.1.8 N/A, Audit certificates

16.1.9 N/A, Documentation of statistical methods.

16.1.10 N/A, Documentation of inter-laboratory standardization methods and quality assurance procedures if used.

16.1.11 N/A, Publications based on the study.

16.1.12 N/A, Important publications referenced in the report.

### 16.2 Patient Data Listings

16.1.2 Discontinued patients. See tables 9.3 and 9.4, Disposition of subjects

16.2.2 Protocol deviations. See section 10.2.

16.2.3 N/A, Patients excluded from the efficacy analysis.

16.2.4 Demographic data, Study 1 and Study 2

16.2.5 Drug concentration data.

16.2.5.1 Plasma PB, Study 1
16.2.5.2 Plasma THMP, Study 1
16.2.5.3 Corrected Urinary THMP, Study 1
16.2.5.4 Urinary THMP, Study 1
16.2.5.5 Corrected Urinary PB, Study 1
16.2.5.6 Urinary PB, Study 1
16.2.5.7 Plasma PB, Study 2
16.2.5.8 Plasma THMP, Study 2

16.2.6 N/A, Individual efficacy response data.

16.2.7 Adverse event listings. See Table 12.1, Table of Adverse Events.

16.2.8 Individualized laboratory measurements.

16.2.8.1 AChE, Study 1
16.2.8.2 BuChE, Study 1
16.2.8.3 AChE, Study 2
16.2.8.4 Side effects scores, Study 1
16.2.8.5 Side effects scores, Study 2

MIDWEST RESEARCH INSTITUTE
425 Volker Boulevard
Kansas City, Missouri 64110
Telephone (816) 753-7600
Telefax (816) 753-8420

March 19, 1998

Commander, USARMC
Attn: MCMR-RCQ-HR
Ms. Yvonne Higgins
504 Scott Street
Fort Detrich, MD 212702-5012

Subject: HSPD Log No. A-7905

Dear Ms. Higgins:

This protocol and its attachments, including a statement of informed consent. are submitted to The Surgeon General's Human Subjects Research Review Board. We believe we have addressed the comments arising from the review conducted on 12 November, 1997. Resubmission of the material was delayed because it was necessary to resolve whether pyridostigmine in 45-mg doses could be obtained for use in the study. It could not, and this revision has been included in the protocol.

Midwest Research Institute (MRI) will provide the sponsor with copies of the protocol. any subsequent protocol amendments, and access to study documents for purposes of study monitoring. MRI will conduct the study according to this protocol except when changes are mutually agreed to in writing, and will comply with the requirements of the appropriate Institutional Review Boards.

Sincerely,

MIDWEST RESEARCH INSTITUTE

Mary R. Cook, Ph.D.
Principal Investigator

Antonio Sastre, Ph.D.
Co-Principal Investigator

Approved:

Bert W. Maidment, Ph.D.
Director
Life Sciences Department

cc: Dr. Ronald Clawson
Dr. David Steele
Dr. Eugene Podrebarac

# Midwest Research Institute
# Biobehavioral Sciences Section
# Protocol Approval

| | |
|---|---|
| Title | Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 1 |
| Authors | Mary R. Cook, Ph.D. and Antonio Sastre, Ph.D. |
| MRI Project No. | 4863 |
| Study Director | Mary R. Cook, Ph.D. |
| Testing Facility Name | Midwest Research Institute<br>425 Volker Boulevard<br>Kansas City, Missouri 64110 |
| Sponsor Name | U.S. Army Medical Acquisition Agency |
| Project Physician | Allen J. Parmet, M.D. |
| Proposed Experimental Start Date | April 15, 1998 |
| Proposed Experimental Termination Date | June 1, 1999 |

**Approvals:**

20 May 98

Bert W. Maidment, Ph.D. — Date
Director, Life Sciences Department

for Eugene G. Podrebarac, Ph.D. — 20 March 1998 — Date
Manager, Quality Assurance

Mary R. Cook — Mar 20, 1998 — Date
Mary R. Cook, Ph.D.
Study Director

# Study Protocol: Individual Differences in Neurobehavioral Effects of Pyridostigmine

Previous studies of the effects of pyridostigmine bromide (PYR) on healthy volunteers have provided valuable information, but many questions remain. Of particular interest are the contribution of PYR, if any, to Gulf War Veterans' illnesses, and the military relevance of individual differences in the reported symptoms and inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) induced by PYR. This project uses two double-blind studies to test specific hypotheses. The major hypotheses to be tested in the research project are that: (a) under well-controlled conditions, the amount of AChE and/or BuChE inhibition observed will be related to alterations in the performance of complex tasks, heart rate variability, and peripherally mediated measures of physiological and sensorimotor functions; (b) individual differences can be differentiated from pharmacokinetic variability by use of a dose-response design, and (c) under heat stress, PYR produces more centrally-mediated effects than it does without heat stress. Plasma and urinary PYR, the major metabolite of PYR, as well as AChE and BuChE, will be measured.

This protocol is for Study 1, which is relevant to hypotheses a and b. Study 1 uses a double-blind, cross-over design. Approximately 72 men and women will be randomly assigned to two groups (30 or 60 mg PYR for 13 doses at 8-hour intervals) with approximately equal numbers of men and women in each dose group. Each subject will also take 13 doses of placebo, and order of PYR and placebo will be counter-balanced. Testing will occur on days 1, 4, and 5 of each drug regimen. The test battery to be administered includes physiological, sensorimotor, and cognitive measures. Tasks were selected for the battery if they showed drug effects in our previous study of the human response to pyridostigmine. Additional tasks were included if they (1) measured important aspects of human function; (2) had a demonstrated history of sensitivity and reliability in previous neurophysiological and/or neurobehavioral testing with human volunteers; (3) were sufficiently challenging for use in a college-educated population; and (4) did not require extensive training time to achieve stable performance. On test days and on day 8, blood will be drawn to quantitate AChE, BChE, pyridostigmine, and the major pyridostigmine metabolite. The planned study will provide important information for evaluating the military consequences of using PYR as a prophylactic drug to aid survival in the event of a chemical warfare attack.

## 1. Background

Pyridostigmine bromide (PYR) is used worldwide for the long-term treatment of myasthenia gravis at doses of 360 mg/day to more than 1,400 mg/day. More recently, low-dose regimens (30 mg, 3 every 8 hours: doctrinal regimen [DR]) have become an important part of the U.S. Armed Forces prophylactic defense against exposure to organophosphate (OP) chemical warfare agents such as sarin. Field use of low-dose PYR

is based on studies of efficacy in animals, and on studies of safety in humans. Most human laboratory studies report few (if any) decrements in performance or adverse effects associated with DR of PYR. However, questions have recently been raised and hypotheses have been formulated about a possible role of PYR, singly or in combination, with insecticides and/or other chemical, immunologic, or stress factors, in the etiology of Gulf War Veterans' illnesses. This collection of illnesses has recently been reported as having central nervous system (CNS) origins, and a pharmacologically questionable mechanism has been proposed whereby the Gulf War Syndrome results from an OP-induced delayed neuropathy caused by PYR in combination with insecticides.

Several pivotal questions in the evaluation of some of these hypotheses are whether there are CNS effects of the ostensibly peripheral drug PYR, and how those effects, if any, could persist long after discontinuation of the drug. The current belief is that the ionic nature of PYR prevents its passage across the blood-brain barrier (BBB). However, some of the reported functional alterations resulting from PYR (e.g., flicker fusion frequency or vigilance) are CNS processes. While there is little doubt that under nonstressful laboratory conditions and low doses, penetration of PYR across the BBB into the CNS is minimal, the data are much weaker or non-existent for ranges of environmentally relevant temperature and stress conditions. Recently, the Medical Corps of the Israel Defense Forces reported that mice subjected to a stressful 4-min forced swim exhibited a temporary breakdown of the BBB. This breakdown allowed PYR to enter the brain and inhibit brain AChE with the same effectiveness as the central-acting inhibitor physostigmine. Other large molecules normally excluded from the brain by the BBB (e.g., an Evan's Blue-albumin complex) also penetrated the brain under these conditions. These findings are based on, and consistent with, earlier work in rodents indicating that cold stress or mild heat stress can *reversibly* increase the BBB permeability. If these observations were applicable to humans, plausible scenarios exist whereby effects of such transient breakdowns of the BBB might lead to persistent effects. It is not possible to evaluate carefully this or other hypotheses, however, with the existing data on humans.

Previous functional human CNS studies have, by and large, failed to examine appropriate, sensitive measures with adequate sample sizes at a range of environmentally relevant temperatures and conditions. Their experimental designs have also failed to account for known absorptional variability and pharmacokinetic complexities of PYR. This has resulted in studies with large individual variations in plasma PYR, as large as would be expected in a deliberate dose-response study, without the controls inherent in such a study design. The net result is a collection of studies that, due to lack of statistical power and to other methodological issues, would have likely failed to detect a central response to PYR even if one exists. Study 1 was designed to take these factors into account.

Study 1 will help determine if there are functional CNS consequences of PYR use. Such responses, if found, are expected to be subtle and to require sensitive measures and robust experimental designs to detect. Second, it will document whether the large, previously reported individual differences in AChE and BuChE inhibition and PYR

levels are reflected in physiological and performance measures (whether central or peripheral) and whether such differences have military significance. Finally, the study will provide the U.S. Army with a more complete body of knowledge for optimal use of PYR as a prophylactic OP-defense agent if a future large-scale deployment is needed.

## 2. Study Objectives

The following major questions will be answered by Study 1.

1. Is there a relationship between PYR ingestion, ChE inhibition, and functional responses? Present data do not allow multivariate correlation between plasma PYR levels, degree of AChE and/or BuChE inhibition, and functional responses. Different conclusions have been drawn about the relationship between inhibition and response. We will clarify the reasons for the reported discrepancies by simultaneous measurement of plasma and urinary PYR and AChE and BuChE inhibition, and by relating the values obtained to functional responses in dose-response studies under well-controlled conditions.

2. Can true individual differences in responses to PYR be distinguished from pharmacokinetic variability? While individual differences in responses to PYR are known, as are the ranges of PYR pharmacokinetic variations, in vitro measures have failed to predict in vivo individual differences. We will distinguish pharmacokinetic variation from true individual differences by using a two-point dose-response study with simultaneous functional and biochemical measures.

## 3. Materials and Methods

### 3.1 Study Design

This study will use a double-blind cross-over design and two PYR levels (30 and 60 mg three times/day; a given subject will receive only one dose level). Prior to entering the drug intake part of the experiment, each subject (S) will spend up to 10 hours becoming familiar with the tasks in the two task batteries. During this time, a blood sample for baseline determination of BuChE and AChE will be obtained. After training and baseline procedures have been completed, the subject (S) will begin Phase 1 of the experiment. Ss will return to the laboratory two weeks after the initial dose to begin Phase 2, which will be identical to Phase 1 except that the other pill (PYR or PL) will be administered. When both phases have been completed for a given S, he or she will receive another physical examination and be released from the study. Subjects will be paid $225 for each phase of the study and will receive a completion bonus of $100 after completion of the final physical examination.

## 3.2 Study Population

### 3.2.1 Sample Size

Selection of the appropriate sample size is critical. When sample size is too large, resources are wasted; when it is too small, statistical tests do not have the power to detect an effect even if it does exist, and negative results can not be interpreted with confidence. Power analysis (Cohen, 1977) of our previous PYR study (N = 24, one dose group) on measures similar to those proposed here indicate that a sample size of 24 per dose group would be adequate for the function with the lowest effect size. Since both men and women are to be included in the study, and since little is known about variance in these measures in women taking pyridostigmine, we believe that sample size must, at minimum, be 36 (approximately 18 men and 18 women) per dose group. We believe this sample size will be adequate for two reasons. First, we will be using measures with less inherent variability than in our previous study, and this will increase statistical power. Second, we will use a higher dose for one of the groups; effect size should be larger for the 60-mg group than for the 30-mg group. Furthermore, the fact that two dose levels will be used will make data interpretation easier.

### 3.2.2 Recruitment and Inclusion Criteria:

Ss will be recruited from local colleges, universities, and research organizations using posters on bulletin boards and announcements in newspapers and newsletters. A sample ad/announcement is shown in Attachment 1. A sufficient number of Ss will be recruited to complete the evaluation on approximately 36 men and 36 women. Men and women will be separately and randomly assigned to one of two dose groups. Half of each gender/dose group will first receive PYR followed by PL and the other half will receive PL followed by PYR.

Men and women who are interested in participating will be asked to call a project staff member, who will explain the purpose, procedures, risks, and benefits of participating. If the potential volunteer is interested, he or she will be interviewed to determine whether preliminary study inclusion criteria are met:

- no chronic disease or disorder
- not taking any prescription medication other than birth control
- no acute illness that required bed rest in the last month
- willing to abstain from alcohol and over-the-counter drugs other than vitamins during the drug administration and testing phases of the program
- able to speak, read and write English
- not pregnant and not planning to become pregnant
- normal (corrected) vision and hearing
- no use of illicit drugs

### 3.2.3 Exclusion Criteria

An appointment will be made with the project physician for a physical examination and urine test for drug use. In addition to the routine physical examination (blood chemistries, electrocardiogram, etc.) the medical monitor will exclude potential subjects who show evidence of:

- latent myasthenia gravis
- asthma
- broncho-constrictive disease
- dysrhythmias
- hypo- or hypertension
- prostatitis
- urinary obstructions
- ulcers
- pregnancy (plasma hCG test obtained as part of physical exam and repeated prior to each dosing week)
- GI obstructions
- weight less than 120 pounds
- seizure disorders
- psychiatric problems
- homozygotes for the "atypical" BuChE mutation using each S's dibucaine number

Only volunteers who, in the opinion of the project physician, can safely ingest doses of PYR up to 60 mg every 8 hours will be admitted to the testing phase of any of the experiments.

## 4. Study Plan

### 4.1 Investigational Material

PYR, supplied by the Department of the Army in Lot no. 325035, Bottle no. BN96947 and PL, supplied by the Department of the Army in Lot no. C191538-01, Bottle no. BN97293, has been supplied to MRI by USAMMDA. Dosing schedule, packaging, labeling, and storage of both PYR and PL will be conducted by MRI staff members who have no other connection with the study or its results. Each dose will be packaged in a blister pack and labeled with the subject's identification number, day, and time of day. Only the sponsor, the project physician, the medical monitor, and the individual in charge of dose preparation and the QA unit will have access to the dose schedule.

## 4.2 Material Tracking

Prepared doses of pyridostigmine and placebo will be kept in a locked lab; the pyridostigmine will be kept refrigerated. A log will be kept of doses prepared by the repository staff. When project staff members check out doses, they will sign for the doses they took, and will be responsible for returning unused pills, if any, to the repository.

## 4.3 Procedures

### 4.3.1 Informed Consent

Those volunteers who meet preliminary criteria will come to the laboratory for a personal interview. The principal or co-principal investigator will again explain the purposes and procedures, risks and benefits of the program, and answer any questions the volunteer has. The volunteer will then read the statement of informed consent. To assure that the volunteer understands the risks and benefits, he/she will be required to summarize them before actually signing the statement of informed consent. A copy of the consent form will be given to the volunteer to keep. The consent form is shown in Attachment 2.

### 4.3.2 Dosing

The studies will be conducted under the US Army's existing Investigational New Drug application. Formulated PYR and PL will be supplied by USAMMDA. PYR or PL will be administered by MRI staff at approximately 0800, 1600, and 2400 hours. If, because of work or class schedules, it is impossible for a subject to come to MRI for the 1600 or 2400 hr pills, he/she will be allowed to take it elsewhere, but will be required to call MRI to confirm that he/she has done so. If no call is received within 15 min of the scheduled dosing time, MRI staff will call and remind the subject to take the pill. No subject will be allowed to take more than one pill per day without supervision, and because of monitoring and food requirements, all subjects must take the 0800 pill at MRI.

## 4.4 Data Collection

### 4.4.1 Vital Signs

Pulse rate (auscultation), oral temperature (ovulation thermometer) and blood pressure (sphygmomanometer) will be measured before administering the 0800 pill each day.

### 4.4.2 Subjective Effects

Each morning before the administration of the 0800 pill the subject will complete the symptom check list. During the performance batteries, the subject will complete subjective fatigue and workload scales. At the time of the 0800 pill, the experimenter will inquire how the subject is feeling in general and will record the response. At the end of each phase, the subject will complete a questionnaire about his/her experience during that phase.

### 4.4.3 Body Fluid Sampling

Blood samples, will be obtained by venipuncture immediately before the performance batteries on days' 4 and 5 and on day 8 of each phase. Urine samples will be obtained immediately before the blood draw. Approximately one ounce of blood will be required at each collection. Studies to optimize sample collection, treatment, and storage are still underway.

### 4.4.4 Test Battery

The test battery, which will be administered in two parts, has been reviewed with and approved by the Contracting Officer's Representative. It is important to keep testing time short, to allow better control of levels of PYR, AChE, and BuChE at the time of testing. Thus, the entire battery has been divided into two units, each requiring about 45 minutes to administer. As described below, Battery A focuses on physiological and sensorimotor measures, and Battery B on cognitive and performance measures. Half the Ss in each dose-order group will be tested on Battery A on Day 4 and Battery B on Day 5; the other half will be tested in reverse order. On Day 1 of each phase, the Ss will be tested on the battery that is administered on Day 4.

**BATTERY A**

| Tasks | Time |
|---|---|
| Pattern Reversal Visual Event-related Potential (VEP) | 5 min |
| Brain Stem Auditory Potential (BSAP) | 4 min |
| Heart Rate Variability (HRV), Continuous Blood Pressure | 15 min |
| Visual Function | 5 min |
| Critical Flicker Fusion (CFF) | 3 min |
| Hand Steadiness Test | 1 min |
| Grip Strength Test | 1 min |
| Workload and Fatigue Scales | 5 min |
| TOTAL | 39 min |

Battery B consists of 12 computer-based tasks, with a primary focus on measures of higher-order cognitive abilities (memory, attention, complex processing, and time sense). Given the effect of pyridostigmine on the motor system, this battery also includes a Finger Tapping task (dominant, nondominant, and alternating hands) to assess motor fluency, and an unstable Visual Tracking task to assess visual/motor integration.

**BATTERY B**

| Origin | Task | Function |
|---|---|---|
| ANAM | Simple Reaction Time | Motor Performance |
| ANAM | 2-Choice Reaction Time | Speeded Decision Making |
| ANAM | Visual Tracking (VT) | Visual/motor Coordination |
| ANAM | Sternberg Memory Test (Sets 4 and 6) | Memory Scanning |
| ANAM | Dual task (VT/STM) | Attention-Shared |
| ANAM | Running Memory | Short-term Memory |
| ANAM | Math Processing | Mental Arithmetic |
| NES2 | Pattern Memory | Visual-spatial Memory |
| NES2 | Switched Attention | Attention-Distraction |
| NES2 | Symbol Digit Substitution | Perceptual Speed/Coding |
| NES2 | Grammatical Reasoning | Complex Processing |
| NES2 | Continuous Performance | Attention-Sustained |
| | Workload and Fatigue Scales | Subjective Effects |
| TOTAL | | |

Anam = Automated Neuropsychological Assessment Metrics Test Battery
Nes2 = Neurobehavioral Evaluation System 2 Test Battery

## 4.5 Data Management

A log is kept of equipment calibration records, decisions with regard to specific experiments and protocols, and deviations from protocol. All data are uniquely coded for study, S, session, and events within the session. Data that must be entered into a computer database are entered independently by two staff members, and computer verified; nonclerical disagreements are resolved by the PI. Databases are created using Microsoft Access for Windows and are networked for team access. Daily system backups allow the identification of changed files, so that the PI can verify that the changes are appropriate and have been properly documented.

## 4.6 Statistical Analysis

All statistical analyses will be conducted using standard packages such as BMDP-

Dynamic and Systat; both of these programs are fully compatible with Microsoft Access. The primary method of analysis will be multivariate analysis of variance for repeated measures (i.e., BMDP-4V). Each study contains a large number of endpoints to be analyzed. Multivariate groupings of these variables will primarily use a systems approach; endpoints that have inherent interdependencies will be analyzed together. In addition, preliminary correlation matrices will be computed to identified additional groupings that should be treated multivariately. The Huynh-Feldt epsilon correction for lack of sphericity will be used when appropriate. Appropriate post-hoc analyses will be conducted to clarify significant interactions.

# 5. Study Management

## 5.1 Study Monitoring

Before the 0800 pill is administered each day, the log of all food consumed in the last 24 hours will be collected and reviewed; oral temperature, blood pressure, pulse rate and answers to a brief questionnaire on side effects (General Response Questionnaire, Attachment D) will be obtained; and the S will eat a standard breakfast. Ss who show signs of illness (oral temperature 99.6°F or greater; pulse rate 20% or more below baseline or below 50 bpm; diastolic blood pressure based on disappearance of Korotkoff sounds outside the range 50-90 mm/Hg, specific pattern of response on the General Response Questionnaire as shown in Attachment 3) will be immediately referred to the medical monitor. The medical monitor will have the ultimate authority to decide whether the S continues participation in the study. Her resume is shown in Attachment 4. Any referral of a subject to the medical monitor will be considered an adverse event, and will be documented whether or not it is considered to be related to the ingestion of pyridostigmine. Occurrence of adverse events will also be communicated to the project physician (see Attachment 5 for resume.)

## 5.2 Follow-ups

Three, six, and twelve months after a subject finishes the study, he or she will be contacted by MRI staff to determine whether any effects that the subject thinks might be due to participation in this study have occurred. If the subject has observed potential effects, he or she will be referred to the medical monitor.

## 5.3 Adverse Event Report

The form to be used for documentation of adverse events is shown in Attachment 6. Serious adverse experiences will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality (301) 619-2165; and the documentation will be faxed (301) 619-7803 to that office. A

written report will follow the initial telephone call within three working days. The sponsor will report any adverse events to the FDA.

### 5.4 Criteria for Subject Withdrawal

The medical monitor has the authority to remove any subject from the study. Ss can withdraw at any time if they choose to do so. Such non-medical withdrawals are usually due to changes in schedule that make it impossible to continue the protocol; family illness or emergency; or inability to comply with the protocol (unable to learn/perform the task battery; unable to obtain blood samples in a routine manner).

## 6. Ethics

### 6.1 Institutional Review Boards

This study and its consent form have been reviewed and approved by MRI's Institutional Review Board for Human Subjects. MRI's Multiple Projects Assurance (effective July 1, 1982, and approved through March 31, 2001) sets out Institutional Review Board (IRB) responsibilities and the procedures that will be used to protect human subjects. The current Multiple Projects Assurance (M-1051) complies with the Federal Policy for the Protection of Human Subjects (56 *FR* 28003), also known as the Common Rule, which became effective on August 19, 1991. The Common Rule established basic standards that are now honored by 16 different Federal departments and agencies. The study will also be reviewed and approved by the Surgeon General's Human Subjects Research Review Board.

### 6.2 Protocol Amendments

Protocol amendments will be signed by the investigator, dated, numbered sequentially, and approved by the sponsor, MRI's IRB, and the Surgeon General's HSRRB. If the protocol amendment alters the study design, increases risk to the subject, or in some other way affects the consent form, a revised consent form will be submitted with the amended protocol.

### 6.3 Study Monitoring

Study monitors representing the sponsor will visit MRI, and will review desired study monitoring procedures with MRI's Quality Assurance Unit and with the co-principal investigators. Both external and internal study monitors will be given access to the records of each individual's participation in the study, and to the source documents from which these records were prepared. If requested by the sponsor, MRI will allow representatives of the Food and Drug Administration access to study documents.

# Attachment 1

MRI

# VOLUNTEERS NEEDED FOR AN

# IMPORTANT RESEARCH PROJECT

**IF YOU ARE BETWEEN 18 AND 35 YEARS OF AGE, IN GOOD HEALTH, AND INTERESTED IN PARTICIPATING AS A PAID VOLUNTEER IN A RESEARCH PROJECT**

**WE WOULD LIKE TO TALK WITH YOU.**

**For more information about this important research project,**

**CALL**

**Ariel Baker**

**753-7600, EXTENSION 1374**

# Attachment 2

DRAFT

MIDWEST RESEARCH INSTITUTE
VOLUNTEERS' INFORMED CONSENT

Study #1
Project # 4863
Revision date: 01/26/98
Revision #1

Individual Differences in Neurobehavioral Effects of Pyridostigmine: Study 1

I,_____residing at

_____

_____

hereby acknowledge and certify to the following:

1. I hereby volunteer and consent to be a subject in a research study sponsored by the U. S. Army Medical Research and Material Command (USAMRMC) and conducted at Midwest Research Institute by Drs. Mary R. Cook and Antonio Sastre. I understand this study will evaluate the short-term effects of pyridostigmine bromide on physiology and performance in normal, healthy young men and women. Pyridostigmine has a long history of use in the medical treatment of a condition called myasthenia gravis. It has been alleged that pyridostigmine bromide is associated with Persian Gulf War veterans' illnesses. Pyridostigmine is important to the Army because it has properties that enable it to protect people in the event of a chemical warfare attack. The Food and Drug Administration, however, has not approved pyridostigmine for use in healthy people and I understand its use is investigational in this research study. The most frequent side effects of pyridostigmine are upset stomach, cramps, gas, diarrhea, and excessive salivation. Pyridostigmine should be avoided when a woman is pregnant. I am also aware that in a previous study at MRI, only a few of the 25 healthy, young men who took pyridostigmine reported any symptoms, and these consisted of mild stomach upset, gas and feelings of tiredness. I also understand that this is a double-blind study. This means that during any given phase of the experiment, pyridostigmine may actually be in the pills I take, or it may not. The investigators will not know, and I will not know, which pill is which. In this way, any effects due to pyridostigmine can be separated from those that might be due to a person's expectations about taking pyridostigmine.

I understand I will receive free a complete medical examination at the start of the study. This evaluation will include medical history, drug screen, urinalysis, electrocardiogram, blood chemistry, complete blood count, lung function test, and medical examination. For women, the examination will include a pregnancy test. The physician will tell me about any problems he/she finds during the evaluation, and advise me about follow-up. I will then come to MRI to be trained to perform tests that measure my memory, attention, perception, and sensory abilities. During training, sensors will be attached to my head and wrist to measure my brain waves, pulse and blood pressure. I understand that sensor attachment is painless and presents no risk to my health. Training will require about 10 hours of my time spaced over a week.

I will then be randomly assigned to one of two groups. One group takes 60 mg pyridostigmine, every 8 hours (180 mg/day) and one takes 30 mg every 8 hours (90 mg/day); both groups take placebo. These doses of pyridostigmine are less than the doses typically used by medical patients (120 mg 6 times/day;

720 mg/day). The study will be performed in two phases, separated by six days off. Each Phase will last eight days, and each will involve the same sequence of activities. I understand I will be asked to come to MRI to take pills every eight hours for the first four days of each phase, followed by one additional pill on the fifth day. I will have my blood pressure, pulse, and temperature recorded. I will complete a food diary and a questionnaire about any symptoms I may be experiencing. Blood samples (about 1 ounce) will be collected via venipuncture from a vein in my arm on days 1, 4, 5 and 8. On days 4 and 5, I will provide urine samples and perform the tests I learned earlier. I will keep a diary of what I eat and drink for the first 4 days of each Phase. MRI will provide breakfast and lunch for me on certain days. At the end of Phase 2, I will visit the project physician again for a brief follow-up medical examination. Three, six and 12 months after I finish the study, I will be contacted by MRI staff to determine whether I have experienced any effects that I think might be due to my participation in this study. If so, they will arrange for further medical evaluation.

I agree to not use drugs or alcohol during the study and to inform the investigators of any medications I may need to take. I understand that standard medical procedures will be followed when drawing blood, but that bruising or soreness can sometimes occur. I further understand that this is a basic research study, and that I will not benefit from being in it, except that I will receive a full medical examination at no charge, and I will be reimbursed for the time and effort required for participation. If I complete all study requirements, I will receive a total of $600 ($50 for training, $225 for each phase, and $100 completion bonus); if not, I will be paid $25.00 per day of actual participation.

2. I have been given, in my opinion, an adequate explanation of the nature, duration, and purpose of the study, the means by which the study will be conducted, and any possible inconvenience, hazards, discomfort, risks, and adverse effects on my health which could result from my participation.

3. I understand my questions concerning procedures which affect me will be answered fully and promptly by either Dr. Mary R. Cook, Principal Investigator, Dr. Antonio Sastre, Co-Principal Investigator, or by Dr. Eugene Podrebarac, Chairman of the MRI Institutional Review Board for Human Studies, which reviewed and approved this study (816/753-7600). The address of the Institute is 425 Volker Boulevard, Kansas City, MO.

4. I understand that I have the right to withdraw my consent and to discontinue participation in this experiment at any time without prejudice regardless of the status of the experiment and regardless of the effect of such withdrawal on the objectives and results of the experiment; and I also understand that my participation in the experiment may be terminated at any time by the investigator in charge of the project.

5. I agree that any information obtained from me, by MRI, or its authorized representatives, in connection with this study may be utilized by MRI in publications and reports without identifying me. Because the use of pyridostigmine is investigational for this study, I am also aware that representatives of the Food and Drug Administration and/or the U.S. Army Research and Materiel Command may wish to review the records of my participation and perhaps contact me to ask specific questions about my experiences. I understand that MRI agrees with this policy of openness in this type of study, and that it will provide personally identifying information about me to allow these agencies to contact me if they so wish. I understand this information will be limited to the following: my name, address, social security number, the name of this study, and the dates of my participation in it. This information will be

maintained by the USAMRMC in its confidential Volunteer Registry Data Base. The intent of this procedure is two fold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

6. If I experience any symptoms I feel should be reviewed with a physician, I can call the medical monitor, who will schedule an appointment with me as soon as possible. The United States Department of Defense is funding this research project. Should I be injured as a direct result of participating in this research project, I will be provided medical care, at no cost to me, for that injury. I will not receive any injury compensation, only medical care. I understand that this is not a waiver or release of my legal rights. I further understand that I should discuss this issue thoroughly with the Principal Investigator before enrolling in this study. Other than the medical care that may be provided (and the other benefits stated above in section # 1 of this consent form), there is no other compensation available for my participation in this research study.

7. I will be given a copy of this consent form to keep.

My age is ____; The date of my birth is_____

I am executing this Volunteer's Consent as my free act and deed.

Today's date is _____, 19_____

Executed in the presence of each other

_____Date:_____
Signature of Volunteer

_____Date:_____
Signature of Investigator

# Attachment 3

4863PP

# GENERAL RESPONSE QUESTIONNAIRE
## INTERIM REFERRAL KEY

DRAFT

**INSTRUCTIONS:**

**** = Refer to Dr. Mary Brothers if SOMEWHAT OR GREATER**

***** = MUST BE MARKED IN CONJUNCTION WITH EACH OTHER FOR REFERRAL**

**All other symptoms must be marked as indicated on the GRQ Referral Key and IN CONJUNCTION WITH 2 OR MORE OTHER SYMPTOMS.**

**GRQ REFERRAL KEY:**

| DESCRIPTION: | Did not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 1. Weakness | | | | | | X | X |
| 2. Trouble speaking | | | X | X | X | X | X |
| 3. Chills | | | X | X | X | X | X |
| 4. Blind spots in eyes** | | | X | X | X | X | X |
| 5. Temper outbursts | | | X | X | X | X | X |
| 6. Chest pain** | | | X | X | X | X | X |
| 7. Excessive thirst | | | | | | X | X |
| 8. Nausea | | | | | | X | X |
| 9. Skin rash | | | | | | X | X |
| 10. Numbness | | | | | | X | X |
| 11. Headaches*** | | | | | | X | X |
| 12. Stiff neck*** | | | X | X | X | X | X |
| 13. Night sweats | | | | | | X | X |
| 14. Depression | | | | | | X | X |
| 15. Nose bleeds | | | | | | X | X |
| 16. Unusual belching | | | | | | X | X |
| 17. Trouble swallowing | | | | | | X | X |
| 18. Blurred/double vision** | | | X | X | X | X | X |
| 19. Body aches | | | | | | X | X |
| 20. Swollen lymph nodes | | | | | | X | X |

| DESCRIPTION: | Did not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 21. Urination problem | | | | | X | X | X |
| 22. Shortness of breath | | | | | X | X | X |
| 23. Bloating | | | | | | X | X |
| 24. Fainting | | | | | X | X | X |
| 25. Dizziness | | | | | X | X | X |
| 26. Memory impairment | | | | | X | X | X |
| 27. Sore tongue | | | | | | X | X |
| 28. Vomiting | | | | | X | X | X |
| 29. Heartburn | | | | | | X | X |
| 30. Bleeding gums | | | | | | X | X |
| 31. Fearfulness/anxiety | | | | | | X | X |
| 32. Diarrhea | | | | | | X | X |
| 33. Heart palpitations** | | | X | X | X | X | X |
| 34. Ringing in ears | | | | | | X | X |
| 35. Flatulence/passing gas | | | | | | X | X |
| 36. Hand tremors/shaking | | | | | | X | X |
| 37. Persistent cough | | | | | | X | X |
| 38. Skin itching | | | | | | X | X |
| 39. Fever | | | | | | X | X |
| 40. Nervousness | | | | | | X | X |
| 41. Abdominal pain | | | | | | X | X |
| 42. Sleep disturbance | | | | | | X | X |
| 43. Dark or bloody urine** | | | X | X | X | X | X |
| 44. Fatigue | | | | | | X | X |
| 45. Constipation | | | | | | X | X |

# Attachment 4

PII Redacted

**Curriculum Vitae - Dr. Mary E. Brothers**

**MARY ELIZABETH (CENTNER) BROTHERS, M.D., FACOEM, FAADEP**

[redacted] [redacted]

**Office Address:** dba, **Midwest Occupational Medicine®,** Owner
3037 Main Street, Suite 201
Kansas City, Missouri 64108-3323

**Office Phone/FAX:** (816) 561-3480 (answering machine after hours)
(816) 561-4043 - Fax

[redacted] [redacted]

[redacted] [redacted]

**Education:** Bishop Miege High School, Mission, Kansas; College Prep Program, 1963-1967
Saint Mary College, Leavenworth, Kansas; BA in Biology, with Honors, 1971

**Medical Education:**

**1971-1974** University of Kansas School of Medicine, Kansas City, Kansas M.D. in September, 1974; 3 year curriculum ('74 B)

**Post-Graduate Medical Education:**

Sept - Dec, 1974 KU: electives in emergency medicine, radiology and anesthesiology

Jan - June, 1975 Externship in General Surgery and Orthopedics, Eisenhower VA Medical Center, Leavenworth, Kansas

June '95 - July 28, 1979 Four year Residency in General Surgery, Eisenhower VA Medical Center; Chief Resident 1978-1979. (Former Program Chief - Mary P. McAnaw, MD, FACS

1982-1984 "Mini" Residency in Occupational Medicine, University of Cincinnati, Cincinnati, Ohio; (144 hours); Sidney Lerner, MD, FACOM, Director (deceased)

September 1994 Began graduate program for MPH, University of Kansas

Medical Center. 1st year, 1994-1995 (epidemiology, biostatistics, public health policy/admin., Environmental health). Anticipate completion of course work in Spring of 1998 and degree by Fall, 1999.

**Medical Licensure:**

| | |
|---|---|
| **04/18/77** | National Board of Medical Examiners |
| **12/07/77** | **Kansas** # 017191 (currently "exempt" status) |
| **04/13/79** | **Missouri** # MD R9252 |

**Medical Boards/Fellowship:**

| | |
|---|---|
| 05/05/87 | **Fellow,** ACOEM (formerly American Occupational Medical Association.) - **FACOEM** |
| Nov 1989 | **Fellow,** American Academy of Disability Evaluating Physicians - **FAADEP** |
| Feb 1997 | **Board Certified, Preventive Medicine/Occupational Medicine** 01/20/97 - examinee # 23833 |

**Summary of Medical Practice:**

| | |
|---|---|
| 07/31/79 - Present | Entered into practice of industrial injury with Paul J. Centner, MD, FACS, (father) at 2727 Main Street, Kansas City, Missouri. [Part-time until 1983, then full-time] |
| **In addition:** | |
| 1980-07/15/81 | Medical Director for Midwest Grain, Inc., (formerly Midwest Solvents), Atchison, Kansas. Helped to establish company wellness and Occ Med programs. On courtesy staff, Atchison Community Hospital from 12/19/79-01/21/82. |
| 05/80-06/81 | Part-time staff and instructor in general surgery, Eisenhower VAMC, Leavenworth, Kansas. |
| 07/82-03/83 | Assisted as locum tenens in Occupational Medicine for Dr. James Hall, Landmark Medical Clinic, Kansas City, Missouri. On staff at Liberty Hospital, Liberty, Missouri during this period. |

| | |
|---|---|
| 1988-1992 | Purchased practice from Dr. Centner; practice incorporates Occupational Medicine and Disability Evaluation; practice name changed to **Midwest Occupational Medicine®** 1991-1992, at time of relocation to Union Hill Commons. |

**Hospital Staff Appointments:**

| | |
|---|---|
| 1979-1989 | St. Mary Hospital, Kansas City, Missouri (ceased to exist 1989 at purchase by Trinity Lutheran); active staff in general surgery. |
| 05/80-06/81 | Eisenhower VA, Leavenworth, Kansas, part-time staff surgeon. |
| 12/79-01/82 | Atchison Community Hospital, courtesy staff in general surgery. |
| 07/82-03/83 | Liberty Hospital, Liberty, Missouri, courtesy staff. |
| 1989-present | Trinity Lutheran Hospital, Kansas City, Missouri; active staff, department of Family Practice, sub-section of Occupational Medicine. |
| 1989-06/25/97 | Baptist Medical Center, Kansas City, Missouri. Adjunct staff in General Surgery. Resigned, 06/25/97. |
| 1992-1996 | Menorah Medical Center, Kansas City, Missouri; active staff, department of Family Practice/Section of Occupational Medicine. (Resigned when Hospital moved to Kansas, 1996.) |
| 1997 | North Kansas City Hospital - application pending. |

**Professional Memberships/Offices Held:**

**American College of Occupational/Environmental Medicine:**
**(Great Plains COEM - local chapter)**

| | |
|---|---|
| 1979-present | Membership |
| 1981-1982 | Secretary-treasurer |
| 1982-1983 | Second Vice-president |
| 1983-1984 | First Vice-president |
| 1984-1985 | President-elect |
| 1985-1986 | President |

| | |
|---|---|
| 1986-1987 | Past-president |
| 1989-1992 | Delegate to ACOEM |
| 1992-1995 | Second term as delegate to ACOEM |
| 1996-1999 | Alternate delegate to ACOEM |
| 1987-1991 | Member, Committee on Ethical Practice |
| 1990-1992 | Editor, Newsletter of the Section on Work Fitness/Disability Evaluation |
| 1992 | Alternate for election to three year term on the ACOEM Board of Directors |

**American Academy of Occupational Medicine - elected a member 11/87**

**American Medical Women's Association**

| | |
|---|---|
| Present | Life member |
| 1984-1986 | Secretary-treasurer, Kansas City |
| 1986-1988 | Vice-president and President-elect |
| 1988-1990 | President |
| 1985 | Faculty, Regional conference on Women in Medicine, Kansas City, Missouri |
| 1989 | First Legislative Conference on Politics of Women's Medicine, Washington, D.C. |

**American Medical Association**

| | |
|---|---|
| 1979-present | Member except for Jan-August 1992, due to practice relocation expenses. Rejoined August, 1992. |

**Metropolitan Medical Society of Kansas City (formerly Jackson County Medical Society)**

| | |
|---|---|
| 1980-present | Member |
| 1984 | Election Committee Chairperson |
| 1985-1988 | Public Relations Committee; Chairperson 1986-1988 (concerned with public complaints about physicians) |

| | |
|---|---|
| 1988-1990 | Medico-legal Liaison Committee Chairperson (dealt with liaison between physicians and bar association) |
| 11/17/88 | Attended local leadership conference, Kansas City, Missouri |

**Missouri State Medical Society**

| | |
|---|---|
| 1980-1991 | Member |

**Kansas State Medical Society**

| | |
|---|---|
| 1980-1982 | Member during practice in Kansas |

**Kansas City Surgical Society**

| | |
|---|---|
| 09/15/83-1991 | Member; resigned end of 1991 to devote full-time practice to Occupational Medicine CME activity |

**Teaching Appointments:**

| | |
|---|---|
| Spring, 1975 | Faculty, Saint Mary College, Leavenworth, Kansas; Histology and Micro technique. |
| 1980-06/10/81 | Part-time instructor in General Surgery, Eisenhower VA Medical Center. |
| 1987-present | Preceptor in Occupational Medicine; Trinity Lutheran Hospital Family Medicine Residency (formerly St. Mary's Hospital Family Medicine.) Scott Thompson, MD, Director. |

**Directorships:**

| | |
|---|---|
| Late 1980's | Co-Director, (with Dr. Centner), SHARE Program for Occupational Health Nursing, St. Mary's Hospital, Kansas City, Missouri. |
| 10/1992-12/31/93 | Co-Director, MedWorks Managed Occupational Health Network, Menorah Medical Center, Kansas City, Missouri. |
| 1994-1995 | MedWorks Director/Advisor; Mariner Rehabilitation (formerly Pinnacle Rehabilitation). |

**Curriculum Vitae - Dr. Mary E. Brothers**

**Consultant:**

| | |
|---|---|
| 10/01/92-10/1995 | Contract Occupational Physician Consultant, Federal Occupational Health-US Public Health Service, Region VII. |
| Fall, 1997 | Pending application to resume consulting position for Region VII, Public Health Service. |

**Hospital Committee Work:**

| | |
|---|---|
| St. Mary's Hospital | By-laws<br>Medical Records & Audit Chairperson, 1983-1986<br>Tissue Sub-committee, 1984-1988<br>ER/Outpatient Committee<br>Developed the Ambulatory Surgery Unit with Sr. Susan Scholl, SSM |
| Trinity Lutheran Hospital | By-laws, 1989-present<br>ER/Outpatient Committee, 1989-1996<br>Physician's Health Committee, 1997-present |

**Lectures:**

| | |
|---|---|
| 09/27-29/75 | Chairperson, panel on ER Medical Care, AMWA Regional Conference, Kansas City, Missouri |
| 07/09/80 | High Pressure Injection Injury; Leavenworth CME circuit Eisenhower VAMC |
| 07/27/89 & 10/26/89 | Two-part lecture on "Permanent Partial Disability Determination Within the Workers' Compensation System", for staff of OHS, Dr. Ed Kinports, Director |
| 11/02/89 | Rating Workers' Compensation Injuries - the Physician's Role; Fourth Annual Missouri Work Comp Seminar (Mo. Bar/UMKC Law School), Allis Plaza, Kansas City |
| 04/30/90 | Confidentiality of Company Medical Records-The Private Practice Experience; ACOEM Post-grad seminar in Ethics; American Occupational Health Conference, Houston, Texas |
| 04/28/91 | Committing Truth - The Occupational Physician on the Firing Line; ACOEM Post-grad seminar in Ethics; |

| | |
|---|---|
| | American Occupational Health Conference, San Francisco, California |
| 07/28/92 | Lecture on Disability Evaluation and Workers' Compensation; Physical therapy-orthopedic study group, Trinity Lutheran Hospital |
| 03/10/94 | Organophosphate Pesticide Poisoning, Kansas City, E.P.A. |
| 02/01/95 | Cumulative Trauma Disorders, Praxair Surface Technologies, Inc., Kansas City, Missouri |

**Publications:**

| | |
|---|---|
| 1971 | (Unpublished) Honors research paper on Chemoattractants in Fasciola hepatica and snail hosts; Saint Mary College, Leavenworth, Kansas |
| 1971 | An Analysis of Particulate Matter in the Lungs and Air Sacs of Columba livia; section of NSF-SOS Report on "Air and Water Pollution in Atchison, Kansas". Benedictine College Research Grant |
| 1990 | "You're Just the Company Doctor"; issue of the Kansas City Health Journal, in conjunction with Baptist Medical Center |

**Awards:**

| | |
|---|---|
| 1977; 1978 | Outstanding Young Women of America |

**Political Experience:**

See addendum "A"

**Continuing Medical Education:**

| | |
|---|---|
| 07/16/79-present | Physician's Recognition Award of the AMA |

See Addendum "B"

**Other:**

| | |
|---|---|
| 07/13/80-present | Aviation Medical Examiner for the FAA; completed the |

Senior Examiner's Seminar, Oklahoma City, in October, 1985.

August, 1990 - update seminar, Kansas City, Missouri

February, 1995 - update seminar, Savannah, Georgia

Fall, 1993 - Present

Appointed to serve as Committee member, Mid-America Coalition on Health Care Committee on Workers' Compensation, Kansas City, Missouri; background work on Robert Wood Johnson Grant applications project. Various presentations to KCMO business community, 1995-1996.

**Personal Information:**

[redacted]

PII Redacted

[redacted]

[redacted]

**Personal Memberships**

American Horticulture Society
The Audubon Society
The Nature Conservancy
Nash Car Club of America/Historic Trails Region
Smithsonian Institution

**Curriculum Vitae - Dr. Mary E. Brothers**

**Addendum "A" - Political Experience**

In August of 1980, after returning to the general surgical staff of the Eisenhower VA Medical Center on a part-time basis, I became aware of the existence of a questionable drug research study then ongoing in the Center. The study was being performed by the former Chief of Psychiatry (now deceased), and my opinion of it was requested by the former Chief of Surgery, Mary P. McAnaw, MD, FACS.

After examining a portion of the study records and research memos I was concerned that there was evidence of impropriety and I subsequently established contact with the VA's Inspector General to request a further investigation. I was also requesting an investigation by the IG into the proposed and ongoing attempt to remove the Chief of Surgery from her position at the Leavenworth VAMC. The two of us, in the company of a former staff psychologist, undertook the role of "whistle-blowers" to effect a complete investigation.

As a result of our combined activities in this matter the former Chief of Surgery was demoted and transferred to her present position at the VAMC, Kansas City, Missouri, where she has advanced to the position of Assistant Chief of Surgery. Both she and I sued the VA, and the Center Chief of Staff, and (former) Center Director in the Federal Court in Topeka, Kansas. Dr. McAnaw ultimately lost her suit in her position as a full-time federal employee. My suit was ongoing between 1982 and 1989; my contention was that I had been terminated from part-time employment and denied a full-time staff surgeon position because of retaliation for "whistle-blowing". In January of 1989, a jury in Topeka awarded over $ 90,000 in wage loss and $ 100,000 in punitive damages against the VA in my suit. However the suit had been filed and argued using a "Biven's" defense; the damage awards were a precedent at the time and were subsequently overturned by the U.S. District Appeals Court, Denver, Colorado, in October 1989 and remanded to the Office of Special Counsel (OSC). The case and verdict were under scrutiny by the attorneys of the Government Accountability project (GAP) in Washington through 1991.

During the "whistle-blower" period I was involved with the local staffs of both Senators Dole and Kassebaum, and of former Kansas Representative Jim Jeffries. The FDA ultimately supported all of the allegations, and also identified improprieties in a prior drug study by the same investigator, resulting in his signed agreement to do no further drug research. The situation received wide coverage in the media, including the Kansas City Times, Federal Times, WNEV-TV, Boston, and the case was featured in the book "The Whistleblowers" by Myron & Penina Glazer (Basic Books, NY, c. 1989). In May of 1989 I lectured to Dr. Glazer's sociology class at Smith College on the case.

As result of this case I participated in Representative Pat Schroeder's House Hearings on the OSC in 1985 and testified for Senators Pryor, Levin & Grassley in July

1987 at hearings for the "Whistleblower Protection Act". In November of 1991 I testified at oversight hearings on whistleblowing in the VA for Representative Ted Weiss, and appeared live on "Crier and Company", via Atlanta.

## Addendum "B" - Continuing Medical Education:

### Occupational Medicine:

| | |
|---|---|
| 1980-present | Attendance at local meetings of Great Plains College of Occupational & Environmental Medicine, and the annual "Hungate" Seminar. In 1986, I served as the Hungate Conference Chairperson.<br>Hungate Planning Committee Member, 1996; 1997 |
| April, 1985 | AOMA - American Occupational Health Conference, Kansas City. Post-graduate planning committee for this AOHC. |
| 4/27-05/01/86 | AOHC; Denver, Colorado |
| 04/23-29/87 | AOHC; New Orleans, Louisiana |
| 10/24-28/87 | Fall State of the Art Conference, San Antonio, Texas. AOMA and Academy merge to form the ACOM. |
| 04/27-05/02/88 | AOHC; Philadelphia, Pennsylvania (Obtain Fellowship) |
| 04/29-05/05/89 | AOHC; Boston, Massachusetts |
| 10/30-11/03/89 | Fall State of the Art Conference, Baltimore, Maryland |
| January 1990 | Medical Review Officer Training (MRO), Chicago, Illinois |
| 04/30-05/04/90 | AOHC; Houston, Texas |
| 10/08-12/90 | Fall State of the Art Conference, Pittsburgh, Pennsylvania |
| 04/26-05/03/91 | AOHC; San Francisco, California |
| 10/25-31/91 | Fall State of the Art Conference, and 2nd MRO training seminar, St. Louis, Missouri |
| 05/02-08/92 | ACOEM (name change) AOHC; Washington, D.C. |
| 04/26-30/93 | AOHC; Atlanta, Georgia; course on Medical Surveillance ASPHS Regional meeting, Atlanta. |

| | |
|---|---|
| 10/93 | Fall State of the Art; core course in Environmental Medicine; Dallas, Texas. |
| 04/18-22/94 | AOHC; Chicago, Illinois. |
| 10/94 | Fall State of the Art Conference; Denver, Colorado. |
| 04/29-05/03/96 | AOHC; San Antonio, Texas. |
| 03/1996 | Epidemiology and Prevention of Vaccine-Preventable Diseases; CDC Telecommunications Course, Kansas City, Missouri |
| 08/24-28/96 | 1996 Preventive Medicine Review Course, (ACPM), Washington, D.C. |
| 11/04/96 | Board Exam, Preventive/Occupational medicine, Chicago, Illinois. |

**Workers' Compensation & Disability Evaluation:**

| | |
|---|---|
| 05/16/84 | Satellite Video-teleconference; CTD's and Ergonomics, Kansas City, Missouri. |
| 06/07-08/84 | AMA Conference on Introduction to the Guides to the Evaluation of Impairment & Disability, 2nd Ed., Chicago, Illinois. |
| 10/27-29/86 | Impairment Evaluation & Disability Considerations, Department of Orthopedic Hand Surgery, University of Michigan, Ann Arbor. |
| 06/09-13/86 | Principles & Practice of Industrial Toxicology, 26th Annual course, Wayne State University, Detroit, Michigan. |
| 09/26/86 | 1st Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 10/15-16/87 | UMKC Heartland Labor & Employment Law Institute, Kansas City, Missouri. |
| 11/20/87 | 2nd Annual Missouri Work Comp Seminar, Kansas City, Missouri. |

| | |
|---|---|
| 11/18/88 | 3rd Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 04/08-09/89 | AADEP Clinical Overview Course, Chicago, Illinois. |
| 04/12/89 | NIOSH Spirometry Training Course, Research Medical Center, Kansas City, Missouri. |
| 08/07-09/89 | Current Topics in Occupational Safety, "Prevention of Upper Limb Injuries", University of Michigan School of Engineering, Ann Arbor, Michigan. |
| 09/20-21/89 | AADEP Clinical Training Conference, Chicago, Illinois. |
| 11/02/89 | 4th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 07/1990 | Seminar on Workers' Compensation & Occupational Medicine, Hyannis, Massachusetts. |
| 11/02-03/90 | Annual AADEP Scientific Session & Symposium, Las Vegas, Nevada. |
| 11/07/90 | 5th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 10/22/91 | 6th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 11/14-16/91 | Annual AADEP Conference, Kansas City, Missouri. |
| 04/16/93 | Rehabilitation of the Injured Worker, Kansas City, Missouri. |
| 05/11/93 | Maternity Issues in the Workplace, Kansas City, Missouri. |
| 05/14/93 | Hungate Seminar in Occupational Medicine, Kansas City, Missouri. |
| 09/22-24/93 | Impact Hearing Course on Occupational Hearing Loss and Hearing Conservation/CAOHC certified for five years (09/24/93); certificate # 35543. |
| 11/93 | Annual AADEP Conference, San Diego, California. |

| | |
|---|---|
| 05/13-14/94 | AADEP Conference on IMEs, Kansas City, Missouri. |
| 05/20-21/94 | Hungate Seminar in Occupational Medicine, Overland Park, Kansas. |
| 06/24-25/94 | DATTI Conference-Breath Alcohol Analysis, Charlotte, North Carolina. |
| 04/22/95 | Hungate Seminar in Occupational Medicine, Kansas City, Missouri. |
| 06/09-12/95 | ACOEM Seminar-Fundamentals of and Advanced IME Exams, Atlanta, Georgia. |
| 11/02-24/95 | Annual AADEP Scientific Session & Symposium, Washington, D.C. |
| 04/1996 | Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 02/26/97 | Impaired Physician - Richard Irons, MD - Trinity Lutheran Hospital, Kansas City, Missouri. |
| 03/07-08/97 | Hungate Seminar in Occupational Medicine, Overland Park, Kansas. |
| 04/01/97 | Evaluating Disability Under Social Security, St. Joseph Health Center, Kansas City, Missouri. |

**FAA Training Seminars:**

| | |
|---|---|
| 1980 | Initial Appointment, Memphis, Tennessee. |
| 1985 | Senior Examiner Seminar, Oklahoma City, Oklahoma. |
| 1990 | Kansas City Update. |
| 1995 | Savannah Update. |

**General Surgery CME Activity:**

| | |
|---|---|
| 05/18-20/77 | Symposium on "Hernia", Creighton University, Omaha, Nebraska. |

| | |
|---|---|
| 05/17-18/79 | "Pitfalls in Surgery" |
| 02/1980 | "SESAP III" surgery review (155 hours) - self assessment. |
| 09/13-14/80 | Kansas ACS Chapter Meeting, Wichita, Kansas. |
| 1983 | "SESAP IV" surgery review - self assessment. |
| 10/02-14/83 | Cook County Specialty Review Course in general Surgery, Chicago, Illinois. |
| 09/15/83-1991 | Member, Kansas City Surgical Society - attended most conferences during this time. |

**Other CME:**

| | |
|---|---|
| 09/20-21/84 | Interqual: Quality Controls-Tools for Assuring Effective Care, Kansas City, Missouri. |
| 03/13-15/88 | National Conference on Health Fraud, co-sponsored by the FDA and St. Mary's Hospital (Dr. John Renner), Allis Plaza, Kansas City, Missouri. |
| 12/06/90 | Kansas City Bar Conference on Tort Cases, Liability Actions and "Applied Kinesiology", Lance Welch Conference Center, Kansas City, Missouri. |
| 06/1992 | Second Annual Family Medicine Update, Trinity Lutheran Hospital, Kansas City, Missouri. |
| 04/23/93 | Maxillo-facial Seminar, Trinity Lutheran Hospital, Kansas City, Missouri. |
| 10/07/93 | American Heart Association BLS Training, Menorah Medical Center, Kansas City, Missouri. |
| 06/08/94 | Kansas City Coalition on Health Care-Symposium on Preventive Medicine and Self-Care. |
| 1990-present | CME Conferences sponsored by Trinity Lutheran Hospital, variety of topics. |
| | 1996-1997 Topics: include Violence in Society/Workplace, Travel Medicine - A.J. Parmet, M.D., |

| | |
|---|---|
| | Update on H. Pylori - Barry Marshall, M.D., Medical Humanities - Marjorie Sirridge, M.D. |
| 09/12/97 | Red Cross Health Care Providers BLS training, Midwest Occupational Medicine® (through St. Mary's Blue Springs), Kansas City, Missouri. |

**Special Projects:**

| | |
|---|---|
| 1993-1995 | Medical Consultant, cumulative trauma prevention research project, Smith Orthopedic Company, Topeka, Kansas - and MAMTC. |
| 1993-present | Kansas City Coalition on Health Care - Workers Compensation Draft Proposal; physician team member. (Robert Wood Johnson Grant proposal). Pilot project funded 1996. |

**Misc. Award: (update) -**

| | |
|---|---|
| 04/01/93-04/01/96 | PRA Award of the American Medical Association. |

# Attachment 5

**Allen J. Parmet**

PII Redacted

Curriculum vitae as of May 31, 1997

Office:Midwest Occupational Medicine
3037 Main, Suite 201
Kansas City, MO 64108
(816) 561-3480
FAX 561-4043

[redacted]

Education

Undergraduate : United States Air Force Academy - B.S. 1972
Medical School: University of Kansas - M.D. 1976
Internship : David Grant Medical Center,
Travis AFB, California - 1977
Residency : Phase I - University of Texas
School of Public Health at
Houston - M.P.H. 1981

Phase II - USAF School of Aerospace
Medicine Brooks AFB, Texas - 1982

Fellowship : Space Medicine - NASA/Johnson
Space Center, Houston, Texas - 1982

Post-Graduate Work: University of Kansas School of Medicine, Department of Toxicology 1995-

License

Kansas #17322 December 9, 1977
Texas #F1185 June 12, 1978
Missouri #R2G63 August 22, 1986
Colorado #31655 April 9, 1992

Educational Short Courses

Aerospace Medicine Primary, USAF School of Aerospace Medicine, Brooks AFB, TX, 1977

Combat Casualty Care Course, Brooke Army Medical Center, Ft. Sam Houston, TX, 1982.
Forensic Accident Investigation, Armed Forces Institute of Pathology, Walter Reed Army Instiute of Research, Washington, DC, 1983

Crash Investigators Course, Arizona State University, 1983

Aircraft Accident Investigation Course, University of Southern California Safety Systems Institue, Los Angeles, 1988.

Certificates & Examinations

National Board of Medical Examiners Certificate #176115
American Board of Preventive Medicine Certification:
Aerospace Medicine-Diplomate January 27, 1983
Occupational Medicine-Diplomate January 31, 1989
Medical Review Officer Certification Council-June 13, 1993
American Board of Forensic Examiners-Sept, 1996

Medical Job History

1994 - Medical Director, Trans World Airlines

1993-95 Medical Director, St. Lukes's Occupational Medicine Group, Kansas City, Missouri

1995- Adjunct Faculty for Aviation Safety, Institute of Safety and Systems Management, University of Southern California, Los Angeles, California

1992 - Great Plains College of Occupational and Environmental Medicine:

President, 1996-97
1st Vice-President, 1995-6
2nd Vice-President, 1994-5
Secretary-Treasurer, 1993-4

1992-94 Consultant, Mid-America Coalition on Health Care/Workers' Compensation Task Group, Kansas City, Missouri

1992- Adjunct Professor, Department of Aerospace

Medicine, USAF School of Aerospace Medicine, Brooks AFB, TX

1990- 94 Adjunct Assistant Professor of Preventive Medicine and Biometrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD

1988- Associate Clinical Professor, Dept. of Community Medicine Wright State University School of Medicine, Dayton, OH

1987 - Associate Editor, **Aviation, Space and Environmental Medicine**

1987 - 92 Professor, Department of Aerospace Medicine, United States Air Force School of Aerospace Medicine, Brooks AFB, TX:

Course Director, Aerospace Medicine Primary, 1987, 88, 89 & 91.

Course Director, Operational Aeromedical Problems 1988, 89, 92.

Course Director, Health Professions Scholarship Program, 1990, 91 & 92.

Course Director, Aeromedical Readiness and Management Course, 1990, 91 & 92.

Course Director, Global Medicine Course, 1991 & 92.

Deputy Director, Residency in Aerospace Medicine, 1989 - 92.

1985 - 87 Associate Professor of Health Sciences, Chapman College Extension, Los Angeles, CA. Courses taught: Epidemiology, Genetics, Infectious Disease.

1984 - 96 Series Editor, "Cases From the Aerospace

Medicine Residents' Teaching File" in
Aviation Space and Environmental Medicine

1984 - 87 Space Transportation System Medical Director/
Chief of Aerospace Medicine, Vandenberg AFB, CA

1982 - 84 Chief of Flight Evaluations, School of
Aerospace Medicine, Brooks AFB, Tx

1979 - 80 Flight Surgeon, Randolph AFB Clinic, Tx

1977 - 79 Flight Surgeon, Officer Training School Clinic,
Lackland AFB, Tx

Other Activities

1982-1986 Member, Education and Training Committee;
1988-1992 Aerospace Medical Association

1984-87 Member, NASA/USAF Space Transportation System
Personnel Assurance Program Review Committee

1986-89 Member, History and Archives Committee;
Aerospace Medical Association

1987-89 Chairman, Reinartz Education and Training
1990-92 Committee; Society of USAF Flight Surgeons

1982-1986 Member, USAF Manned Spaceflight Engineer
Selection Panel

1987-1991 Member, USAF Astronaut Nomination Panel

1987- Member, USAF School of Aerospace Medicine
Residency Advisory Committee

1991- Member, Awards Committee (1992- Vice-Chair);
Aerospace Medical Association

1993- Senior Aviation Medical Examiner, Federal
Aviation Administration

1993-96 Chairman, Occupational Medicine Section, St.

Lukes Hospital Department of Medicine.

1993-1995 Member, Infection Control Committee, St. Lukes Hospital Department of Medicine.

1995- Chairman, Quality Assurance Committe, St. Lukes Hospital Department of Medicine.

Honors

Fellow, American College of Preventive Medicine
Fellow, Aerospace Medical Association
Fellow, International Association of Aviation and Space Medicine
Fellow, American College of Forensic Examiners

Awards

Society of USAF Flight Surgeons Howard Unger Annual Award for Best Publication - 1984
USAF Meritorious Service Medal - 1984
USAF Meritorious Service Medal, 1st OLC - 1987
USAF Meritorious Service Medal, 2nd OLC - 1992
Strategic Air Command Flight Surgeon of the Year - 1985
Peter T. Bohan Lecturer, University of Kansas - 1986
Outstanding Clinical Instructor for the Residency in Aerospace Medicine - 1989

Associations

American Medical Association
Aerospace Medical Association
American College of Occupational & Environmental Medicine
American College of Preventive Medicine
American College of Forensic Examiners

Publications (Sole or first author unless noted)

Original Articles

"Treatment of Neovascular Glaucoma with Transscleral Panretinal Cryotherapy", (Co-author) Ophthalmology, Nov. 1980, 87 (11): 1106 - 1111

"Nonsexual Transmission of Gonorrhea to a Child" (with H.J. Lipsitt), New England Journal of Medicine, Aug 16, 1984, 470

"A Clinical Challenge: How Many Ways Can You Skin a Cat", Aviation Space and Environmental Medicine, 55 (10): 946-7, 1984

"Case from the Aerospace Medicine Residents' Teaching File" #1: Toxic Peripheral Neuropathy, Sacroilitis and Mitral Valve Prolapse", Aviation Space and Environmental Medicine, 55 (11): 1057-69 1984

"Feedback #1", Aviation Space and Environmental Medicine, 55(11): 1059, 1984

"Case from the Aerospace Medicine Residents' Teaching File #2: On an aviator with an Acoustic Neuroma", Aviation Space and Environmental Medicine, 55 (12): 1151-53, 1984

"Feedback #2: My Best Case, My Worst Case", Aviation Space and Environmental Medicine, 55 (12): 1153, 1984.

"Case from the Aerospace Medicine Residents' Teaching File #3: An Aviator with Idiopathic Dialated Cardiomyopathy", Aviation Space and Environmental Medicine, 56 (1): 62-65, 1985

Feedback #4, Aviation Space and Environmental Medicine, 56 (3): 274, 1985

Feedback, #7, Aviation Space and Environmental Medicine, 56 (11); 1118-1119, 1985

Feedback #9, Aviation Space and Environmental Medicine, 56(12); 1228, 1985

"Space Shuttle at Vandenberg", Military Medicine, 150 (11); A1-A3, 1985

"Drain That Swamp", Military Medicine, 151 (1); 60-63, 1986

Feedback #8, Aviation Space and Environmental Medicine, 57 (1); 84, 1986

Letter, Aviation Space and Environmental Medicine, 57 (1);85, 1986

"Case from the Aerospace Medicine Residents' Teaching File #14: An Aviator with Hodgkin's Disease", (Co-author) Aviation Space and Environmental Medicine, 57(8): 805-7, 1986

Feedback #14, Aviation Space and Environmental Medicine, 57 (8): 807, 1986

"Case from the Aerospace Medicine Residents' Teaching File #15, An Aviator with Chronic Lymphocytic Leukemia", (Co-author) Aviation, Space and Environmental Medicine, 57(11):1109-11, 1986

Feedback #15: Aviation, Immunity and AIDS, Aviation, Space and Environmental Medicine, 57(11):1111, 1986

Feedback #17, Aviation, Space and Environmental Medicine, 58(4):381, 1987

"The Early Birds of 1911", Aviation Space and Environmental Medicine, 58 (3): 276-79, 1987

Feedback #21, Aviation, Space and Environmental Medicine, 59(1):88, 1988

"Case from the Aerospace Medicine Residents' Teaching File #31: Methemaglobinemia", Aviat. Space Environ. Med., 1989, 60(5):465-6.

"Case from the Aerospace Medicine Residents' Teaching File #45: An aviator with Melanoma" (Co-author), Aviat. Space Environ. Med. 1991; 62(7):694-6.

"Body Volume Changes During Simulated Microgravity: Auditory Changes, Segmental Fluid Redistribution, and Regional Hemodynamics", (with LD Montgomery), Annals of Biomedical Engineering, 1993, 21:417-433.

"Sixty for Ten" (Editorial), Aviat. Space Environ. Med., 1994, 65:670.

"Case from the Aerospace Medicine Residents' Teaching File #60: An aviator with erythema multiformae", Aviat. Space Environ. Med., 1994, 65:671-73.

"Survey of the American Board of Preventive Medicine Examination-1994", Occupational and Environmental Medicine Report, 1995, 9(8):66-67.

"Case from the Aerospace Medicine Residents' Teaching File #62: An aviator with lead poisoning and peripheral neuropathy", Aviat. Space Environ. Med., 1995, 66(11):1107-1109.

"Case from the Aerospace Medicine Residents' Teaching File #63: Three aviators presenting with hypoxic symptoms as manifestation of underlying systemic diseases", Aviat. Space Environ. Med., 1995, 66(12):1215-1217.

Awaiting Publication:

"Occupational Exposure to Clostridium tetanus and Tetanus Toxin", Mil. Med., 199 .

Books, Chapters and Review Articles

"Seasonal Protection through Voluntary Programs", Occupational Health and Safety, 50 (11): 27-30, 1981

"You're the Flight Surgeon", Aviation, Space and Environmental Medicine, May 53 (5): 512, 1982

"Chapter 25: Space Medicine" in AFM 160-1, Aerospace Medicine, December 1983

Asthma Self-Assessment Program (Contributor), Aviation, Space and Environmental Medicine, 55 (2): 156, 1984
"Heart Facts", Professional Pilot, Oct 1987, pg 12.

"Heart Facts Part 2", Professional Pilot, Dec 1987, pg 32.

"Aircraft Accident Search and Rescue (SAR) Operations", Aeromedical & Training Digest, Vol. 2, No. 3, July 1988

"Chapter 24: Missile Medicine" in AFM 161-18, Flight Surgeon's Guide, JA Bishop, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Jan 1989.

"Chapter 25: Space Medicine" (Co-author) in AFM 161-18, Flight Surgeon's Guide, JA Bishop, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Jan 1989.

Study Guide for Preventive Medicine Certification 1989, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1989.

"TOP KNIFE #24: Toxicologic and Radiation Hazards of Fighter Aviation Operations" (videotape and notetaking guide), from TOP KNIFE video CME series, National Guard Bureau, Washington, D.C., Sept 1989.

"Toxicology in Aviation", Aeromedical & Training Digest, Vol 4, Issue 1, January, 1990, Pg 43-47.

Study Guide for Preventive Medicine Certification 1990, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1990.

"Flight Surgeons", MILITARY MEDICINE, 155(12):A4, 1990

"Book Review: Journey into Space", ASEM, 1991, 62(2):182.
"Book Review: Aviation Medicine", ASEM, 1991, 62(2):182.

Study Guide for Preventive Medicine Certification 1991, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1991.

"Chapter 24: Missile Medicine" in AFM 161-18, Flight Surgeon's Guide, RC Whitton, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Dec 1991.

"Chapter 25: Space Medicine" (Co-author) in AFM 161-18, Flight Surgeon's Guide, RC Whitton, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Dec 1991.

Study Guide for Preventive Medicine Certification 1992, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1992.

Study Guide for Preventive Medicine Certfication 1993,
(Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM
Health Information, Boston, MA, 1993.

Book Review: Space Medicine & Physiology, ASEM, 65(6):583, 1994.

Book Review: Chemical Exposures, ASEM, 65(6):584, 1994.

Study Guide for Preventive Medicine Certification 1994,
(Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM
Health Information, Boston, MA, 1994.

Book Review: Phantom Risk-Scientific Inference and the Law, ASEM, 65(7):677, 1994.

Repetitive Use Injury: Diagnosis, Treatment and Prevention, Kansas Medicine, 95(9):1193-4, 1994.

Book Review: Operation Crossroads, ASEM, 66(2):182, 1995.

Book Review: Textbook of Military Medicine-Occupational Health, ASEM, 66(2):182, 1995.

Medical Standards, AOPA Pilot, 38(2):24-25, 1995.

Study Guide for Preventive Medicine Certification 1995,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1995.

Book Review: The Preastronauts, ASEM, 66(11):1115, 1995.

Book Review: Dark Sun, the Making of the Hydrogen Bomb, ASEM, 67(2):188, 1996.

Book Review: Hunter's Occupational Medicine, 8th Edition, ASEM, 67(2):187, 1996.

Chapter 35: Aviation and the Environment. *In* **Fundamentals of Aerospace Medicine, 2nd Edition,** Edited by RL DeHart, Lea & Febiger, Philadelphia, 1996.

Study Guide for Preventive Medicine Certification 1996,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1996.

Hepatitis A: Diagnosis, Treatment and Prevention, Kansas Medicine, 97(1):14-5, 1996.

Book Review: Occupational Medicine in Aviation, ASEM, 67(7):665, 1996.

Fatigue and Flight, PLANE Safe, 1(3):3-5, 1996.

Book Review: Toxic Exposures, ASEM, 68(2):165 ,1997.

Book Review: Science, Nonscience and Nonsense, ASEM, 67(2):165 ,1997.

Book Review: Science, Nonscience and Nonsense, ASEM, 67(2):165-6,1997.

Study Guide for Preventive Medicine Certification 1997,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1997.

Book Review: Pilot Judgement and Resource Management, ASEM, 68(6);548, 1997

Book Review: Toxicology, ASEM, 68(6):548,1997.

Book Review: Why Buildings Fall Down, ASEM, 68(6):548, 1997.

Awaiting Publication:

Occupational Medicine and Physical Therapy: Statistics of Self Referral, In "New England Journal of Medicine".

Book Review: Dead Men Do Tell Tales, ASEM, 68(): ,1997.

Book Review: The Man Who Grew Two Breasts, ASEM, 68(): ,1997.

Book Review: Bad Blood, ASEM, 68(), 1997

Book Review: The Nazi Doctors, ASEM, 68(), 1997

Book Review: Issues in International Occupational and Environmental Medicine, ASEM, 68(), 1997

Abstracts and Presentations

"Unilateral Hearing Loss in USAF Aviators", Aerospace Medical Association 53rd Annual Scientific Meeting, Miami Beach, FL, May 1982

"Space Medicine, An Overview" (Keynote Address) Operational Aeromedical Problems Course, Brooks AFB January 1983

"Auditory Effects of Antiorthostic Simulation of Weightlessness", Asthma Annual Scientific Meeting, May 1984

"Segmental Hemodynamic Responses to Antiorthostatic Simulation of Weightlessness" (Co-author), Asthma Annual Scientific Meeting, May 1984

"Changes in Calf Volume due to Antiorthostatic Simulation of Weightlessness" (Co-author), Asthma Annual Scientific Meeting, May 1984

"Medical Support of Space Shuttle Operations at Vandenberg Launch Site", Operational Aeromedical Problems 1985, Brooks AFB, Jan 85 and Strategic Air Command Chiefs of Aerospace Medicine Conference, Offutt AFB, May 85.

"Human Factors in Military Space", AIAA Military Space Shuttle Operations Meeting (Secret) - May 28, 1986

"Medical Aspects of a Titan Missile Mishap" presented at Asthma Annual Scientfic Meeting, May 13, 1987

"Human Factors in Accident Investigation", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 2, 1988.

"Toxicological Effects of Propellants and Fuels in Aircraft Accidents", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 2, 1988.

"Aircraft Accident Search and Rescue Operations", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 3, 1988 and Aerospace Medicine Primary, Oct 24, 1988, March 15, 1989, August 17, 1989, April 11, 1990, August 31, 1990.

"Beryllium Rocket Fuels-a Physician's View", Joint Army-Navy-NASA-Air Force Safety & Environmental Protection Subcommittee Meeting (Secret), Naval Postgraduate School, Monterrey, CA, May 24, 1988.

"Comparing Air Force and Navy Aerospace Medicine", Association of Military Osteopathic Physicians and Surgeons 7th National Conference. San Diego, CA. March 30, 1989.

"Space Medicine - Where Do We Go From Here?" NASA Aerospace Safety Advisory Panel. Dallas, Texas, April 5, 1989.

"Leaving the Cradle", St. Louis Academy of Science and the St. Louis Science Foundation, St. Louis, Mo, July 20, 1989.

"Human Factors in Aircraft Accidents", 36th Annual Flying Physicians Association Scientific Meeting, Vancouver BC, Canada, August 6, 1990.

"What is Acceptable Risk (of Decompression Sickness)?", Hypobaric Decompression Sickness Workshop, Brooks AFB, October 18, 1990. Proceedings published 1994, by Aerospace Medical Association.

"Aeromedical Support of Combat Operations", Aerospace Medical Association 62nd Annual Scientific Meeting, Cincinnati, Ohio, May 9, 1991.

"Human Factors in Flight", Grand Round-University of Utah, Salt Lake City, UT, Nov. 9, 1991.

"USAF Aeromedical Problems During OPERATIONS DESERT SHIELD/STORM", Aerospace Medical Association 63rd Annual Scientific Meeting, Miami, FL, May 14, 1992.

"Flight Surgeon Self-Assessment Review", Panel Member,
Aerospace Medical Association 63rd Annual Scientific Meeting, Miami, FL, May 14, 1992.

"The Medical Provider's Role in Workers' Compensation", Workers' Compensation Seminar, Kansas City Professional Education Institute, Kansas City, MO, May 14, 1993.

"How to Manage New Industrial Illnesses: Carpal Tunnel Syndrome, Stress, Trauma and Other Maladies of the 90's", Workers' Comp Update 1993, Council on Education in Management, Walnut Creek, CA, Sept 15, 1993.

"Methods by Which Occupational and Environmental Medicine Puts Workers Back on the Job", Company Productivity and Return to Work Programs, Menninger Return to Work Center, Kansas City, MO, Oct 29, 1993.

"Role of the Medical Review Officer", Company Productivity and Return to Work Programs, Menninger Return to Work Center, Kansas City, MO, Oct 29, 1993 and Columbia, MO, March 6, 1994, Employee Assistance Program Center, Kansas City, MO, May 25, 1995.

"The Medical Provider's Role in Workers' Compensation" at KCPEI Workers' Compensation Seminar, Kansas City, Mo, May 14, 1994. and Menninger Return to Work Seminar, Columbia, MO, March 6, 1994.

"Aviation and Transportation Law: Drugs and Alcohol", Missouri Bar Association Annual Meeting, Kansas City, MO, Sept 22, 1994.

"Environmental Emergencies", Great Plains College of Occupational and Environmental Medicine, Kansas City, Mo, Sept 22, 1994.

"Toxicology", Carroll P. Hungate Postgraduate Seminar on Occupational and Environmental Health, Great Plains College of Occupational and Environmental Medicine, Overland Park, KS, March 11, 1995.

"Preparing for the Occupational Medicine Board Examination", lecture & seminar director, American Occupational Health Conference, Las Vegas, NV, May 1, 1995.

"Developing and Managing a Medical Surveillance Program", American Industrial Hygiene Conference, Kansas City, MO, May 20, 1995.

"Travel Medicine", Grand Rounds, Trinity Lutheran Hospital, Kansas City, MO, June 19, 1996; Medicine Grand Rounds, St. Luke's Hospital, Kansas City, MO, July 5, 1996.

"Crash Survival, Protection and Investigation", Physics and Biology Colloquium, Benedictine College, Atchison, KS, February 24, 1997.

"Occupational Health for Travelers", Carroll P. Hungate Postgraduate Seminar on Occupational and Environmental Health, Great Plains College of Occupational and Environmental Medicine, Overland Park, KS, March 8, 1997.

"Medical Aspects of Air Travel", with RB Rayman and DP Millett, Aerospace Medical Association Annual Scientific Meeting, Chicago IL, May 13. 1997.

"Cabin Air Quality", Aerospace Medical Association Annual Scientific Meeting, Chicago IL, May 13. 1997.

Lectures

"Physiology of Manned Space Flight" lectures delivered at USAF School of Aerospace Medicine to medical student classes, Jul and Aug 1982, June and July 1983, June and July 1984 and June and July 1985

"Rocket Fuels and Chemical Hazards" lecture delivered to Santa Barbara Co Paramedics, June 14, 1985, Oct 17, 1985, and February 21, 1986 and USAF Hospital Vandenberg Professional Staff - July 2,1985 and Lompoc Community Hospital Professional Staff, June 30,1986

"Acquired Immune Deficiency Syndrome" lecture delivered to USAF Hospital Vandenberg Professional Staff, Sept 30, 1985 and Dental Staff Oct 2, 1985

"Space Medicine - An Update" SAC Hospital Commanders' Conference, Offutt AFB, Oct 1985

"Medical Aspects of Manned Space Flight", University of Kansas, May 16, 1986 and to Health Profession Scholarship Students at USAFSAM, Brooks AFB, TX on 2 July and 21 July 1986, 22 June & 12 July 1987, 24 June & 27 July 89, 27 June & 26 July 1991 and to Advanced Aeromedical Course for Allied Medical Officers on 9 Feb 1987, 20 & 22 Jan 88, 19 & 20 Jan 89, 17 & 18 Jan 1990, 23 & 24 Jan 1991, 27 & 28 Jan 1992, 27 Jan 1993 and to Residents in Aerospace Medicine, 30 Nov 87 , 4 Feb 89, 2 April 90, 17 & 18 Dec 1990, 28 & 30 Aug 91, 27 Aug 93, 2 Aug 94 and to Aerospace Medicine Primary Course, 13 Nov 1987, 10 Apr 1988, 1 Sept 1988, 8 Nov 1989, 19 April 1990, 23 August 1990, 19 April 1991, 8 Nov 91, 7 April 92 and Grand Rounds, Geisinger Medical Center, Danville, PA on 7 Feb 1988 and Luzerne County Medical Society, Wilkes-Barre, PA on 8 Feb 1989 and Oregon Institute of Technology, Klamath Falls, OR on 27 March 1990 and Utah Surgical Society, Salt

Lake City, UT, 5 Nov 1991.

"Hazardous Materials and the Space Shuttle Program", 4th Annual Pre-Hospital Care Conference, Santa Barbara, CA, June 23, 1986.

"Missile Medicine", Aerospace Medicine Primary Course, Brooks AFB, TX, July 22, 1986, Oct 18, 1986, Feb 8, 1987, Aug 21, 1987, Oct 5, 1987, March 17, 1988, July 27, 1988, Oct 13, 1988, March 20, 1989, Aug 1, 1989, Feb 14, 1990, August 1, 1990, March 21, 1991, Aug 15, 1991, Oct 15, 1991 and March 12, 92.

"Sexually Transmitted Diseases and Military Preventive Medicine", to Aerospace Medicine Primary Course, Brooks AFB, 6 Aug 1987, Oct 15, 1987, March 11, 1988, 5 Aug, 1988, Oct 11, 1988, March 20, 1989, July 27, 1989, Oct 6, 1989, Feb 15, 1990, August 2, 1990, Oct 4, 1990, March 13, 1991, August 16, 1991, Oct 4, 1991 and March 27, 1992.

"Role of the Flight Surgeon" (lecture) presented to AMP, Brooks AFB, Oct 2, 1987, March 7, 1988, 25 July 88, 4 Oct 88, 4 Mar 89, 24 Jul 89, 3 Oct 89, 12 Feb 90, 30 July 90, 2 Oct 90, 11 Mar 91, 28 Jul 91, 3 Oct 91, 9 Mar 92; Bioenvironmental Engineering Course, 2 Feb 89, 22 Aug 89, 26 Jan 90, 22 August 90, 1 Feb 91, 21 Aug 91, 7 Feb 92; Environmental Health Officer's Course, 5 July 89, 3 Oct 89, 26 Jan 90; Health Professions Scholarship Program, 5 June & 3 July 90, 4 June & 1 July 91.

"Introduction to Toxicology" (lecture) presented to Aerospace Medicine Primary Course, Brooks Air Force Base, Oct 6, 1987, March 10, 1988, 2 Aug 88, 26 Jul 89, 16 Feb 90, 2 Aug 90, 10 Oct 90, 15 Mar 91, 20 Aug 91, 8 Oct 91, 31 Mar 92, 1 Nov 93, 16 Mar 94, 16 Aug 94, 28 Oct 94, 18 Mar 95, 16 Aug 95, 20 Oct 95, 14 Aug 96, 16 Oct 96, 2 Apr 97.

"Fuels and Propellants" (lecture) presented to AMP, Brooks AFB, Oct 5, 1987, March 17, 1988, 28 July 88, 13 Oct 88, March 20, 1989, Aug 1, 1989, Feb 16, 1990, August 2, 1990, Oct 10, 1990, March 21, 1991, August 20, 1991, Oct 8, 1991, March 12, 1992, November 1, 1993, March 16, 1994, Aug 16, 1994, Oct 28, 1994, March 18, 1995, August 14, 1995, Oct 20, 1995, Aug 14, 1996, Oct 16, 1996, April 2, 1997 and Wright State University on Nov 18, 1988, University of Texas School of Public Health at Houston on April 10, 1989 and April 16, 1990, AAMIMO on April 18, 1988, Jan 19, 1989 Jan 18, 1990 and April 1, 1991 and RAM on Sept 14, 1989.

"Human Factors in Aircraft Accident Prevention", Aerospace Medicine Supervisor Course 1988, Brooks AFB, May 27, 1988 and Aerospace Medicine Primary Course, 10 Aug 88, 19 Oct 88, March 27, 1989, August 7, 1989, Oct 18, 1989, April 4, 1990, August 10, 1990, Oct 16, 1990, April 3, 1991, August 1, 1991, Oct 17, 1991, March 13, 1992 and Embry Riddle University Extension, Randolph AFB Human Factors

Course, Oct 11, 1989, August 22, 1990 and Aerospace Physiologists Course, 18 July 1989.

"Flight Surgeon Operations" (lecture), Battlefield Medical Operations Course, Brooks AFB, July 12, 1989 and Aerospace Physiologists course, July 18, 1989.

"Adjuncts to Airway and Ventillation" (lecture), Advanced Cardiac Life Support Course, Brooks AFB, July 19, 1989.

"Industrial Operations" (lecture) Environmental Health Officers Course, July 5, 1989; Aerospace Medicine Primary Course July 26, 1989, Oct 5, 1989, Feb 14, 1990, August 3, 1990, Oct 10, 1990, March 15, 1991, August 20, 1991, Oct 8, 1991, March 31, 1992 and Flight Surgeon Course, Defense and Civil Institute of Environmental Medicine, Toronto, Ontario, Nov 6, 1989.

"Medical Terminology" (lecture) Bioenvironmental Engineers Course, August 23, 1989.

"Human Physiology for Engineers" (8 hours of lecture) Bioenvironmental Engineers Course, August 24 & 25, 1989, Jan 26 & 27, 1990, August 23 & 24, 1990, Feb 4 & 5, 1991, August 22 & 23, 1991.

"Medical Readiness and Disaster Response" (lecture) Environmental Health Officers Course, Sept 14, 1989.

"Mishap Investigation" (lecture), Advanced Medical Standards Course, Sept 19, 1989.

"Crash Survival" (lecture), AMP Course, Oct 18, 1989, April 4, August 10, 1990, April 5, 1991, August 1, 1991, October 17, 1991, March 13, 1992.

"Myocardial Infarction" (lecture), Advanced Cardiac Life Support Course, Brooks AFB, Jan 17, 1990.

"Senior Flight Surgeon Examination Review Seminar", Operational Aeromedical Problems Course, Brooks AFB, Jan 24, 1990.

"Disaster Management Seminar", Operational Aeromedical Problems Course, Jan 25, 1990.

"Aeromedical Problems of Tactical Air Operations", Health Professions Scholarship Program, June 6 & July 5, 1990, June 5 & July 3, 1991.

"Aeromedical Problems of Strategic and Airlift Operations", Health Professions

Scholarship Program, June 7 & July 5, 1990, June 5 & July 3, 1991.

"Aeromedical Problems of Training Programs and Reconaissance Operations", Health Professions Scholarship Program, June 8 & July 6, 1990, June 6 & July 24, 1991.

"Monitoring and Dysrhythmias" Advanced Cardiac Life Support Course, Brooks AFB, July 9, 1990.

"Preparing for the Senior Flight Surgeons' Exam", Association of Military Surgeons of the United States 97th Annual Meeting, Nashville, Tennessee, November 15, 1990.

"Impact Acceleration", Aerospace Physiologist Course, Brooks AFB, July 9, 1991, University of Kansas Department of Preventive Medicine Grand Rounds, Feb. 20, 1992.

"Disaster Planning, Management and Medical Response", Lancaster County Civil Defense/Airshow Planning, Lincoln, Nebraska, August 27, 1991.

"Aeromedical Medicine", Grand Round at University of Utah School of Medicine, Salt Lake City Utah, Nov. 6, 1991.

"Human Factors in Air Force Helicopter Mishaps", 1st Coast Guard Aeromedical Problems Course, CGS Mobile, Alabama, Feb 28, 1992.

"Space Shuttle Contingency Operations", 1st Coast Guard Aeromedical Problems Course, CGS Mobile, Alabama, Feb 28, 1992.

"History of Aerospace Medicine", Residency in Aerospace Medicine, Brooks AFB, TX, July 1, 1992 and Advanced Aerospace Medicine for International Medical Officers, Brooks AFB, TX, Jan 26, 1993.

"Occupational Arthritis and Rheumatologic Problems", The Rheumatology Center, Kansas City, MO, Jan 16, 1993.

"AIDS and Buisness: Impact on the Workplace" St. Luke's Outreach, Kansas City, MO, May 12 & July 29, 1993.

"Basic Statistics", OB-GYN Grand Rounds, St. Luke's Hospital, Kansas City, MO, Sept 24, 1993.

"Drugs and Alcohol", Aviation Medical Seminar/Federal Aviation Administration, Chicago, IL, June 25, 1994, May 11, 1995, Memphis, TN, Aug 27, 1995.

"Aviation Toxicology", Aviation Medical Seminar/Federal Aviation Administration,

Chicago, IL, June 26, 1994, Anaheim, CA, May 12, 1995, Memphis, TN, Aug 27, 1995.

"Transport by Air of the Ill and Injured", Chicago, IL, June 26, 1994, Anaheim, CA, May 12, 1995, Memphis, TN, Aug 27, 1995.

"Aviation Physiology", Basic Aviation Medical Examiners Seminar, Civil Aeromedical Institute, Mike Monroney Aeronautical Center, Oklahoma City, OK, Nov 14, 1994, April 4, 1995, Sept 16, 1996, June 2, 1997.

"Biomedical Factors in Accident Prevention: Part I-Altitude Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 4, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part II-Acceleration Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 4, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part III-Perception in Flight", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 5, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part IV-Environmental Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 9, 1997, April 9, 1997.

"Biomedical Factors in Accident Prevention: Part V-Self-Imposed Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 9, 1997, April 9, 1997.

"Biomedical Factors in Accident Prevention: Part VI-Drugs, Alcohol and Health Issues", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 8, 1997, April 9, 1997.

"Human Factors-Theme and Objectives" Aviation Medical Seminar/Federal Aviation Administration: Tampa, FL, Dec 2, 1995; Denver CO, Mar 8, 1996; Minneapolis, MN, Aug 3, 1996; Dallas, TX, Oct 18, 1996 Washington, DC, Apr 4, 1997.

"Human Performance" Aviation Medical Seminar/Federal Aviation Administration: Tampa, FL, Dec 3, 1995; Denver, CO, Mar 9, 1996; Minneapolis, MN, Aug 4, 1996: Dallas, TX, Oct 18, 1996, Washington, DC, Apr 5, 1997.

"Crashworthiness/Survival" Aviation Medical Seminar/
Federal Aviation Administration: Tampa, FL, Dec 3, 1995; Denver, CO, Mar 9, 1996; Minneapolis, MN, Aug 4, 1996: Dallas, TX, Oct 18, 1996, Washington, DC, Apr 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part I-Altitude Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part II-Acceleration Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part III-Perception in Flight", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part IV-Environmental Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part V-Self-Imposed Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part VI-Drugs, Alcohol and Health Issues", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part VII-Medical Forsenics and the Crash Scene-Hazards seen and unseen.", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

# Attachment 6

| MIDWEST RESEARCH INSTITUTE<br>STANDARD OPERATING PROCEDURE | Effective Date:<br><br>Page 1 of 4 | Code: MRI-4863<br>SOP # 2<br>Revision: 0 |
|---|---|---|
| LIFE SCIENCES DEPARTMENT<br><br>SUBJECT: Identification and Reporting of Adverse Events (Specific to Project 4863) | Approved:<br><br>Department Director ____ Date<br><br>Section Manager ____ Date | |
| | Released by QAU:<br><br>Manager, Quality Assurance ____ Date | |

1. **INTRODUCTION**

1.1 This document contains operating procedures for the identification and reporting of adverse events that might occur during the performance of Project 4863.

2. **SCOPE**

2.1 The procedures herein provide specific definitions of adverse events, and for the procedures to be used to document and report such events.

3. **RESPONSIBILITY**

3.1 The Section Manager is responsible for the content of this SOP and will assure that the work is performed by qualified staff.

3.2 The Principal Investigator will ensure that designated staff performing this work have appropriate training and/or experience, and are familiar with this SOP.

3.3 Staff members performing the work described in this SOP are responsible for reading, understanding and complying with the requirements of this SOP.

4. **DEFINITIONS**

4.1 An ***adverse event*** is any illness or injury that occurs while a volunteer subject is participating in a study, whether or not it is considered to be related to the drug or device under study. This definition includes intercurrent illnesses and injuries, and exacerbations of preexisting conditions.

4.2. A ***serious adverse event*** is any experience that suggests a significant hazard, contraindication, side effect or precaution. Any experience that is fatal or life threatening, is permanently disabling, or requires inpatient hospitalization, is a serious adverse event.

4.3 An ***unexpected adverse event*** is any adverse experience that is not identified in nature, severity or frequency in the current description of the drug under test in the Physicians's Desk Reference or in the Investigator's Brochure.

## 5. REPORTING OF ADVERSE EVENTS

Any observation/experience on the part of the subject or of the experimenters who are dealing with the subject that results in referral of the subject to the medical monitor will be considered an adverse event. Such triggers include oral temperature of 99.6°F or more; pulse rate more than 20% below baseline value or below 50 bpm; diastolic blood pressure based on disappearance of Korotkov sounds outside the range 50-90 mm/Hg; or any of the pre-specified trigger pattern of responses to the General Response Questionnaire. When an adverse event has been identified, complete the form shown in Attachment 1, Report of Adverse Event. The original of the form is sent to the Principal Investigator for inclusion in the confidential project files, and to the medical monitor for inclusion in the medical files for the subject.

## 6. REPORTING OF SERIOUS AND UNEXPECTED ADVERSE EVENTS

Serious and unexpected adverse experiences must be reported immediately by telephone to the USAMRC Deputy Chief of Staff for Regulatory Compliance and Quality. The Prinicipal or Co-Principal Investigator will, if available, make this call. If neither is available, the most senior project staff member should do so. During work hours, call 301-619-2165. If the serious unexpected adverse event occurs outside regular working hours, it is necessary to also send a facsimile of the adverse event to 301-619-7803. A copy of the Report of Adverse Event form is to be mailed within three working days of the occurrence of the adverse event. The written report is sent to: US Army Medical Research and Materiel Command, ATTN:MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012. The written report should include a description from the medical monitor of the medical steps taken and the current status of the patient.

# REPORT OF ADVERSE EVENT

Contract: DAMD-17-97-C-7070 MRI No. 4863

Test Article: Pyridostigmine Bromide 30 or 60 mg every 8 hours.

Principal Investigator: Mary R. Cook, Ph. D.
Midwest Research Institute
425 Volker Boulevard
Kansas City MO., 64110
816-753-7600, ext. 1162

Co-Principal Investigator: Antonio Sastre, Ph. D.
Same Address, ext. 1157

Medical Monitor: Mary C. Brothers, M. D.
Midwest Occupational Medicine
3037 Main, Suite 201
Kansas City, MO., 64108
816-561-3480

Subject Identification Number:____ Subject Initials: ____ DoB_____ Gender _____

Ethnicity: _____ Date dosing began: _____ Date dosing ended:_____

Date of symptom onset: _____ Date of resolution:_____

Experimenter who made referral: _____

Description of signs/symptoms:

Action taken:

Relationship to study drug:

Concomitant medications, if any (dose, route and duration of treatment, date of last dose)

_____ _____

P.I. or Co-P.I. Signature Date

## 7. REVISIONS/REVIEW HISTORY

7.1 Initial Issue, Effective (Date): Revision 0

4863

MIDWEST RESEARCH INSTITUTE
425 Volker Boulevard
Kansas City, Missouri 64110
Telephone (816) 753-7600
Telefax (816) 753-8420

June 29, 1998

Ronald E. Clawson, Ph.D.
USAMMDA
Attn: MCMR-UMP
622 Neiman Street
Fort Detrick, MD 21702-5009

Dear Dr. Clawson:

Enclosed is a copy of Amendment No. 1 for the protocol for our study, "Individual Differences in Neurobehavioral Effects of Pyridostigmine". I am also furnishing copies to Dr. Steele, the chair of MRI's IRB, the project physician and the medical monitor. A copy of this letter will also be sent to Ms. Mohler. Please call me if you have any comments or questions.

Sincerely,

Mary Cook

Mary R. Cook, Ph. D.
Principal Investigator

cc: Dr. Steele
Ms. Mohler
Dr. Sastre
Dr. Parmet
Dr. Brothers

# Midwest Research Institute
# Biobehavioral Sciences Section
# Protocol Amendment Number 1

| | |
|---|---|
| Title | Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 1 |
| Authors | Mary R. Cook, Ph.D. and Antonio Sastre, Ph.D. |
| MRI Project No. | 4863 |
| Study Director | Mary R. Cook, Ph.D. |
| Testing Facility Name | Midwest Research Institute<br>425 Volker Boulevard<br>Kansas City, Missouri 64110 |
| Sponsor Name | U.S. Army Medical Acquisition Agency |
| Project Physician | Allen J. Parmet, M.D. |
| Date of Amendment | June 29, 1998 |

**Approvals:**

Richard D Brown for — June 29, 1998

Bert W. Maidment, Ph.D.
Director, Life Sciences Department — Date

Eugene G Podrebarac — June 29, 1998

Eugene G. Podrebarac, Ph.D.
Manager, Quality Assurance — Date

Mary R Cook — June 29, 1998

Mary R. Cook, Ph.D.
Study Director — Date

Dr. Ronald E. Clawson
Contracting Officer's Representative
USA MMDA — Date

## Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 1

1. Change proposed experimental start date to July 1, 1998, and proposed experimental termination date to September 15, 1999. (page 1 of 11)

   Rationale: Delays due to preparation for conducting the study under Good Clinical Practice and in developing the assay for pyridostigmine and its major metabolite have postponed the start date.

2. Change "sarin" to "soman" (page 2 of 11)

   Rationale: At request of FDA reviewer

3. Change Section 3.1, last sentence (page 4 of 11), to read "Subjects will be paid $50.00 for training, $225 for each phase of the study, and will receive a completion bonus of $100 after completion of the final physical examination."

   Rationale: Payment for training was inadvertently omitted from the text.

4. Change Section 4.1, line 5, to read "Each dose will be packaged in a blister pack and labeled with the subjects identification number, phase (week 1, week 2), and dose number within the phase." (page 6 of 11)

   Rationale: This change will make it easier for the personnel who administer the doses to assure that no doses have been missed.

5. Change Section 4.2, lines 1 and 2 to read, "Prepared doses of pyridostigmine and placebo will be kept refrigerated in a locked laboratory." (page 7 of 11)

   Rationale: To protect the double-blind nature of the experiment, both pyridostigmine and placebo must be cold when checked out of the repository by project staff. If some doses are cold and some are not, it would indicate to the staff member that the doses that are not cold are placebo.

6. Section 4.3.1 (page 7 of 11), change the second sentence to read "The Principal (M. Cook) or co-principal (A. Sastre) investigator or the project co-ordinator (M. Gerkovich) will again explain the purpose and procedures...."

   Rationale: To provide for occasions when both Dr. Cook and Dr. Sastre are unavailable.

7. Change Section 4.3.2, sentence 3 to read, "PYR or PL will be administered by MRI staff at approximately 0800, 1600, and 2400 hours; administration will be within 20 minutes of the scheduled administration time for the subject." (page 7 of 11)

Rationale: Because of class schedules and other commitments, a subject's morning dose can be scheduled for any time from 7:30 to 8:30. The other doses are scheduled at 8 hour intervals, starting with the morning dose. Since subjects are sometimes delayed or must rearrange a schedule because of an unexpected event, a range of 20 minutes before and after a scheduled dose time will be considered to be within the protocol.

8. Add section 4.3.3., page 7 of 11 to read:

   4.3.3 Randomization

   The Principal Investigator will use random numbers to assign subject numbers to (1) order of pyridostigmine versus placebo, (2) dose level, and (3) order of testing battery A and battery B. This randomization will be checked by a senior staff member. Since the Principal Investigator needs to be blind to conditions, the initial randomization will be given to the scientist in charge of packaging the doses. She will rotate the randomization to assure that the PI is unaware of the dose order or dose level for any given subject.

   Rationale: Additional information requested by FDA reviewer.

9. Add text to Section 4.4 to provide an overall description of a volunteer's participation.

   Subjects come to the laboratory first for an informed consent session during which the methods, procedures, benefits and risks are explained and the subject provides informed consent. After a physical examination indicates that the subject is appropriate for study participation, he or she comes to the laboratory for four separate training sessions over a one-week period. In the first dosing week, the subject comes to the lab for dosing every 8 hours, beginning Monday morning and ending after the Friday morning dose. On Monday, Thursday and Friday, subjects come to the laboratory at about 3 ½ hours after the morning dose to give blood samples, and participate in performance and physiological test batteries. On Thursday and Friday, a urine sample is also collected. On the Monday after the last dose of the sequence, the subject comes to the laboratory for a blood sample, and is reimbursed for the first phase of participation. The subject is released for a week, and then starts the sequence all over again for the second dosing week. After the second dosing week, the subject participates in an exit physical examination, and then returns to the laboratory for final reimbursement.

   Rationale: Additional information requested by FDA reviewer

10. Delete Section 4.4.3 (page 8 of 11) and replace with, "Blood samples will be obtained by venipuncture before the performance batteries on days 1, 4, and 5, and again on

day 8, of each phase. Urine samples will be obtained before the blood draws on days 4 and 5. Approximately one ounce of blood will be required at each collection."

Rationale: Clarification of original text.

11. Section 4.4.4 (page 9 of 11) Change the last sentence of the first paragraph to read "On Day 1 of each phase, the subjects will be tested on the battery that is administered on Day 5."

    Rationale: Correction of a typographical error.

12. Section 4.4.4 (page 9 of 11), Battery B: delete Finger Tapping Task from text (lines 4 and 5).

    Rationale: This task was left in the text in error. The Finger Tapping Task was deleted because the function to be tested is assessed by other tasks in the battery.

13. Section 4.4.4 table on page 9 of 11: Delete the continuous performance task from the battery.

    Rationale: Including a continuous performance task long enough to be valid increased battery time so much that testing could no longer occur during the targeted time period after the most recent dose of pyridostigmine or placebo.

14. Section 6.1 page 11 of 11, change the second sentence to read, " MRI's Multiple Projects Assurance (effective July 1, 1982, and now approved through March 31, 2001, sets out Institutional Review Board.

    Rationale: Clarify text

15. Attachment 2: Replace the consent form with a revised version that includes information on the collection of lymphocytes, as well as a release form to be signed by the volunteer. The revised consent form and release form have been reviewed and approved by the Midwest Research Institute Institutional Review Board for Human Subjects, and sent to the Contracting Officer's Representative and the Surgeon General's IRB on June 9, 1998.

    Rationale: Collection of lymphocytes was not included in the previous version of the consent form. Lymphocytes were added to the project by contract amendment.

16. Attachment 6: Replace the form to be used for documentation of adverse events with a new form provided by the Contracting Officer's Representative.

    Rationale: Make procedures comply with most recent regulatory guidelines.

Sbjid:_____
Call#_____

MIDWEST RESEARCH INSTITUTE
VOLUNTEERS' INFORMED CONSENT

Study #1
Project # 4863
Revision date: 05/21/98
Revision 3.0

Individual Differences in Neurobehavioral Effects of Pyridostigmine: Study 1

I,_____residing at

_____

_____

hereby acknowledge and certify to the following:

1. I hereby volunteer and consent to be a subject in a research study sponsored by the U. S. Army Medical Research and Materiel Command (USAMRMC) and conducted at Midwest Research Institute by Drs. Mary R. Cook and Antonio Sastre. I understand this study will evaluate the short-term effects of pyridostigmine bromide on physiology and performance in normal, healthy young men and women. Pyridostigmine has a long history of use in the medical treatment of a condition called myasthenia gravis. It has been alleged that pyridostigmine bromide is associated with Persian Gulf War veterans' illnesses. Pyridostigmine is important to the Army because it has properties that enable it to protect people in the event of a chemical warfare attack. The Food and Drug Administration, however, has not approved pyridostigmine for use in healthy people and I understand its use is investigational in this research study. The most frequent side effects of pyridostigmine are upset stomach, cramps, gas, diarrhea, and excessive salivation. Pyridostigmine should be avoided when a woman is pregnant. I am also aware that in a previous study at MRI, only a few of the 25 healthy, young men who took pyridostigmine reported any symptoms, and these consisted of mild stomach upset, gas and feelings of tiredness. I also understand that this is a double-blind study. This means that during any given phase of the experiment, pyridostigmine may actually be in the pills I take, or it may not. The investigators will not know, and I will not know, which pill is which. In this way, any effects due to pyridostigmine can be separated from those that might be due to a person's expectations about taking pyridostigmine.

I understand I will receive free a complete medical examination at the start of the study. This evaluation will include medical history, drug screen, urinalysis, electrocardiogram, blood chemistry, complete blood count, lung function test, and medical examination. For women, the examination will include a pregnancy test. The physician will tell me about any problems he/she finds during the evaluation, and advise me about follow-up. I will then come to MRI to be trained to perform tests that measure my memory, attention, perception, and sensory abilities. During training, sensors will be attached to my head and wrist to measure my brain waves, pulse and blood pressure. I understand that sensor attachment is painless and presents no risk to my health. Training will require about 10 hours of my time spaced over a week.

I will then be randomly assigned to one of two groups. One group takes 60 mg pyridostigmine, every 8 hours (180 mg/day) and one takes 30 mg every 8 hours (90 mg/day); both groups take placebo. These doses of pyridostigmine are less than the doses typically used by medical patients (120 mg 6 times/day; 720 mg/day). The study will be performed in two phases, separated by six days off. Each Phase will last eight days, and each will involve the same sequence of activities. I understand I will be asked to come to MRI to take pills every eight hours for the first four days of each phase, followed by one additional pill on the fifth day. I will have my blood pressure, pulse, and temperature recorded. I will complete a food diary and a questionnaire about any symptoms I may be experiencing. Blood samples (about 1 ounce) will be collected via venipuncture from a vein in my arm on days 1, 4, 5 and 8. White blood cells from some of these samples will be sent to another laboratory for special analysis, and I understand that, for this reason, I will be asked to sign a donation form. On days 4 and 5, I will provide urine samples and perform the tests I learned earlier. I will keep a diary of what I eat and drink for the first 4 days of each Phase. MRI will provide breakfast and lunch for me on certain days. At the end of Phase 2, I will visit the project physician again for a brief follow-up medical examination. Three, six and 12 months after I finish the study, I will be contacted by MRI staff to determine whether I have experienced any effects that I think might be due to my participation in this study. If so, they will arrange for further medical evaluation.

I agree to not use drugs or alcohol during the study and to inform the investigators of any medications I may need to take. I understand that standard medical procedures will be followed when drawing blood, but that bruising or soreness can sometimes occur. I further understand that this is a basic research study, and that I will not benefit from being in it, except that I will receive a full medical examination at no charge, and I will be reimbursed for the time and effort required for participation. If I complete all study requirements, I will receive a total of $600 ($50 for training, $225 for each phase, and $100 completion bonus); if not, I will be paid $25.00 per day of actual participation.

2. I have been given, in my opinion, an adequate explanation of the nature, duration, and purpose of the study, the means by which the study will be conducted, and any possible inconvenience, hazards, discomfort, risks, and adverse effects on my health which could result from my participation.

3. I understand my questions concerning procedures which affect me will be answered fully and promptly by either Dr. Mary R. Cook, Principal Investigator, Dr. Antonio Sastre, Co-Principal Investigator, or by Dr. Eugene Podrebarac, Chairman of the MRI Institutional Review Board for Human Studies, which reviewed and approved this study (816/753-7600). The address of the Institute is 425 Volker Boulevard, Kansas City, MO.

4. I understand that I have the right to withdraw my consent and to discontinue participation in this experiment at any time without prejudice regardless of the status of the experiment and regardless of the effect of such withdrawal on the objectives and results of the experiment; and I also understand that my participation in the experiment may be terminated at any time by the investigator in charge of the project.

5. I agree that any information obtained from me, by MRI, or its authorized representatives, in connection with this study may be utilized by MRI in publications and reports without identifying me. Because the use of pyridostigmine is investigational for this study, I am also aware that representatives of the Food and Drug Administration and/or the U.S. Army Medical Research and Materiel Command may

wish to review the records of my participation and perhaps contact me to ask specific questions about my experiences. I understand that MRI agrees with this policy of openness in this type of study, and that it will provide personally identifying information about me to allow these agencies to contact me if they so wish. I understand this information will be limited to the following: my name, address, social security number, the name of this study, and the dates of my participation in it. This information will be maintained by the USAMRMC in its confidential Volunteer Registry Data Base. The intent of this procedure is two fold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

6. If I experience any symptoms I feel should be reviewed with a physician, I can call the medical monitor, who will schedule an appointment with me as soon as possible. The United States Department of Defense is funding this research project. Should I be injured as a direct result of participating in this research project, I will be provided medical care, at no cost to me, for that injury. I will not receive any injury compensation, only medical care. I understand that this is not a waiver or release of my legal rights. I further understand that I should discuss this issue thoroughly with the Principal Investigator before enrolling in this study. Other than the medical care that may be provided (and the other benefits stated above in section # 1 of this consent form), there is no other compensation available for my participation in this research study.

7. I will be given a copy of this consent form to keep.

My age is ____; The date of my birth is_____

I am executing this Volunteer's Consent as my free act and deed.

Today's date is _____, 19_____

Executed in the presence of each other

_____ _____ Date:_____

Signature of Volunteer Initials

_____Date:_____

Signature of Investigator

MIDWEST RESEARCH INSTITUTE
SAMPLE DONATION FORM

**Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 1**

I, _____residing at

_____

voluntarily and freely donate blood samples to the study sponsor, the U. S. Army Medical Research and Materiel Command, and hereby relinquish all right, title, and interest to said items. The samples donated will not contain any information that identifies me personally.

_____ Date:_____
Signature of Volunteer

_____ Date:_____
Signature of Experimenter

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #

UF/Dist report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

| 1. Patient identifier<br>In confidence | 2. Age at time of event:<br>or<br>Date of birth: | 3. Sex<br>☐ female<br>☐ male | 4. Weight<br>____ lbs<br>or<br>____ kgs |
|---|---|---|---|

**A. Suspect Medical Device**

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____

| 3. Date of event (mo/day/yr) | 4. Date of this report (mo/day/yr) |
|---|---|
| | |

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2

| 2. Dose, frequency & route used | 3. Therapy dates (if unknown, give duration) from/to (or best estimate) |
|---|---|
| #1 | #1 |
| #2 | #2 |

| 4. Diagnosis for use (indication) | 5. Event abated after use stopped or dose reduced |
|---|---|
| #1 | #1 ☐ yes ☐ no ☐ doesn't apply |
| #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

| 6. Lot # (if known) | 7. Exp. date (if known) | 8. Event reappeared after reintroduction |
|---|---|---|
| #1 | #1 | #1 ☐ yes ☐ no ☐ doesn't apply |
| #2 | #2 | #2 ☐ yes ☐ no ☐ doesn't apply |

9. NDC # – for product problems only (if known)
   – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

**B. Suspect Medical Device**

1. Brand name

2. Type of device

| 3. Manufacturer name & address | 4. Operator of device<br>☐ health professional<br>☐ lay user/patient<br>☐ other: ____ |
|---|---|
| | 5. Expiration date (mo/day/yr) |
| 6.<br>model # ____<br>catalog # ____<br>serial # ____<br>lot # ____<br>other # | 7. If implanted, give date (mo/day/yr)<br>8. If explanted, give date (mo/day/yr) |

9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

**C. Suspect Medical Device**

| 1. Name, address & phone # | phone # |
|---|---|
| | |

| 2. Health professional? | 3. Occupation | 4. Initial reporter also sent report to FDA |
|---|---|---|
| ☐ yes ☐ no | | ☐ yes ☐ no ☐ unk |

FDA

FDA Form 3500A (1/96)

**Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.**

MIDWEST RESEARCH INSTITUTE
425 Volker Boulevard
Kansas City, Missouri 64110
Telephone (816) 753-7600
Telefax (816) 753-7380

FACSIMILE TRANSMISSION REQUEST

DATE: June 29 1998

TO: Ron Dawson

FROM: Mary Cook

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# Midwest Research Institute
# Biobehavioral Sciences Section
# Protocol Approval

| | |
|---|---|
| Title | Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 2 (revised) |
| Author | Mary R. Cook, Ph.D. and Antonio Sastre, Ph.D. |
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| Study Director | Mary R. Cook, Ph.D. |
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| Project Physician | Allen J. Parmet, M.D. |
| Proposed Experimental Start Date | April 1, 2000 |
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**Approvals:**

Richard D. Brown — 3/23/00
Richard D. Brown — Date
Director, Life Sciences Division

Eugene G. Podrebarac — 3/23/00
Eugene G. Podrebarac, Ph.D. — Date
Manager, Quality Assurance and
Chair, Institutional Review Board

Mary R. Cook — March 29th, 2000
Mary R. Cook, Ph.D. — Date
Study Director

# Preface

This revised protocol and its attachments, including a statement of informed consent and materials to be used for volunteer recruitment, are submitted to The Surgeon General of the Army's Human Subjects Research Review Board. Midwest Research Institute (MRI) will provide the sponsor with copies of the protocol, any subsequent protocol amendments, and access to study documents for purposes of study monitoring. MRI will exert its best efforts to conduct the study according to this protocol except when changes are mutually agreed to in writing, and will comply with the requirements of the appropriate Institutional Review Boards.

MIDWEST RESEARCH INSTITUTE

Mary R. Cook, Ph.D.
Principal Investigator

for Antonio Sastre, Ph.D.
Co-Principal Investigator

Approved:

Richard D. Brown
Director, Life Sciences Division

# Contents


Preface ..... ii
Tables ..... iv
Attachments ..... iv
Synopsis ..... v

1. Background ..... 1

2. Study Objectives ..... 3

3. Materials and Methods ..... 4
   - 3.1 Study Design ..... 4
   - 3.2 Study Population ..... 4

4. Study Plan ..... 6
   - 4.1 Investigational Material ..... 6
   - 4.2 Material Tracking ..... 6
   - 4.3 Procedures ..... 7
   - 4.4 Data Collection ..... 7
   - 4.5 Data Management ..... 12
   - 4.6 Statistical Analysis ..... 12

5. Study Management ..... 12
   - 5.1 12
   - 5.2 Medical Monitoring ..... 13
   - 5.3 Follow-Up ..... 14
   - 5.4 Adverse Event Report ..... 14
   - 5.5 Criteria for Volunteer Withdrawal ..... 14

6. Ethics ..... 14
   - 6.1 Institutional Review Boards ..... 14
   - 6.2 Protocol Amendments ..... 15
   - 6.3 Study Monitoring ..... 15

7. References ..... 15

# Tables

Table 1. Accuracy and Precision of Analysis for THMP and pyridostigmine in Plasma.....10
Table 2. Test Battery.....11

# Attachments

Attachment 1–Sample Study Announcement
Attachment 2–Statement of Informed Consent
Attachment 3–Investigator's Brochure
Attachment 4–Symptom Check List
Attachment 5–Resume, Project Physician
Attachment 6–Resume, Medical Monitor
Attachment 7–Adverse Event Report Form

# Individual Differences in Neurobehavioral Effects of Pyridostigmine
# Protocol for Study 2

## Synopsis

Previous studies of the effects of pyridostigmine bromide (PB) on healthy volunteers have provided valuable information, but many questions remain. Of particular interest are the contribution of PB, if any, to Gulf War Veteran's illnesses, and the military relevance of individual differences in the reported symptoms and inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) induced by PB. MRI has recently completed the first of two double-blind studies designed to test the following specific hypotheses: (a) under well-controlled conditions, the amount of AChE and/or BuChE inhibition observed will be related to alterations in the performance of complex tasks, heart rate variability, and peripherally mediated measures of physiological and sensorimotor functions; (b) individual differences can be differentiated from pharmacokinetic variability by use of a dose-response design; and (c) under heat stress, PB will produce more centrally-mediated effects than it does without heat stress. Endpoints in the completed study included plasma and urinary PB, 3-hydroxy-N-methylpyridinium bromide (THMP), the major metabolite of PB, AChE, and BuChE. Manuscripts describing this study are now being prepared for submission to peer-reviewed journals. Section 1 (Background) describes the major findings.

The protocol described here is for Study 2, which is relevant to hypotheses (a) and (c). Study 2 uses a randomized, double-blind, cross-over design. Approximately 12 men and 12 women will be randomly assigned to two test-order groups, with approximately equal numbers of men and women in each group. Each volunteer will take 13, 30-mg doses of PB at 8-hour intervals. Each volunteer will also take 13 doses of placebo (PL). One group will be administered PB during the first testing week and placebo during the second testing week. The dosing regimen will be reversed for other group (i.e., order of administration of PB and PL will be counterbalanced). The effects of PB vs PL will be evaluated on days 4 and 5 of each test week. On one test day in each week, the volunteers will be evaluated in a hot environment; on the other test day, they will be evaluated at normal room temperature. Testing will take about one hour, and will be counterbalanced so that half the volunteers in each gender group will be tested first in the heat, and half will be tested first at ambient temperature. The test battery to be administered includes physiological, motor, and cognitive measures. Tasks were included in the battery if they showed PB effects in our recently-completed study performed under this contract, or if they showed promise of clarifying unresolved questions raised by the first study or recent literature. Blood samples will be obtained prior to the first dose of PB or PL, on each test day, and on the Monday following each of the two dosing weeks to quantitate AChE, BuChE, PB, and THMP. Study 2 will provide important information for evaluating the military consequences of using PB as a prophylactic drug to aid survival in the event of a chemical warfare attack in hot environments.

# 1. Background

PB is used worldwide for the long-term treatment of myasthenia gravis at doses of 360 mg/day to more than 1,400 mg/day. More recently, low-dose regimens (30 mg, 3 × day: doctrinal regimen [DR]) have become an important part of the U.S. Armed Forces prophylactic defense against exposure to organophosphate (OP) chemical warfare agents such as soman. Field use of low-dose PB is based on studies of efficacy in animals and on studies of safety in humans (e.g., Gall, 1981). Most human laboratory studies report few (if any) decrements in performance or adverse effects associated with DR of PB. However, questions have recently been raised and hypotheses have been formulated about a possible role of PB, singly or in combination with insecticides and/or other chemicals, immunological or stress factors, in the etiology of Gulf War Veteran's illnesses (Golomb, 1999). This collection of illnesses has recently been reported as having central nervous system (CNS) origins, and a pharmacologically questionable mechanism has been proposed whereby Gulf War illnesses result from an OP-induced delayed neuropathy caused by PB in combination with insecticides (Haley, Kurt and Horn, 1997).

Several pivotal questions in the evaluation of such hypotheses are whether there are CNS effects of the ostensibly peripheral drug PB, and how those effects, if any, could persist long after discontinuation of the drug. The current belief is that the ionic nature of PB prevents its passage across the blood-brain barrier (BBB). However, some of the reported functional alterations resulting from PB (e.g., flicker fusion frequency, Borland et al., 1985, or changes in vigilance Graham and Cook, 1984) are, at least in part, CNS processes. While there is little doubt that use of low doses under nonstressful laboratory conditions leads to minimal penetration of PB across the BBB into the CNS, the data are much weaker or non-existent for environmentally relevant temperature ranges and stress conditions. Recently, the Medical Corps of the Israel Defense Forces reported that mice subjected to a stressful 4-min forced swim exhibited a temporary breakdown of the BBB (Friedman et al., 1996). This breakdown allowed PB to enter the brain and inhibit brain AChE with the same effectiveness as the centrally-acting inhibitor physostigmine. Other large molecules normally excluded from the brain by the BBB (e.g., an Evan's Blue-albumin complex) also penetrated the brain under these conditions. These findings are based on, and consistent with, earlier work in rodents indicating that cold stress or mild heat stress can reversibly increase the BBB permeability. If these observations were applicable to humans, plausible scenarios would exist whereby effects of such transient breakdowns of the BBB might lead to persistent effects. It is not possible to evaluate carefully this or other hypotheses, however, with the existing data on humans.

Biomedical data suggest that humans may not exhibit alterations in permeability of the BBB with hot temperatures (e.g., 95°F). If this is the case, PB would not exhibit enhanced penetration into the CNS under these conditions. As previously noted, PB has been used worldwide for over 40 years for the long-term treatment of myasthenia gravis at doses of 360 mg/day to more than 1,400 mg/day. The vast majority of these patients are ambulatory, and many live in areas of the world and regions of the U.S. where temperatures routinely exceed 95°F during the summer months. If heat-induced increases

in permeability of the BBB leading to enhanced CNS penetration of PB were a common occurrence, one might reasonably expect the worldwide medical literature to contain reports of CNS effects of PB in myasthenic patients. This is especially true since the Israeli results indicate that if PB were to succeed in crossing the BBB and thereby reach the CNS, it would have easily discernable effects on CNS function. However, a search of the biomedical literature from 1966 to the present via the National Library of Medicine fails to reveal a single clinical report or observation of such CNS effects. Equally negative results have been reported in tests of PB in humans during rest and exercise in dry heat performed at the U.S. Army Research Institute of Environmental Medicine (e.g., Wenger et al., 1993). These results combined make it very unlikely that summer-like temperatures (e.g., 95°F) routinely alter the permeability of the BBB.

However, previous functional human CNS studies have, by and large, failed to examine appropriate, sensitive measures with adequate sample sizes at a range of environmentally relevant temperatures and conditions. The hypotheses and supporting data obtained in mice by the Medical Corps of the Israel Defense Forces (Friedman et al., 1996) are tenable, albeit unlikely. In addition, those hypotheses and data received considerable attention in the recently-released Rand Corporation Report on PB by Dr. Beatrice Golomb (1999). For all of these reasons it is important to examine this issue in an appropriately controlled study with validated and sensitive measures, as we are proposing here.

Previous experimental designs have also failed to account for known absorptional variability and pharmacokinetic complexities of PB. This has resulted in studies with large individual variations in plasma PB, as large as would be expected in a deliberate dose-response study, without the controls inherent in such a study design. The net result is a collection of studies that, due to lack of statistical power and to other methodological issues, probably would not have detected a central response to PB even if one exists. Our recently-completed Study 1 was designed to take these factors into account. This study used a double-blind, placebo-controlled, crossover design. Half the volunteers received PL and PB, 30 mg every 8 hrs. The other half received PL and PB, 60 mg every 8 hrs. A total of 36 men and 31 women completed the study.

No serious adverse effects were observed. Incidence of side effects was extremely low, and those side effects that were reported were mild. Each morning, volunteers completed a 45-item symptom check list; 13 of the items have previously been reported to be side effects of PB. The scale used was 0 (did not occur) to 6 (extremely bothersome) and reflects both the frequency and the severity of side effects. The maximum score for each dosing week for previously reported side effects was 390 (13items x maximum item score of 6 x 5 days). Volunteers on the 30 mg-regimen reported fewer side effects than those on the 60 mg-regimen, but the difference was not significant. The most commonly-reported side effects for both regimens were mild flatulence, nausea, abdominal discomfort, or diarrhea. Only one volunteer (in the 30 mg-regimen) of the 67 volunteers reported being "quite a bit" bothered by any side effects. The mean symptom score was 6.6 of a possible 390 for the PB week, and 3.4 of a possible 390 for the PL week.

The major findings in Study 1 include effects on the cardiovascular system, reaction times, memory, tracking error, and tasks that involved rapid switching of attention. All significant effects related to performance indicated an improvement of performance by PB. Heart rate variability (HRV) during an orthostatic stress test was altered by PB. Percent low frequency power, a measure that is predominantly a reflection of sympathetic nervous system activity, was increased by the 60 mg-regimen when volunteers were supine; when they were standing, the PB effect disappeared. The 30 mg-regimen did not alter percent low power. PB lowered percent high frequency power, which is an established measure of parasympathetic nervous system (vagal) function. This effect was greater for the 60 mg than for the 30 mg-regimen. Percent high frequency power was also affected by the volunteer's position; effects of PB were found when the volunteer was supine, but not when the volunteer was standing. PB also lowered mean heart rate in men who were taking the 60 mg-regimen; heart rate was lowered by both doses for women.

PB improved reaction time for all the performance tasks taken together, and did so significantly for both running memory and switched attention tasks. Reaction time was faster when volunteers were taking PB. PB also decreased tracking error when volunteers were required to perform a tracking task alone and simultaneously with a memory task. This effect was greater for the tracking task when performed alone, and was greater for the 60-mg regimen than for the 30-mg regimen.

Our proposed Study 2 takes advantage of the methods developed for our recently-completed study, and also of the results that were obtained. The tests that will be performed have been shown to be sensitive in detecting actions of PB, and the results we obtained have enabled us to perform statistical power calculations that ensure that an appropriate number of volunteers will be examined. The pattern, type, small magnitude and low frequency of adverse effects that were observed, even with a 60 mg every 8 hr regimen, suggest that our volunteers will not be exposed to any significant risk. The biomedical and experimental literature on use of PB in humans in hot environments is likewise reassuring that the combination of summer-like heat (95°F) and PB intake will not create a health risk for our volunteers.

## 2. Study Objectives

The major objectives of Study 2 are: (1) to determine whether the effects observed in Study 1 can be replicated in a similar sample of volunteers; and (2) to determine whether brief exposure to environmental heat alters the metabolism of PB, or the relationship between plasma PB, AChE or BuChE inhibition, and functional response. The study should provide the U.S. Army with a more complete body of knowledge for optimal use of PB as a prophylactic, OP-defense agent if a future large-scale deployment is required.

# 3. Materials and Methods

Deviations from this protocol will be documented, and the documentation for deviations in study design study population, or dosing will be communicated to the MRI IRB and to the Surgeon Generals HSRRB.

## 3.1 Study Design

This study will use a double-blind cross-over design. Potential volunteers will be interviewed by telephone to determine whether they meet initial criteria for participation. Those who do will visit the laboratory for an informed consent session, and, if they decide to volunteer, will by examined by the project physician to assure that they meet all medical criteria. Informed consent procedures and criteria for participation are described below in greater detail. Prior to entering the drug intake part of the experiment, each volunteer will spend up to 6 hours becoming familiar with the tasks in the task battery. During this time period, blood for baseline determination of PB, THMP, BuChE, and AChE will be obtained between 1100 and 1130 hrs. After training and baseline procedures have been completed, the volunteers will begin Phase 1 of the experiment. Men and women will be separately and randomly assigned to one of two order groups. One order group will receive PB (30 mg every 8 hours) followed by PL and the other will receive PL followed by PB. Volunteers will return to the laboratory one week after the initial dose to begin Phase 2, which will be identical to Phase 1 except that the other pill (PB or PL) will be administered. During each dosing week, the volunteer will take PB or PL every eight hours, for a total of 13 doses. On Thursday and Friday of each dosing week, physiological, motor, and cognitive tests will be performed. On one day the tests will be done in the heat (95°F), and on the other at 75°F. Testing will take about one hour. When both phases have been completed for a given volunteer, he or she will receive another physical examination and be released from the study. Volunteers will receive $50 for training, $225 for each phase of the study, and a completion bonus of $100 after completion of the final physical examination. Volunteers who begin taking PB or PL, and who do not complete the 13 dose regimen, will receive $25 for each completed day.

## 3.2 Study Population

### 3.2.1 Sample Size

Selection of the appropriate sample size is critical. When sample size is too large, resources are wasted; when it is too small, statistical tests do not have the power to detect an effect even if it does exist, and negative results can not be interpreted with confidence. Power analysis (Cohen, 1977) of data from the 30 mg-regimen group in Study 1 indicates that a total sample size of 24 would be adequate to detect relevant effects with alpha at 0.05 and beta at 0.80.

### 3.2.2 Recruitment and Inclusion Criteria

Volunteers will be recruited from local colleges, universities, research organizations, and the local community using posters on bulletin boards and announcements in newspapers and newsletters. A sample announcement is shown in Attachment 1. A sufficient number of volunteers will be recruited to complete the evaluation on approximately 12 men and 12 women. Men and women who are interested in participating will be asked to call a project staff member, who will explain the purpose, procedures, risks, and benefits of participating. If the potential volunteer is interested, he or she will be interviewed to determine whether the following preliminary, study inclusion criteria are met:

- age 18-35;
- no chronic disease or disorder;
- not taking any prescription medication that is known to alter the action or the metabolism of PB, or any of the measures to be obtained;
- no acute illness that required bed rest in the last month;
- willing to abstain from alcohol and over-the-counter drugs other than vitamins and pain reliever during the drug administration and testing phases of the program;
- able to speak, read and write English;
- not pregnant and not planning to become pregnant;
- normal (corrected) vision and hearing;
- no use of illicit drugs;
- not employed by a pesticide company or chronically exposed to pesticides.

### 3.2.3 Informed Consent

Those volunteers who meet preliminary criteria will be asked to come to the laboratory for a personal interview. The principal investigator, co-principal investigator, or study coordinator will again explain the purposes and procedures, risks and benefits of the program and answer any questions the volunteer has. The volunteer will then read the statement of informed consent. To assure that the volunteer understands the risks and benefits, he/she will be required to verbally summarize them before actually signing the statement of informed consent. A copy of the consent form will be given to the volunteer to keep. The consent form is shown in Attachment 2.

### 3.2.4 Exclusion Criteria

An appointment will be made with the project physician for a physical examination, plasma dibucaine test, and urine test for drug use. In addition to the routine physical examination (blood chemistries, electrocardiogram, etc.) the project physician will exclude potential volunteers who show evidence of:

- latent myasthenia gravis
- asthma
- broncho-constrictive disease
- cardiac dysrhythmias
- hypo- or hypertension
- prostatitis
- urinary obstruction
- gastric ulcers
- pregnancy (plasma hCG test)
- GI obstructions
- seizure disorders
- homozygotes for the atypical BuChE mutation using each volunteer's plasma dibucaine number

Only volunteers who, in the opinion of the project physician, can safely ingest 30 mg PB every eight hours for 13 doses will be admitted to the testing phase of the study.

# 4. Study Plan

## 4.1 Investigational Material

The Investigators Brochure is shown in Attachment 3. PB, manufacturer's code 325035 in Lot # BN96947 and PL, manufacturer's code C191538-01, will be supplied to MRI by U.S. Army Medical Material Development Activity (USAMMDA). Dosing schedule, packaging, labeling, and storage of both PB and PL will be conducted by MRI staff members, under the supervision of Dr. Dora Arneson; they will have no other connection with the study or its results. Each dose will be packaged in a blister pack and labeled with the volunteers identification number, phase, and dose number. Only the sponsor, the medical monitor, Dr. Arneson, and staff reporting to Dr. Arneson will have access to the dose schedule.

## 4.2 Material Tracking

Prepared doses of PB and PL will be kept refrigerated in a locked laboratory under Dr. Arneson's supervision. When project staff members check out doses, they will sign for the doses they took, and will be responsible for returning unused pills, if any, to the repository.

## 4.3 Procedures

### 4.3.1 Dosing

The study will be conducted under the US Army's existing Investigational New Drug application (#23509), and will follow Good Clinical Practices (GCP) guidelines. Formulated PB and PL will be supplied by USAMMDA. PB or PL will be administered by MRI staff at approximately 0800, 1600 and 2400 hours. If, because of work or class schedules, it is impossible for a volunteer to come to MRI for the 1600 or 2400 hr pills, he or she will be allowed to take it elsewhere, but will be required to call MRI to confirm that he or she has done so. If no call is received within 15 min of the scheduled dosing time, MRI staff will call and remind the volunteer to take the pill. Our goal is to limit volunteers to no more than one pill per day without supervision, and because of monitoring and food requirements, all volunteers must take the 0800 pill at MRI. The time at which each dose is taken will be documented. Our aim is to have all pills ingested within 20 minutes of the scheduled dose time.

### 4.3.2 Randomization

The Principal Investigator will use random numbers to assign volunteer numbers to order of PB versus PL, and order of testing at ambient temperature versus testing during heat exposure, within each gender group. This randomization will be checked by a senior staff member. Since the Principal Investigator needs to be blind to conditions, the initial randomization will be given to Dr. Arneson. She will rotate the randomization to assure that the PI is unaware of the dose order for any given volunteer.

## 4.4 Data Collection

Volunteers will come to the laboratory first for an informed consent session during which the methods, procedures, benefits, and risks are explained and the volunteer provides written informed consent. After a physical examination indicates that the volunteer is appropriate for study participation, he or she will come to the laboratory for three training sessions over approximately one week. In each of the two dosing weeks, the volunteer will come to the laboratory for dosing every 8 hours beginning Monday morning and ending after the Friday morning dose. On Thursday and Friday, the volunteer will return to the laboratory about 3 1/2 hours after the morning dose to give a blood sample, and to perform the test battery. On one day, the battery will be performed in our environmental chamber at approximately 75°F, and on the other day, it will be performed in the environmental chamber at approximately 95°F.

Our environmental chamber is constructed of stainless steel, and all wall seams are sealed and waterproofed. The dimensions are 9 × 12 × 8.5 ft high. A programmable controller is used to set and regulate temperature and humidity in the chamber. The environmental chamber features a temperature range of –60°F to 180°F. The

environmental chamber's air flow recirculates at 3,000 cfm (approximately 2.5 air changes per minute) and is baffled to reduce velocity and enhance distribution. For the heat condition of this study the temperature will be maintained at 95 ± 2°F and 30 ± 3% RH; for the control condition, the temperature will be maintained at 75 ± 2°F and 30 ± 3% RH. Multiple voltage, thermocouple, thermistor, and frequency inputs with analog outputs are available for monitoring purposes. On testing days, the temperature and humidity of the chamber will be continuously monitored by a research assistant to document and insure correct chamber performance.

We have used the environmental chamber in several large programs to investigate the thermal performance of various devices, and also to provide controlled temperature and humidity environments for studies involving human subjects. Our environmental chamber has been used successfully with human subjects in full environmental (MOPP) suits and also using treadmills. Most recently, it was used in support of the USAMMDA-sponsored study "Potential Systemic Absorption of the Topical Skin Protectant (TSP)," HSPD Log No. A-8555. Because the noise level in the chamber is approximately 85dB, volunteers will wear earphones that reduce ambient noise level to 29dB.

While a volunteer will equilibrate to 75°F in a few minutes, equilibration from ambient temperature to 95°F could take over 1 hour. To shorten the period of equilibration, we will use a heat overshoot method previously developed and calibrated at MRI. The environmental chamber will be initially set at 110°F, the volunteer exposed to that temperature for a pre-determined time (based on the volunteer's weight), and then the chamber will be lowered to 95°F within one minute. The equilibration time at 110°F will not exceed 10 min, and has previously been found to be well-tolerated by volunteers. Testing will then begin; total time in the chamber will be about one hour. To avoid confounding, volunteers will remain in the chamber for the same length of time before testing on both testing days. Before the first dose on the Monday of the second dosing week, a blood sample will be drawn to document AChE and BuChE activity and plasma PB and THMP levels. On the Monday after the last dose of PB and PL has been administered, the volunteer will return to the laboratory to provide a final blood sample. Three months after participation, the volunteer will be contacted and interviewed about any physical problems that he or she attributes to participation in the study.

### 4.4.1 Vital Signs

Pulse rate (auscultation), oral temperature (ovulation thermometer) and blood pressure (sphygmomanometer) will be measured before administering the 0800 pill each day.

### 4.4.2 Subjective Effects and Food Diary

Beginning the day before the first dose of either PB of PL, volunteers will use a food diary to record what they eat and drink. The staff member who administers the morning dose reviews the diary and, if necessary, reminds the volunteer to comply with the instructions. No formal analysis of food diary data is planned. It is reviewed by the P1 or CO-P1, and any consumption of alcohol or marked change in eating patterns is noted for reference during data analysis and interpretation. Each morning before the administration of the 0800 pill the volunteer will complete the symptom check list. Attachment 4 includes both the check list and the scoring key. After each test battery, the volunteer will complete computerized subjective fatigue and workload scales.

### 4.4.3 Blood Fluid Sampling

Blood samples will be obtained by venipuncture on Monday morning of each dosing week before the pill is taken, before the test batteries on Days 4 and 5 of each dosing week, and again on the Monday morning following the final dose. Approximately one ounce of blood will be required at each collection.

### 4.4.4 Blood Processing

The PB-enzyme complex breaks down rapidly at body and room temperatures. We therefore developed a protocol that minimizes breakdown by rapidly chilling blood, and maintaining it chilled throughout all processing procedures until it is stored under frozen conditions. ACD and EDTA Vacutainer® tubes are pre-chilled in a refrigerator (2° to 8°C). After blood samples are collected from volunteers by venipuncture, the ACD and EDTA tubes are placed into an ice-water slurry. The tubes are centrifuged for ~ 20 min at ~ 2800 g forces (~ 3500 rpm) at ~ 5°C.

For plasma BuChE determinations, plasma from EDTA tubes is aliquoted in 0.5 mL volumes into cryovials and stored at ~ –20°C. For red cell AChE determinations, erythrocytes from ACD tubes are diluted with equal volume of RBC buffer (0.1 M citrate phosphate buffer with 4% Triton X-100, pH of 6.0 ± 0.1). This RBC/buffer mixture is then aliquoted in ~ 500-µL volumes into four cryovials and stored at ~ –80°C. For plasma PB and THMP determinations, plasma is aliquoted in 1.0-mL volumes from ACD tubes into three appropriately labeled 1-dram vials and stored at ~ –80°C. For lymphocytes and erythrocytes that will be shipped for DNA analysis to another USAMMDA- sponsored laboratory, either the buffy coat layer or an aliquot of erythrocytes are removed, placed into a cryovial, and stored at ~ –80°C.

### 4.4.5 Analysis of Pyridostigmine and its Major Metabolite in Plasma

Methods were developed for the concomitant determination of PB and its metabolite (3-hydroxy-n-methylpyridinium bromide; THMP) in human plasma. The same HPLC system is used to separate and quantify PB and THMP. The HPLC system and parameters that are used for plasma include an isocratic pump equipped with a programmable UV detector, autosampler with a refrigerated tray (~ 6°C) and a data system. Standard curves are constructed by spiking control plasma to contain ~ 5, ~ 10, ~ 50, or ~ 100 ng/mL of both PB and THMP.

The method for the analysis of PB/THMP in plasma incorporates various sequences of HPLC system/method suitability verifications. As is evident from Table 1, the accuracy and precision observed with this method are excellent:

**Table 1. Accuracy and Precision of Analysis for THMP and pyridostigmine in Plasma**

| THMP (n=6) | | | |
|---|---|---|---|
| Actual ng/mL | Determined ng/mL | % RSD | % Recovery |
| 97.76 | 102.0 | 2.3 | 104 |
| 48.88 | 46.39 | 6.0 | 94.9 |
| 9.78 | 11.13 | 5.3 | 114 |
| Pyridostigmine (n=6) | | | |
| Actual ng/mL | Determined ng/mL | % RSD | % Recovery |
| 102.5 | 104.3 | 3.7 | 102 |
| 51.26 | 48.05 | 5.0 | 93.7 |
| 10.25 | 11.47 | 6.8 | 112 |

### 4.4.6 Quantification of Plasma and Red Blood Cell Cholinesterase

We have quantified red cell (AChE) and plasma (BuChE) with a radioisotopic assay based upon the quantitation of [$^3$H]acetate produced by hydrolysis of labeled [$^3$H]acetylcholine. The sensitive radiometric method of Johnson and Russell (1975) as modified by Nostrandt et al. (1993) was implemented in our laboratory with minor modifications to increase the extraction efficiency of the 3H-labeled acetate into the fluor and reduce sample variation. Our standard substrate is unlabelled acetylcholine iodide (0.015 M) with tracer [acetyl-H$^3$] acetylcholine iodide (0.00023 M).

Our protocol calls for seven separate samples each for plasma and red blood cells (RBC) per volunteer. All seven plasma and RBC samples from a given volunteer are

assayed on the same day to eliminate day-to-day variation. The assay is run in a block without interruption. Assays are run in triplicate for each specimen. A substrate blank is run in triplicate at least every hour once the incubations begin to determine the amount of spontaneous hydrolysis of the acetylcholine. Our internal controls are Bio-Rad Lyphocheck Assayed Controls–Level 1 and 2, which are run in triplicate once daily. Prior to assay, the samples are allowed to thaw in a refrigerator. The blanks, internal controls, and experimental samples are set up and assayed at 26 ± 1°C during a 30-second incubation to minimize dissociation of PB from the enzymes. Total assay volume is 100 µL. Apparent affinity of AChE and BuChE for PB is determined by incubating a sample of enzyme with 3 concentrations of PB (1, 3, 10 X $10^{-7}$ M) for 1 hour at 26°C and then assaying for residual enzyme activity using our standard method.

A validation protocol consistent with GCP criteria was developed and used to validate the cholinesterase assays. We examined the stability of the red cell and plasma enzymes under our optimized conditions. Both activities were stable to storage at ~ –20° and ~ –80°C for several weeks. However, in order to create conditions similar to those observed in vivo, we treated plasma and red cells with 3 x $10^{-7}$ M PB for 1 hour at 26°C. This produced a 30% to 40% inhibition of the plasma enzyme, and about a 20% to 30% inhibition of the red cell enzyme. At this point aliquots of plasma and red cells were stored at ~ –20° and ~ –80°C. Subsequent assay indicated that the enzyme-pyridostigmine complex appeared stable for the duration of our tests.

### 4.4.7 Test Battery

The test battery selected for Study 2 is based on the results of Study 1, and on recent evidence that measures of sensory gating are sensitive to PB in both rats and humans. In selecting the tests, we attempted to keep testing time short, both to reduce the amount of time that subjects would spend in the heat, and to allow better control of levels of PB, AChE and BuChE at the time of testing. The selected battery can be administered in less than 60 min. Except for pre-pulse inhibition (PPI), all of the tasks were used in Study 1. PPI is a measure of sensory gating. It involves presenting the volunteer with auditory startle stimuli, with and without a pre-stimulus signal, and measuring the difference in the eye-blink response to the two types of stimuli. PPI has previously been measured successfully in our laboratory.

**Table 2. Test Battery**

| Tasks | Time (min) |
|---|---|
| Heart Rate Variability HRV) | 18 |
| Hand steadiness test | 1 |
| Grip Strength test | 1 |
| Visual Tracking | 2 |
| Sternberg Memory Task, set size 6 | 4 |
| Switched Attention | 3 |
| Dual memory and tracking tasks | 2 |

| | |
|---|---|
| Running memory | 3 |
| Pre-Pulse Inhibition | 10 |
| Workload and Fatigue Scales | 5 |
| Total | 49 |

### 4.5 Data Management

The data management procedures to be followed are documented in SOPs that are in compliance with GCP. All hardware and software development for computerized data collection and control of task presentation is documented and verified. All data are uniquely coded for study, volunteer number, session and events within the session. Data that must be entered into a computer database are entered independently by two staff members, and computer verified; nonclerical disagreements are resolved by the PI or Co-PI. Because volunteers will be entering the study over several months, a well designed and managed database is necessary. We have extensive experience with complex data and experiment tracking systems. Our database makes it possible to retrieve up-to-date status reports for each volunteer, to record all decisions and/or changes in procedures, and to track the progress of the experiment as a whole. In addition to serving these needs, the database allows efficient review of data, and efficient transfer of data to statistical analysis programs. Databases are created using Microsoft Access for Windows and are networked for team access. Daily system backups allow the identification of changed files, so that the PI can verify that the changes are appropriate and have been properly documented.

### 4.6 Statistical Analysis

All statistical analyses will be conducted using standard packages such as BMDP-Dynamic, Systat and SAS; these programs are fully compatible with Microsoft Access. The primary methods of analysis will be multivariate analysis of variance for repeated measures (i.e., BMDP-4V) and multivariate linear regression. A large number of endpoints will be analyzed. Multivariate groupings of these variables will primarily use a systems approach; endpoints that have inherent interdependencies will be analyzed together. In addition, preliminary correlation matrices will be computed to identify additional groupings that should be treated multivariately. The Huynh-Feldt epsilon correction for lack of sphericity will be used when appropriate. Appropriate post-hoc analyses will be conducted to clarify significant interactions.

## 5. Study Management

### 5.1

Dr. Mary Cook and Dr. Antonio Sastre will serve as Co-principal Investigator. Dr. Cook will be responsible for administrative aspects of the program, and for the collection

of electrophysiological , performance and subjective date. Dr. Sastre will be responsible for chemical and biochemical procedures and analysis. Other staff with major project responsibilities include: Dr. Mary M. Gerkovich, date management and statistical analysis; Dr. Dora Arneson, dose preparation; Mr. Steven J. Hofman, hardware and software systems; Mr. Donald W. Riffle, date collection; Ms. Deborah Dozier, coordination of chemistry and biochemistry; and Ms. Rebecca Peterson, Project Co-Ordinator.

## 5.2 Medical Monitoring

Before entering the study, and after completing participation, each volunteer will be examined by the project physician. The physician selected for this purpose, Allen J. Parmet, M. D., M. P. H., is a diplomat in both aerospace and occupational medicine, and has extensive experience in experiments of this type. His resume is shown in Attachment 5. Before the 0800 pill is administered each day oral temperature, blood pressure, pulse rate and answers to a brief questionnaire on side effects (General Response Questionnaire, GRQ, Attachment 4) will be obtained. Volunteers who show signs of illness (oral temperature 99.6°F or greater; pulse rate 20% or more below baseline or below 50 bpm; diastolic blood pressure based on disappearance of Korotkoff sounds outside the range 50-90 mm/Hg, specific pattern of response on the GRQ as shown in Attachment 4) will be immediately referred to the medical monitor. The physician selected as medical monitor is Mary Brothers, M.D., her resume is shown in Attachment 6. The medical monitor will have the ultimate authority to decide whether the volunteer continues participation in the study.

> **Clause 7.01**
> **Definition:Adverse Event**
> And adverse event temporally related to participation in the study will be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbations of preexisting conditions. All IND. safety reports will include: subject identification number and initials; principal investigator's name and name of the institution conducting the research, subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication (s) including dose, route and duration of treatment, and date of last dose.

Any referral of a volunteer to the medical monitor will be considered an adverse event, and will be documented whether or not it is considered by the medical monitor to be related to the ingestion of PB.

### 5.3 Follow-Up

Three months after a volunteer finishes the study, he or she will be contacted by MRI staff to determine whether any effects that the volunteer thinks might be due to participation in this study have occurred. If the volunteer has observed potential effects, he or she will be referred for further evaluation by the medical monitor.

### 5.4 Adverse Event Report

The form to be used for documentation of adverse events is shown in Attachment 7. Serious adverse experiences will be immediately reported by telephone to the MRI IRB, the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality, and the documentation will be faxed to that office. A written report will follow the initial telephone call within three working days. The sponsor will report any serious adverse events to the FDA.

### 5.5 Criteria for Volunteer Withdrawal

The medical monitor has the authority to remove any volunteer from the study. Volunteers can withdraw at any time if they choose to do so. Such non-medical withdrawals are usually due to changes in schedule that make it impossible to continue the protocol; family illness or emergency; or inability to comply with the protocol (unable to learn/perform the task battery; unable to obtain blood samples in a routine manner).

## 6. Ethics

### 6.1 Institutional Review Boards

This study and its consent form have been reviewed and approved by MRI's Institutional Review Board for Human Subjects. MRI's Multiple Projects Assurance (effective July 1, 1982, and now approved through March 31, 2001) sets out Institutional Review Board responsibilities and the procedures that will be used to protect human subjects. The current Multiple Projects Assurance (M-1051) complies with the Federal Policy for the Protection of Human Subjects (56 *FR* 28003), also known as the Common Rule, which became effective on August 19, 1991. The Common Rule established basic standards that are now honored by 16 different Federal departments and agencies. The study will also be reviewed and approved by the Surgeon General of the Army's Human Subjects Research Review Board (HSRRB).

### 6.2 Protocol Amendments

Protocol amendments will be signed by the investigator, dated, numbered sequentially, and approved by the sponsor, MRI's IRB, and the Surgeon General of the Army's HSRRB. If the protocol amendment alters the study design, increases risk to the volunteer, or in some other way affects the consent form, a revised consent form will be submitted with the amended protocol.

### 6.3 Study Monitoring

Study monitors representing the sponsor will visit MRI, and will review desired study monitoring procedures with MRI's Quality Assurance Unit and with the co-principal investigators. Both external and internal study monitors will be given access to the records of each individual's participation in the study, and to the source documents from which these records were prepared. If requested by the sponsor, MRI will allow representatives of the Food and Drug Administration access to study documents.

## 7. References


Cohen, J., *Statistical Power Analysis for the Behavioral Sciences*, Academic Press, NY, NY (1977).

Johnson, C.D. and R. L. Russell, "A Rapid, Simple Radiometric Assay for Cholinesterase, Suitable for Multiple Determinations," *Anal. Biochem.*, 64, 229-238 (1975).

Nostrandt, A. C., J. A. Duncan, and S. Padilla, "A Modified Spectrophotometric Method Appropriate for Measuring Cholinesterase Activity in Tissue from Carbaryl-treated Animals," *Fund. Appl. Tox.*, 21, 196-203 (1993).

Wenger B., M. D. Quigley, and M. A. Kolka, "Seven-day Pyridostigmine Administration and Thermoregulation During Rest and Exercise in Dry Heat," *Aviat. Space Environ. Med.*, (10), 905-911 (1993).

Golomb, A Review of the Scientific Literature on Persian Gulf War Illnesses. Available from http://www.gulflink.osd.mil/library/randrep/stress/GFI.

Haley, R. W., Kurt, T. L., Horn, J., "Is There a Gulf War Syndrome?" Journal of the American Medical Association, 277(3):215-22, 1997a.

Borland, R. G., Brennan, D. H., Nicholson, A. N., smith, P. A., "Studies on the possible central and peripheral effects in man of a cholinesterase inhibitor (pyridostigmine)," Human Toxicology, 4(3):293-300, 1985 May.

Graham, C., Cook, M. R., "Effects of pyridostigmine on psychomotor and visual performance," Wright-Patterson AFB, OH: USAF Aerospace Medical Research Laboratory, AFOSR-TR-88-0462, 1984.

Friedman, A., Kaufer, D., Shemer, J., Hendler, I., Soreq, H., Tur-Kaspa, I., "Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response," nature Medicine, 2(12):1382-5, 1996 Dec.

Gall, D., "The use of therapeutic mixtures in the treatment of cholinesterase inhibition," Fundamental and Applied Toxicology, 1:214-16, 1981.

# Attachment 1

# Sample Study Announcement

MRI

# EARN UP TO $600

## MEN AND WOMEN VOLUNTEERS ARE NEEDED FOR AN IMPORTANT RESEARCH PROJECT

**MUST BE BETWEEN 18 AND 35, IN GOOD HEALTH, AND INTERESTED IN VOLUNTEERING FOR RESEARCH ON THE SUBTLE EFFECTS OF AN ORAL MEDICATION**

**CALL**
**BECKY AT (816) 753-7600 Ext. 1643**
**OR DON Ext. 1341**

**Midwest Research Institute**
**425 Volker Blvd.**
**Kansas City, Missouri**

Mary R. Cook, Ph.D., Principal Investigator, Ext. 1162

# Attachment 2

## Statement of Informed Consent

Call # _____

**MIDWEST RESEARCH INSTITUTE**
**VOLUNTEER'S INFORMED CONSENT**

Individual Differences in Neurobehavioral Effects of Pyridostigmine: Study 2

I,_____residing at

_____

_____

hereby acknowledge and certify to the following:

1. I hereby volunteer and consent to be a subject in a research study sponsored by the U. S. Army Medical Research and Materiel Command (USAMRMC) and conducted at Midwest Research Institute by Drs. Mary R. Cook and Antonio Sastre. I understand this study will evaluate the short-term effects of the combination of environmental heat and pyridostigmine bromide (PB) on physiology and performance in approximately 24 normal, healthy young men and women. PB has a long history of use in the medical treatment of a condition called myasthenia gravis. It has been alleged that PB is associated with Gulf War Veteran's Illnesses. PB is important to the Army because it has properties that enable it to protect people in the event of a chemical warfare attack. The Food and Drug Administration, however, has not approved PB for use in healthy people and I understand its use is investigational in this research study. The most frequent side effects of PB are upset stomach, cramps, gas, diarrhea, and excessive salivation. I am also aware that in two previous studies at MRI, only a few of the over 90 volunteers who took PB reported any symptoms, and these consisted of mild stomach upset, gas and feelings of tiredness. I understand that administration of PB, as with any other drug, may involve risks to me (or an embryo or fetus) that are currently unforeseeable. I understand that women who participate in this study should avoid becoming pregnant for two weeks after participation in the study. To avoid becoming pregnant, I should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. I also understand that this is a double-blind study. This means that during any given phase of the experiment, PB may actually be in the pills I take, or it may not. The investigators will not know, and I will not know, which pill is which. In this way, any effects due to PB can be separated from those that might be due to a person's expectations about taking PB.

I understand I will receive free a complete medical examination at the start of the study. This evaluation will include medical history, drug screen, urinalysis, electrocardiogram, blood chemistry, complete blood count, lung function test, and medical examination. For women, the examination will include a pregnancy test. The physician will tell me about any problems he/she finds during the evaluation, and advise me about follow-up. I will then come to MRI to be trained to perform tests that measure my memory, attention, and sensory abilities. During training, sensors will be attached to my chest to measure my heartbeat, and below my eyes to measure my eye blink response. I understand that sensor attachment is painless; however, it is remotely possible that the attachment of sensors can cause irritation or scratches in particularly sensitive people. Training will require no more than 6 hours of my time spaced over a week.

Call # _____

I will then be randomly assigned to one of two groups. Both groups take 30 mg PB every 8 hours (90 mg/day), and both groups take placebo. These doses of PB are less than the doses typically used by medical patients (120 mg 6 times/day; 720 mg/day). The study will be performed in two phases, separated by two days off. Each Phase will last five days and each will involve the same sequence of activities. I will keep a diary of what I eat and drink for each of the 12 days of the study. I understand I will be asked to come to MRI to take pills every eight hours for the first four days of each phase, followed by one additional pill on the fifth day. I will have my blood pressure, pulse, and temperature recorded each morning, and I will complete a questionnaire about any symptoms I may be experiencing. I will be asked to provide blood samples (about 1 ounce) via venipuncture from a vein in my arm, once during training, on days 1, 4, and 5 of each phase, and on the Monday following the final dose. I understand that standard medical procedures will be followed when drawing blood, but that bruising or soreness can sometimes occur. To minimize this risk, MRI employs highly trained phlebotomists to conduct blood draws. These samples will be used to find out how much PB is in my blood, and how it has affected my cholinesterase levels. Some of the samples that I am donating under this study may be used by another laboratory for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. Should my donated samples lead to the development of a commercial product, the other laboratory will own it and may take action to patent and license the product. I will not be provided with additional compensation for donating these blood samples and will not receive any notice of future uses of my samples. The samples donated will not contain any information that identifies me personally. I understand that, for this reason, I will be asked to sign a separate donation form. On days 4 and 5, sensors will be attached, and I will perform the tests I learned earlier. On one day, I will perform the tests at room temperature, and on the other day at a temperature of approximately 95°F. This temperature may cause mild discomfort, similar to a hot summer day in Kansas City. Testing will take about one hour. MRI will provide breakfast for me every day that I take pills, and will provide lunch for me on test days. At the end of the study, I will return to MRI for a final blood sample, and will visit the project physician again for a brief follow-up medical examination. Three months after I finish the study, I will be contacted by MRI staff to determine whether I have experienced any effects that I think might be due to my participation in this study. If so, they will arrange for further medical evaluation.

I agree to not use drugs or alcohol during the study and to inform the investigators of any medications I may need to take. I understand that this is a basic research study, and that I will not benefit from being in it, except that I will receive a full medical examination at no charge, and I will be reimbursed for the time and effort required for participation. If I complete all study requirements, I will receive a total of $600 ($50 for training, $225 for each phase and $100 completion bonus). If I should choose to withdraw from the study during a dosing week, I will be paid $25.00 per day of actual participation and I will also be expected to see the project physician for a final medical examination. I will still be contacted three months after my last day of participation to determine whether I've experienced any effects that I think might be due to my participation. If I choose to withdraw during the training week I will be compensated at a rate of $5.00 per hour of training and I will not be contacted for follow up.

2. I have been given, in my opinion, an adequate explanation of the nature, duration, and purpose of the study, the means by which the study will be conducted, and any possible inconvenience, hazards, discomfort, risks, and adverse effects on my health which could result from my participation.

Call # _____

3. I understand my questions concerning procedures which affect me will be answered fully and promptly by either Dr. Mary R. Cook, Principal Investigator, Dr. Antonio Sastre, Co-Principal Investigator, or by Dr. Eugene Podrebarac, Chairman of the MRI Institutional Review Board for Human Studies, which reviewed and approved this study (816/753-7600). The address of the Institute is 425 Volker Boulevard, Kansas City, MO.

4. I understand that I have the right to withdraw my consent and to discontinue participation in this experiment at any time without prejudice regardless of the status of the experiment and regardless of the effect of such withdrawal on the objectives and results of the experiment. I also understand that my participation in the experiment may be terminated at any time by the investigator in charge of the project.

5. I agree that any information obtained from me, by MRI, or its authorized representatives in connection with this study, may be utilized by MRI in publications and reports without identifying me. Because the use of pyridostigmine is investigational for this study, I am also aware that representatives of the Food and Drug Administration and/or the U.S. Army Medical Research and Materiel Command may wish to review the records of my participation and perhaps contact me to ask specific questions about my experiences. I understand that MRI agrees with this policy of openness, and that it will provide personally identifying information about me to these agencies to allow them to contact me if they so wish. I understand this information will be limited to the following: my name, address, social security number, the name of this study, and the dates of my participation in it. This information will be maintained by the USAMRMC in its confidential Volunteer Registry DataBase. The intent of this procedure is two fold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

6. If I experience any symptoms I feel should be reviewed with a physician, I can call the medical monitor, Dr. Mary Brothers (816)561-3480 Home (913)727-6168 , who will schedule an appointment with me as soon as possible. The United States Department of Defense is funding this research project. Should I be injured as a direct result of participating in this research project, I will be provided medical care, at no cost to me, for that injury. I will not receive any injury compensation, only medical care. I understand that this is not a waiver or release of my legal rights. I further understand that I should discuss this issue thoroughly with the Principal Investigator before enrolling in this study. Other than the medical care that may be provided (and the other benefits stated above in section # 1 of this consent form), there is no other compensation available for my participation in this research study.

7. I will be given a copy of this consent form to keep.

Call # _____

My age is ____; The date of my birth is_____

I am executing this Volunteer's Consent as my free act and deed.

Today's date is _____, 19_____

Executed in the presence of each other

| _____ | _____ | Date:_____ | _____ |
|---|---|---|---|
| Name of Volunteer | Signature of Volunteer | | Initials |
| _____ | _____ | Date:_____ | _____ |
| Name of Investigator | Signature of Investigator | | Initials |
| _____ | _____ | Date:_____ | _____ |
| Name of Witness | Signature of Witness | | Initials |

4863
5/4/00

CALL# ____

**MIDWEST RESEARCH INSTITUTE**
**SAMPLE DONATION FORM**

**Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 2**

I, _____residing

at _____

Voluntarily donate any and all blood samples to Midwest Research Institute (MRI). These samples will be used to find out how much Pyridostigmine Bromide is in my blood, and how it has affected my cholinesterase levels. Some of the samples that I am donating under this study may be used by another laboratory for special analysis and may also be used by them for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. Should my donated samples lead to the development of a commercial product, the other laboratory will own it and it is possible that it will be patented and licensed by them. I will not be provided with additional compensation for donating these blood samples and will not receive any notice of future uses of my samples. The samples donated will not contain any information that identifies me personally.

_____ Date:_____
Signature of Volunteer

_____ Date:_____
Signature of Experimenter

_____ Date:_____
Signature of Witness

# Attachment 3

# Investigator's Brochure

## Mestinon Injectable—Cont.

muscularly. It is important to differentiate between cholinergic and myasthenic crises in neonates. (See WARNINGS.)

Mestinon given parenterally one hour before completion of second stage labor enables patients to have adequate strength during labor and provides protection to infants in the immediate postnatal state. For further information on the use of Mestinon Injectable in neonates of myasthenic mothers, see the article by Namba.[7]

NOTE: For information on a diagnostic test for myasthenia gravis, and on the evaluation and stabilization of therapy, please see product information on Tensilon® (edrophonium chloride).

*For Reversal of Nondepolarizing Muscle Relaxants:* When Mestinon Injectable is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) also be given intravenously immediately prior to the Mestinon. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Usually 10 or 20 mg of Mestinon will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported. For additional information on the use of Mestinon for antagonism of nondepolarizing muscle relaxants see the article by Katz[8] and McNall.[9]

Failure of Mestinon Injectable to provide prompt (within 30 minutes) reversal may occur, *e.g.*, in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

### HOW SUPPLIED

Mestinon is available in 2-ml ampuls (boxes of 10) (NDC 0187-3011-10).

### REFERENCES


1. Osserman, KE, Genkins G. Studies in myasthenia gravis: Reduction in mortality rate after crisis. *JAMA*. Jan 1963; 183: 97-101.
2. Osserman, KE, Genkins G. Studies in myasthenia gravis. *NY State J Med*. June 1961; 61:2076-2085.
3. Grob D. Myasthenia gravis. A review of pathogenesis and treatment. *Arch Intern Med*. Oct 1961; 108:615-638.
4. Schwab RS. Management of myasthenia gravis. *New Eng J Med*. Mar 1963; 268:596-597.
5. Schwab RS. Management of myasthenia gravis. *New Eng J Med*. Mar 1963; 268:717-719.
6. Cronnelly R, Stanski DR, Miller RD, Sheiner LB. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther*. 1980; 28:No. 1, 78-81.
7. Miller RD. Pharmacodynamics and pharmacokinetics of anticholinesterase. In: Ruegheimer E. Zindler M, ed. *Anaesthesiology*. (Hamburg, Germany: Congress; Sep 14–21, 1980; 222-223.) (Int Congr. No. 538), Amsterdam, Netherlands: Excerpta Medica; 1981.
8. Breyer-Pfaff U, Maier U, Brinkmann AM, Schumm F. Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther*. 1985; 5:495-501.
9. Foldes FF, McNall PG. Myasthenia gravis: A guide for anesthesiologists. *Anesthesiology*. 23:837-872 Nov-Dec 1962.
10. Namba T, Brown SB, Grob D. Neonatal myasthenia gravis: Report of two cases and review of the literature. *Pediatrics*. 45(3):Mar 1970; 488-504.
11. Katz RL. Pyridostigmine (mestinon) as an antagonist of d-tubocurarine. *Anesthesiology*. 28(3):May-June 1967; 528-534.
12. McNall PG, Wolfson B, Tuazon JG, Siker ES. *Anesth Analg*. 48(6): Nov-Dec 1969;1026-1032.



Manufactured for ICN Pharmaceuticals, Inc.
Costa Mesa, CA 92626
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Nutley, N.J. 07110
Rev. 9-95


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## MESTINON®

*[mes 'tin-on ]*

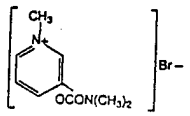
**(pyridostigmine bromide)**

**TABLETS, SYRUP and TIMESPAN® TABLETS**

℞

### DESCRIPTION

Mestinon (pyridostigmine bromide) is an orally active cholinesterase inhibitor. Chemically, pyridostigmine bromide is 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate. Its structural formula is:




Mestinon is available in the following forms: Syrup containing 60 mg pyridostigmine bromide per teaspoonful in a vehicle containing 5% alcohol, glycerin, lactic acid, sodium benzoate, sorbitol, sucrose, FD&C Red No. 40, FD&C Blue No. 1, flavors and water. *Tablets* containing 60 mg pyridostigmine bromide; each tablet also contains lactose, silicon dioxide and stearic acid. *Timespan Tablets* containing 180 mg pyridostigmine bromide; each tablet also contains carnauba wax, corn-derived proteins, magnesium stearate, silica gel and tribasic calcium phosphate.

### ACTIONS

Mestinon inhibits the destruction of acetylcholine by cholinesterase and thereby permits freer transmission of nerve impulses across the neuromuscular junction. Pyridostigmine is an analog of neostigmine (Prostigmin®), but differs from it in certain clinically significant respects; for example, pyridostigmine is characterized by a longer duration of action and fewer gastrointestinal side effects.

### INDICATION

Mestinon is useful in the treatment of myasthenia gravis.

### CONTRAINDICATIONS

Mestinon is contraindicated in mechanical intestinal or urinary obstruction, and particular caution should be used in its administration to patients with bronchial asthma. Care should be observed in the use of atropine for counteracting side effects, as discussed below.

### WARNINGS

Although failure of patients to show clinical improvement may reflect underdosage, it can also be indicative of overdosage. As is true of all cholinergic drugs, overdosage of Mestinon may result in cholinergic crisis, a state characterized by increasing muscle weakness which, through involvement of the muscles of respiration, may lead to death. Myasthenic crisis due to an increase in the severity of the disease is also accompanied by extreme muscle weakness, and thus may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Such differentiation is extremely important, since increases in doses of Mestinon or other drugs of this class in the presence of cholinergic crisis or of a refractory or "insensitive" state could have grave consequences. Osserman and Genkins[1] indicate that the differential diagnosis of the two types of crisis may require the use of Tensilon® (edrophonium chloride) as well as clinical judgment. The treatment of the two conditions obviously differs radically. Whereas the presence of myasthenic crisis suggests the need for more intensive anticholinesterase therapy, the diagnosis of cholinergic crisis, according to Osserman and Genkins,[1] calls for the prompt *withdrawal* of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended.

Atropine may also be used to abolish or obtund gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

For detailed information on the management of patients with myasthenia gravis, the physician is referred to one of the excellent reviews such as those by Osserman and Genkins,[2] Grob[3] or Schwab.[4,5]

*Usage in Pregnancy:* The safety of Mestinon during pregnancy or lactation in humans has not been established. Therefore, use of Mestinon in women who may become pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

*Pediatric Use:* Safety and effectiveness in pediatric patients have not been established.

### PRECAUTION

Pyridostigmine is mainly excreted unchanged by the kidney.[6,7,8] Therefore, lower doses may be required in patients with renal disease, and treatment should be based on titration of drug dosage to effect.[6,7]

### ADVERSE REACTIONS

The side effects of Mestinon are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and [illegible]

carinic side effects can usually be counteracted [illegible] but for reasons shown in the preceding section [illegible] ent is not without danger. As with any compound [illegible] the bromide radical, a skin rash may be encountered [illegible] sional patient. Such reactions usually subside upon discontinuance of the medication.

### DOSAGE AND ADMINISTRATION

Mestinon is available in three dosage forms: [illegible]

*Syrup* —raspberry-flavored, containing 60 mg [illegible] mine bromide per teaspoonful (5 ml). This form [illegible] curate dosage adjustment for children and [illegible] thenic patients who require fractions of 60 mg [illegible] more easily swallowed, especially in the [illegible] tients with bulbar involvement.

*Conventional tablets* —each containing 60 mg [illegible] mine bromide.

*Timespan tablets* —each containing 180 mg pyridostigmine bromide. This form provides uniformly slow [illegible] prolonged duration of drug action; it facilitates [illegible] myasthenic symptoms with fewer individual [illegible] The immediate effect of a 180-mg Timespan tablet is equal to that of a 60-mg conventional tablet, [illegible] duration of effectiveness, although varying in individual patients, averages $2\frac{1}{2}$ times that of a 60-mg dose.

*Dosage:* The size and frequency of the dosage must be adjusted to the needs of the individual patient.

*Syrup and conventional tablets* —The average dose is 60-mg tablets or ten 5-ml teaspoonfuls daily, spaced to provide maximum relief when maximum strength is needed. In severe cases as many as 25 tablets or teaspoonfuls [illegible] may be required, while in mild cases one tablet or [illegible] teaspoonfuls a day may suffice.

*Timespan tablets* —One to three 180-mg tablets, twice daily, will usually be sufficient to control [illegible] however, the needs of certain individuals may [illegible] edly from this average. The interval between doses should be at least six hours. For optimum control, it may be necessary to use the more rapidly acting regular tablets in conjunction with Timespan therapy.

*Note:* For information on a diagnostic test for myasthenia gravis, and for the evaluation and stabilization of therapy, please see product literature on Tensilon® (edrophonium chloride).

### HOW SUPPLIED

*Syrup*, 60 mg pyridostigmine bromide per teaspoonful and 5% alcohol—bottles of 16 fluid ounces (1 pint) (NDC 0187-3012-20).

*Tablets*, scored, 60 mg pyridostigmine bromide—bottles of 100 (NDC 0187-3010-30) and 500 (NDC 0187-3010-40).

*Timespan tablets*, scored, 180 mg pyridostigmine bromide each—bottles of 100 (NDC 0187-3013-50).

Note: Because of the hygroscopic nature of the Timespan tablets, mottling may occur. This does not affect their efficacy.

### REFERENCES


1. Osserman KE, Genkins G. Studies in myasthenia gravis: Reduction in mortality rate after crisis. *JAMA*. 183:97–101.
2. Osserman KE, Genkins G. Studies in myasthenia gravis. *NY State J. Med.* June 1961; 61:2076–2085.
3. Grob D. Myasthenia gravis. A review of pathogenesis and treatment. *Arch Intern Med.* Oct 1961; 108:615–638.
4. Schwab RS. Management of myasthenia gravis. *New Eng J Med.* Mar 1963; 268:596–597.
5. Schwab RS. Management of myasthenia gravis. *New Eng J Med.* Mar 1963; 268:717–719.
6. Cronnelly R, Stanski DR, Miller RD, Sheiner LB. Pyridostigmine kinetics with and without renal function. *Pharmacol Ther.* 1980; 28:No. 1, 78–81.
7. Miller RD. Pharmacodynamics and pharmacokinetics of anticholinesterase. In: Ruegheimer E, Zindler M, ed. *Anaesthesiology*. (Hamburg, Germany: Congress; Sep 14–21, 1980; 222–223.) (Int Congr. No. 538), Amsterdam, Netherlands: Excerpta Medica; 1981.
8. Breyer-Pfaff U, Maier U, Brinkmann AM, Schumm F. Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther.* 1985; 5:495–501.



Manufactured for ICN Pharmaceuticals, Inc.
Costa Mesa, CA 92626
by Hoffmann-La Roche Inc.
Nutley, N.J. 07110
Rev. 1/97


*Shown in Product Identification Guide*

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## OXSORALEN® LOTION 1%

*[ox 'sore "a-len ]*

**(methoxsalen USP, 1%)**

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

# Attachment 4

# Symptom Check List

4863PP
Revision: 1
Effective 7/10/98

SBJID# _____
DATE ___/___/___
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

Data Entry 1st ____; 2nd _____
Rvwd by:_____Date _____
PI Review_____Date _____

## GENERAL RESPONSE QUESTIONNAIRE

**INSTRUCTIONS:** Below, is a list of the kind of symptoms that people sometimes report to their doctor. Please read each symptom carefully. Put an **X** in the box that best describes each symptom: **IF THE SYMPTOM HAS OCCURED IN THE LAST 24 HOURS, PUT AN X IN THE BOX THAT BEST DESCRIBES HOW MUCH YOU WERE BOTHERED OR DISTRESSED BY EACH SYMPTOM.** Check only one selection for each symptom and do not skip any items. If you change your mind, mark one line through your first answer, initial and date it, then put an **X** on your new choice.

**In the last 24 hours, how much were you distressed or bothered by:**

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 1. Weakness | | | | | | | |
| 2. Trouble speaking | | | | | | | |
| 3. Chills | | | | | | | |
| 4. Blind spots in eyes | | | | | | | |
| 5. Temper outbursts | | | | | | | |
| 6. Chest pain | | | | | | | |
| 7. Excessive thirst | | | | | | | |
| 8. Nausea | | | | | | | |
| 9. Skin rash | | | | | | | |
| 10. Numbness | | | | | | | |
| 11. Headaches | | | | | | | |
| 12. Stiff neck | | | | | | | |
| 13. Night sweats | | | | | | | |
| 14. Depression | | | | | | | |
| 15. Nose bleeds | | | | | | | |
| 16. Unusual belching | | | | | | | |
| 17. Trouble swallowing | | | | | | | |
| 18. Blurred/double vision | | | | | | | |
| 19. Body aches | | | | | | | |



This SOP has been updated to move the signature box to the right ~~side~~ side of the page. No changes were made in the actual questionnaire
2/20/00

SBJID#_____
DATE ____/____/____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 20. Swollen lymph nodes | | | | | | | |
| 21. Urination problem | | | | | | | |
| 22. Shortness of breath | | | | | | | |
| 23. Bloating | | | | | | | |
| 24. Fainting | | | | | | | |
| 25. Dizziness | | | | | | | |
| 26. Memory impairment | | | | | | | |
| 27. Sore tongue | | | | | | | |
| 28. Vomiting | | | | | | | |
| 29. Heartburn | | | | | | | |
| 30. Bleeding gums | | | | | | | |
| 31. Fearfulness/anxiety | | | | | | | |
| 32. Diarrhea | | | | | | | |
| 33. Heart palpitations | | | | | | | |
| 34. Ringing in ears | | | | | | | |
| 35. Flatulence/passing gas | | | | | | | |
| 36. Hand tremors/shaking | | | | | | | |
| 37. Persistent cough | | | | | | | |
| 38. Skin itching | | | | | | | |
| 39. Fever | | | | | | | |
| 40. Nervousness | | | | | | | |
| 41. Abdominal pain | | | | | | | |
| 42. Sleep disturbance | | | | | | | |
| 43. Dark or bloody urine | | | | | | | |
| 44. Fatigue | | | | | | | |
| 45. Constipation | | | | | | | |

# GENERAL RESPONSE QUESTIONNAIRE
# INTERIM REFERRAL KEY

## INSTRUCTIONS:

**** = Refer to Dr. Mary Brothers if SOMEWHAT OR GREATER**

***** = MUST BE MARKED IN CONJUNCTION WITH EACH OTHER FOR REFERRAL**

**All other symptoms must be marked as indicated on the GRQ Referral Key and IN CONJUNCTION WITH 2 OR MORE OTHER SYMPTOMS.**

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 1. Weakness | | | | | | O | O |
| 2. Trouble speaking | | | O | O | O | O | O |
| 3. Chills | | | O | O | O | O | O |
| 4. Blind spots in eyes** | | | ** | ** | ** | ** | ** |
| 5. Temper outbursts | | | O | O | O | O | O |
| 6. Chest pain** | | | ** | ** | ** | ** | ** |
| 7. Excessive thirst | | | | | | O | O |
| 8. Nausea | | | | | | O | O |
| 9. Skin rash | | | | | | O | O |
| 10. Numbness | | | | | | O | O |
| 11. Headaches*** | | | | | | *** | *** |
| 12. Stiff neck*** | | | *** | *** | *** | *** | *** |
| 13. Night sweats | | | | | | O | O |
| 14. Depression | | | | | | O | O |
| 15. Nose bleeds | | | | | | O | O |
| 16. Unusual belching | | | | | | O | O |
| 17. Trouble swallowing | | | | | | O | O |
| 18. Blurred/double vision** | | | ** | ** | ** | ** | ** |
| 19. Body aches | | | | | | O | O |

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 20. Swollen lymph nodes | | | | | | O | O |
| 21. Urination problem | | | | | O | O | O |
| 22. Shortness of breath | | | | | O | O | O |
| 23. Bloating | | | | | | O | O |
| 24. Fainting | | | | | O | O | O |
| 25. Dizziness | | | | | O | O | O |
| 26. Memory impairment | | | | | O | O | O |
| 27. Sore tongue | | | | | | O | O |
| 28. Vomiting | | | | | O | O | O |
| 29. Heartburn | | | | | | O | O |
| 30. Bleeding gums | | | | | | O | O |
| 31. Fearfulness/anxiety | | | | | | O | O |
| 32. Diarrhea | | | | | | O | O |
| 33. Heart palpitations** | | | ** | ** | ** | ** | ** |
| 34. Ringing in ears | | | | | | O | O |
| 35. Flatulence/passing gas | | | | | | O | O |
| 36. Hand tremors/shaking | | | | | | O | O |
| 37. Persistent cough | | | | | | O | O |
| 38. Skin itching | | | | | | O | O |
| 39. Fever | | | | | | O | O |
| 40. Nervousness | | | | | | O | O |
| 41. Abdominal pain | | | | | | O | O |
| 42. Sleep disturbance | | | | | | O | O |
| 43. Dark or bloody urine** | | | ** | ** | ** | ** | ** |
| 44. Fatigue | | | | | | O | O |
| 45. Constipation | | | | | | O | O |

# Attachment 5

## Resume, Project Physician

Allen J. Parmet

PII Redacted

Curriculum vitae as of May 31, 1997

Office:Midwest Occupational Medicine
3037 Main, Suite 201
Kansas City, MO 64108
(816) 561-3480
FAX 561-4043

[redacted]

[redacted]

[redacted]

Education

Undergraduate : United States Air Force Academy - B.S. 1972
Medical School: University of Kansas - M.D. 1976
Internship : David Grant Medical Center,
Travis AFB, California - 1977
Residency : Phase I - University of Texas
School of Public Health at
Houston - M.P.H. 1981

Phase II - USAF School of Aerospace
Medicine Brooks AFB, Texas - 1982

Fellowship : Space Medicine - NASA/Johnson
Space Center, Houston, Texas - 1982

Post-Graduate Work: University of Kansas School of Medicine, Department of Toxicology 1995-

License

Kansas #17322 December 9, 1977
Texas #F1185 June 12, 1978
Missouri #R2G63 August 22, 1986
Colorado #31655 April 9, 1992

Educational Short Courses

Aerospace Medicine Primary, USAF School of Aerospace Medicine, Brooks AFB, TX, 1977

Combat Casualty Care Course, Brooke Army Medical Center, Ft. Sam Houston, TX, 1982.
Forensic Accident Investigation, Armed Forces Institute of Pathology, Walter Reed Army Instiute of Research, Washington, DC, 1983

Crash Investigators Course, Arizona State University, 1983

Aircraft Accident Investigation Course, University of Southern California Safety Systems Institue, Los Angeles, 1988.

Certificates & Examinations

National Board of Medical Examiners Certificate #176115
American Board of Preventive Medicine Certification:
Aerospace Medicine-Diplomate January 27, 1983
Occupational Medicine-Diplomate January 31, 1989
Medical Review Officer Certification Council-June 13, 1993
American Board of Forensic Examiners-Sept, 1996

Medical Job History

1994 - Medical Director, Trans World Airlines

1993-95 Medical Director, St. Lukes's Occupational Medicine Group, Kansas City, Missouri

1995- Adjunct Faculty for Aviation Safety, Institute of Safety and Systems Management, University of Southern California, Los Angeles, California

1992 - Great Plains College of Occupational and Environmental Medicine:

President, 1996-97
1st Vice-President, 1995-6
2nd Vice-President, 1994-5
Secretary-Treasurer, 1993-4

1992-94 Consultant, Mid-America Coalition on Health Care/Workers' Compensation Task Group, Kansas City, Missouri

1992- Adjunct Professor, Department of Aerospace

Medicine, USAF School of Aerospace Medicine, Brooks AFB, TX

1990- 94 Adjunct Assistant Professor of Preventive Medicine and Biometrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD

1988- Associate Clinical Professor, Dept. of Community Medicine Wright State University School of Medicine, Dayton, OH

1987 - Associate Editor, **Aviation, Space and Environmental Medicine**

1987 - 92 Professor, Department of Aerospace Medicine, United States Air Force School of Aerospace Medicine, Brooks AFB, TX:

Course Director, Aerospace Medicine Primary, 1987, 88, 89 & 91.

Course Director, Operational Aeromedical Problems 1988, 89, 92.

Course Director, Health Professions Scholarship Program, 1990, 91 & 92.

Course Director, Aeromedical Readiness and Management Course, 1990, 91 & 92.

Course Director, Global Medicine Course, 1991 & 92.

Deputy Director, Residency in Aerospace Medicine, 1989 - 92.

1985 - 87 Associate Professor of Health Sciences, Chapman College Extension, Los Angeles, CA. Courses taught: Epidemiology, Genetics, Infectious Disease.

1984 - 96 Series Editor, "Cases From the Aerospace

Medicine Residents' Teaching File" in
Aviation Space and Environmental Medicine

1984 - 87 Space Transportation System Medical Director/
Chief of Aerospace Medicine, Vandenberg AFB, CA

1982 - 84 Chief of Flight Evaluations, School of
Aerospace Medicine, Brooks AFB, Tx

1979 - 80 Flight Surgeon, Randolph AFB Clinic, Tx

1977 - 79 Flight Surgeon, Officer Training School Clinic,
Lackland AFB, Tx

Other Activities

1982-1986 Member, Education and Training Committee;
1988-1992 Aerospace Medical Association

1984-87 Member, NASA/USAF Space Transportation System
Personnel Assurance Program Review Committee

1986-89 Member, History and Archives Committee;
Aerospace Medical Association

1987-89 Chairman, Reinartz Education and Training
1990-92 Committee; Society of USAF Flight Surgeons

1982-1986 Member, USAF Manned Spaceflight Engineer
Selection Panel

1987-1991 Member, USAF Astronaut Nomination Panel

1987- Member, USAF School of Aerospace Medicine
Residency Advisory Committee

1991- Member, Awards Committee (1992- Vice-Chair);
Aerospace Medical Association

1993- Senior Aviation Medical Examiner, Federal
Aviation Administration

1993-96 Chairman, Occupational Medicine Section, St.

Lukes Hospital Department of Medicine.

1993-1995 Member, Infection Control Committee, St. Lukes Hospital Department of Medicine.

1995- Chairman, Quality Assurance Committe, St. Lukes Hospital Department of Medicine.

Honors

Fellow, American College of Preventive Medicine
Fellow, Aerospace Medical Association
Fellow, International Association of Aviation and Space Medicine
Fellow, American College of Forensic Examiners

Awards

Society of USAF Flight Surgeons Howard Unger Annual Award for Best Publication - 1984
USAF Meritorious Service Medal - 1984
USAF Meritorious Service Medal, 1st OLC - 1987
USAF Meritorious Service Medal, 2nd OLC - 1992
Strategic Air Command Flight Surgeon of the Year - 1985
Peter T. Bohan Lecturer, University of Kansas - 1986
Outstanding Clinical Instructor for the Residency in Aerospace Medicine - 1989

Associations

American Medical Association
Aerospace Medical Association
American College of Occupational & Environmental Medicine
American College of Preventive Medicine
American College of Forensic Examiners

Publications (Sole or first author unless noted)

Original Articles

"Treatment of Neovascular Glaucoma with Transscleral Panretinal Cryotherapy", (Co-author) Ophthalmology, Nov. 1980, 87 (11): 1106 - 1111

"Nonsexual Transmission of Gonorrhea to a Child" (with H.J. Lipsitt), New England Journal of Medicine, Aug 16, 1984, 470

"A Clinical Challenge: How Many Ways Can You Skin a Cat", Aviation Space and Environmental Medicine, 55 (10): 946-7, 1984

"Case from the Aerospace Medicine Residents' Teaching File" #1: Toxic Peripheral Neuropathy, Sacroilitis and Mitral Valve Prolapse", Aviation Space and Environmental Medicine, 55 (11): 1057-69 1984

"Feedback #1", Aviation Space and Environmental Medicine, 55(11): 1059, 1984

"Case from the Aerospace Medicine Residents' Teaching File #2: On an aviator with an Acoustic Neuroma", Aviation Space and Environmental Medicine, 55 (12): 1151-53, 1984

"Feedback #2: My Best Case, My Worst Case", Aviation Space and Environmental Medicine, 55 (12): 1153, 1984.

"Case from the Aerospace Medicine Residents' Teaching File #3: An Aviator with Idiopathic Dialated Cardiomyopathy", Aviation Space and Environmental Medicine, 56 (1): 62-65, 1985

Feedback #4, Aviation Space and Environmental Medicine, 56 (3): 274, 1985

Feedback, #7, Aviation Space and Environmental Medicine, 56 (11); 1118-1119, 1985

Feedback #9, Aviation Space and Environmental Medicine, 56(12); 1228, 1985

"Space Shuttle at Vandenberg", Military Medicine, 150 (11); A1-A3, 1985

"Drain That Swamp", Military Medicine, 151 (1); 60-63, 1986

Feedback #8, Aviation Space and Environmental Medicine, 57 (1); 84, 1986

Letter, Aviation Space and Environmental Medicine, 57 (1);85, 1986

"Case from the Aerospace Medicine Residents' Teaching File #14: An Aviator with Hodgkin's Disease", (Co-author) Aviation Space and Environmental Medicine, 57(8): 805-7, 1986

Feedback #14, Aviation Space and Environmental Medicine, 57 (8): 807, 1986

"Case from the Aerospace Medicine Residents' Teaching File #15, An Aviator with Chronic Lymphocytic Leukemia", (Co-author) Aviation, Space and Environmental Medicine, 57(11):1109-11, 1986

Feedback #15: Aviation, Immunity and AIDS, Aviation, Space and Environmental Medicine, 57(11):1111, 1986

Feedback #17, Aviation, Space and Environmental Medicine, 58(4):381, 1987

"The Early Birds of 1911", Aviation Space and Environmental Medicine, 58 (3): 276-79, 1987

Feedback #21, Aviation, Space and Environmental Medicine, 59(1):88, 1988

"Case from the Aerospace Medicine Residents' Teaching File #31: Methemaglobinemia", Aviat. Space Environ. Med., 1989, 60(5):465-6.

"Case from the Aerospace Medicine Residents' Teaching File #45: An aviator with Melanoma" (Co-author), Aviat. Space Environ. Med. 1991; 62(7):694-6.

"Body Volume Changes During Simulated Microgravity: Auditory Changes, Segmental Fluid Redistribution, and Regional Hemodynamics", (with LD Montgomery), Annals of Biomedical Engineering, 1993, 21:417-433.

"Sixty for Ten" (Editorial), Aviat. Space Environ. Med., 1994, 65:670.

"Case from the Aerospace Medicine Residents' Teaching File #60: An aviator with erythema multiformae", Aviat. Space Environ. Med., 1994, 65:671-73.

"Survey of the American Board of Preventive Medicine Examination-1994", Occupational and Environmental Medicine Report, 1995, 9(8):66-67.

"Case from the Aerospace Medicine Residents' Teaching File #62: An aviator with lead poisoning and peripheral neuropathy", Aviat. Space Environ. Med., 1995, 66(11):1107-1109.

"Case from the Aerospace Medicine Residents' Teaching File #63: Three aviators presenting with hypoxic symptoms as manifestation of underlying systemic diseases", Aviat. Space Environ. Med., 1995, 66(12):1215-1217.

Awaiting Publication:

"Occupational Exposure to Clostridium tetanus and Tetanus Toxin", Mil. Med., 199 .

Books, Chapters and Review Articles

"Seasonal Protection through Voluntary Programs", Occupational Health and Safety, 50 (11): 27-30, 1981

"You're the Flight Surgeon", Aviation, Space and Environmental Medicine, May 53 (5): 512, 1982

"Chapter 25: Space Medicine" in AFM 160-1, Aerospace Medicine, December 1983

Asthma Self-Assessment Program (Contributor), Aviation, Space and Environmental Medicine, 55 (2): 156, 1984
"Heart Facts", Professional Pilot, Oct 1987, pg 12.

"Heart Facts Part 2", Professional Pilot, Dec 1987, pg 32.

"Aircraft Accident Search and Rescue (SAR) Operations", Aeromedical & Training Digest, Vol. 2, No. 3, July 1988

"Chapter 24: Missile Medicine" in AFM 161-18, Flight Surgeon's Guide, JA Bishop, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Jan 1989.

"Chapter 25: Space Medicine" (Co-author) in AFM 161-18, Flight Surgeon's Guide, JA Bishop, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Jan 1989.

Study Guide for Preventive Medicine Certification 1989, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1989.

"TOP KNIFE #24: Toxicologic and Radiation Hazards of Fighter Aviation Operations" (videotape and notetaking guide), from TOP KNIFE video CME series, National Guard Bureau, Washington, D.C., Sept 1989.

"Toxicology in Aviation", Aeromedical & Training Digest, Vol 4, Issue 1, January, 1990, Pg 43-47.

Study Guide for Preventive Medicine Certification 1990, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1990.

"Flight Surgeons", MILITARY MEDICINE, 155(12):A4, 1990

"Book Review: Journey into Space", ASEM, 1991, 62(2):182.
"Book Review: Aviation Medicine", ASEM, 1991, 62(2):182.

Study Guide for Preventive Medicine Certification 1991, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1991.

"Chapter 24: Missile Medicine" in AFM 161-18, Flight Surgeon's Guide, RC Whitton, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Dec 1991.

"Chapter 25: Space Medicine" (Co-author) in AFM 161-18, Flight Surgeon's Guide, RC Whitton, Ed, Department of Aerospace Medicine, Brooks AFB, TX, Dec 1991.

Study Guide for Preventive Medicine Certification 1992, (Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM Health Information, Boston, MA, 1992.

Study Guide for Preventive Medicine Certfication 1993,
(Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM
Health Information, Boston, MA, 1993.

Book Review: Space Medicine & Physiology, ASEM, 65(6):583, 1994.

Book Review: Chemical Exposures, ASEM, 65(6):584, 1994.

Study Guide for Preventive Medicine Certification 1994,
(Co-Author with Nick A. Vlachos & Leland G. Wessel) OEM
Health Information, Boston, MA, 1994.

Book Review: Phantom Risk-Scientific Inference and the Law, ASEM, 65(7):677, 1994.

Repetitive Use Injury: Diagnosis, Treatment and Prevention, Kansas Medicine, 95(9):1193-4, 1994.

Book Review: Operation Crossroads, ASEM, 66(2):182, 1995.

Book Review: Textbook of Military Medicine-Occupational Health, ASEM, 66(2):182, 1995.

Medical Standards, AOPA Pilot, 38(2):24-25, 1995.

Study Guide for Preventive Medicine Certification 1995,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1995.

Book Review: The Preastronauts, ASEM, 66(11):1115, 1995.

Book Review: Dark Sun, the Making of the Hydrogen Bomb, ASEM, 67(2):188, 1996.

Book Review: Hunter's Occupational Medicine, 8th Edition, ASEM, 67(2):187, 1996.

Chapter 35: Aviation and the Environment. *In* **Fundamentals of Aerospace Medicine, 2nd Edition,** Edited by RL DeHart, Lea & Febiger, Philadelphia, 1996.

Study Guide for Preventive Medicine Certification 1996,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1996.

Hepatitis A: Diagnosis, Treatment and Prevention, Kansas Medicine, 97(1):14-5, 1996.

Book Review: Occupational Medicine in Aviation, ASEM, 67(7):665, 1996.

Fatigue and Flight, PLANE Safe, 1(3):3-5, 1996.

Book Review: Toxic Exposures, ASEM, 68(2):165 ,1997.

Book Review: Science, Nonscience and Nonsense, ASEM, 67(2):165 ,1997.

Book Review: Science, Nonscience and Nonsense, ASEM, 67(2):165-6,1997.

Study Guide for Preventive Medicine Certification 1997,
(Co-Author with Nick A. Vlachos & C. Patrick Chalk) OEM
Health Information, Beverly, MA, 1997.

Book Review: Pilot Judgement and Resource Management, ASEM, 68(6);548, 1997

Book Review: Toxicology, ASEM, 68(6):548,1997.

Book Review: Why Buildings Fall Down, ASEM, 68(6):548, 1997.

Awaiting Publication:

Occupational Medicine and Physical Therapy: Statistics of Self Referral, In "New England Journal of Medicine".

Book Review: Dead Men Do Tell Tales, ASEM, 68(): ,1997.

Book Review: The Man Who Grew Two Breasts, ASEM, 68(): ,1997.

Book Review: Bad Blood, ASEM, 68(), 1997

Book Review: The Nazi Doctors, ASEM, 68(), 1997

Book Review: Issues in International Occupational and Environmental Medicine, ASEM, 68(), 1997

Abstracts and Presentations

"Unilateral Hearing Loss in USAF Aviators", Aerospace Medical Association 53rd Annual Scientific Meeting, Miami Beach, FL, May 1982

"Space Medicine, An Overview" (Keynote Address) Operational Aeromedical Problems Course, Brooks AFB January 1983

"Auditory Effects of Antiorthostic Simulation of Weightlessness", Asthma Annual Scientific Meeting, May 1984

"Segmental Hemodynamic Responses to Antiorthostatic Simulation of Weightlessness" (Co-author), Asthma Annual Scientific Meeting, May 1984

"Changes in Calf Volume due to Antiorthostatic Simulation of Weightlessness" (Co-author), Asthma Annual Scientific Meeting, May 1984

"Medical Support of Space Shuttle Operations at Vandenberg Launch Site", Operational Aeromedical Problems 1985, Brooks AFB, Jan 85 and Strategic Air Command Chiefs of Aerospace Medicine Conference, Offutt AFB, May 85.

"Human Factors in Military Space", AIAA Military Space Shuttle Operations Meeting (Secret) - May 28, 1986

"Medical Aspects of a Titan Missile Mishap" presented at Asthma Annual Scientfic Meeting, May 13, 1987

"Human Factors in Accident Investigation", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 2, 1988.

"Toxicological Effects of Propellants and Fuels in Aircraft Accidents", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 2, 1988.

"Aircraft Accident Search and Rescue Operations", AMTI Sixth Annual Conference on Aviation Physiology and Training, Environmental Techtonics, Southampton, PA, May 3, 1988 and Aerospace Medicine Primary, Oct 24, 1988, March 15, 1989, August 17, 1989, April 11, 1990, August 31, 1990.

"Beryllium Rocket Fuels-a Physician's View", Joint Army-Navy-NASA-Air Force Safety & Environmental Protection Subcommittee Meeting (Secret), Naval Postgraduate School, Monterrey, CA, May 24, 1988.

"Comparing Air Force and Navy Aerospace Medicine", Association of Military Osteopathic Physicians and Surgeons 7th National Conference. San Diego, CA. March 30, 1989.

"Space Medicine - Where Do We Go From Here?" NASA Aerospace Safety Advisory Panel. Dallas, Texas, April 5, 1989.

"Leaving the Cradle", St. Louis Academy of Science and the St. Louis Science Foundation, St. Louis, Mo, July 20, 1989.

"Human Factors in Aircraft Accidents", 36th Annual Flying Physicians Association Scientific Meeting, Vancouver BC, Canada, August 6, 1990.

"What is Acceptable Risk (of Decompression Sickness)?", Hypobaric Decompression Sickness Workshop, Brooks AFB, October 18, 1990. Proceedings published 1994, by Aerospace Medical Association.

"Aeromedical Support of Combat Operations", Aerospace Medical Association 62nd Annual Scientific Meeting, Cincinnati, Ohio, May 9, 1991.

"Human Factors in Flight", Grand Round-University of Utah, Salt Lake City, UT, Nov. 9, 1991.

"USAF Aeromedical Problems During OPERATIONS DESERT SHIELD/STORM", Aerospace Medical Association 63rd Annual Scientific Meeting, Miami, FL, May 14, 1992.

"Flight Surgeon Self-Assessment Review", Panel Member,
Aerospace Medical Association 63rd Annual Scientific Meeting, Miami, FL, May 14, 1992.

"The Medical Provider's Role in Workers' Compensation", Workers' Compensation Seminar, Kansas City Professional Education Institute, Kansas City, MO, May 14, 1993.

"How to Manage New Industrial Illnesses: Carpal Tunnel Syndrome, Stress, Trauma and Other Maladies of the 90's", Workers' Comp Update 1993, Council on Education in Management, Walnut Creek, CA, Sept 15, 1993.

"Methods by Which Occupational and Environmental Medicine Puts Workers Back on the Job", Company Productivity and Return to Work Programs, Menninger Return to Work Center, Kansas City, MO, Oct 29, 1993.

"Role of the Medical Review Officer", Company Productivity and Return to Work Programs, Menninger Return to Work Center, Kansas City, MO, Oct 29, 1993 and Columbia, MO, March 6, 1994, Employee Assistance Program Center, Kansas City, MO, May 25, 1995.

"The Medical Provider's Role in Workers' Compensation" at KCPEI Workers' Compensation Seminar, Kansas City, Mo, May 14, 1994. and Menninger Return to Work Seminar, Columbia, MO, March 6, 1994.

"Aviation and Transportation Law: Drugs and Alcohol", Missouri Bar Association Annual Meeting, Kansas City, MO, Sept 22, 1994.

"Environmental Emergencies", Great Plains College of Occupational and Environmental Medicine, Kansas City, Mo, Sept 22, 1994.

"Toxicology", Carroll P. Hungate Postgraduate Seminar on Occupational and Environmental Health, Great Plains College of Occupational and Environmental Medicine, Overland Park, KS, March 11, 1995.

"Preparing for the Occupational Medicine Board Examination", lecture & seminar director, American Occupational Health Conference, Las Vegas, NV, May 1, 1995.

"Developing and Managing a Medical Surveillance Program", American Industrial Hygiene Conference, Kansas City, MO, May 20, 1995.

"Travel Medicine", Grand Rounds, Trinity Lutheran Hospital, Kansas City, MO, June 19, 1996; Medicine Grand Rounds, St. Luke's Hospital, Kansas City, MO, July 5, 1996.

"Crash Survival, Protection and Investigation", Physics and Biology Colloquium, Benedictine College, Atchison, KS, February 24, 1997.

"Occupational Health for Travelers", Carroll P. Hungate Postgraduate Seminar on Occupational and Environmental Health, Great Plains College of Occupational and Environmental Medicine, Overland Park, KS, March 8, 1997.

"Medical Aspects of Air Travel", with RB Rayman and DP Millett, Aerospace Medical Association Annual Scientific Meeting, Chicago IL, May 13. 1997.

"Cabin Air Quality", Aerospace Medical Association Annual Scientific Meeting, Chicago IL, May 13. 1997.

Lectures

"Physiology of Manned Space Flight" lectures delivered at USAF School of Aerospace Medicine to medical student classes, Jul and Aug 1982, June and July 1983, June and July 1984 and June and July 1985

"Rocket Fuels and Chemical Hazards" lecture delivered to Santa Barbara Co Paramedics, June 14, 1985, Oct 17, 1985, and February 21, 1986 and USAF Hospital Vandenberg Professional Staff - July 2,1985 and Lompoc Community Hospital Professional Staff, June 30,1986

"Acquired Immune Deficiency Syndrome" lecture delivered to USAF Hospital Vandenberg Professional Staff, Sept 30, 1985 and Dental Staff Oct 2, 1985

"Space Medicine - An Update" SAC Hospital Commanders' Conference, Offutt AFB, Oct 1985

"Medical Aspects of Manned Space Flight", University of Kansas, May 16, 1986 and to Health Profession Scholarship Students at USAFSAM, Brooks AFB, TX on 2 July and 21 July 1986, 22 June & 12 July 1987, 24 June & 27 July 89, 27 June & 26 July 1991 and to Advanced Aeromedical Course for Allied Medical Officers on 9 Feb 1987, 20 & 22 Jan 88, 19 & 20 Jan 89, 17 & 18 Jan 1990, 23 & 24 Jan 1991, 27 & 28 Jan 1992, 27 Jan 1993 and to Residents in Aerospace Medicine, 30 Nov 87 , 4 Feb 89, 2 April 90, 17 & 18 Dec 1990, 28 & 30 Aug 91, 27 Aug 93, 2 Aug 94 and to Aerospace Medicine Primary Course, 13 Nov 1987, 10 Apr 1988, 1 Sept 1988, 8 Nov 1989, 19 April 1990, 23 August 1990, 19 April 1991, 8 Nov 91, 7 April 92 and Grand Rounds, Geisinger Medical Center, Danville, PA on 7 Feb 1988 and Luzerne County Medical Society, Wilkes-Barre, PA on 8 Feb 1989 and Oregon Institute of Technology, Klamath Falls, OR on 27 March 1990 and Utah Surgical Society, Salt

Lake City, UT, 5 Nov 1991.

"Hazardous Materials and the Space Shuttle Program", 4th Annual Pre-Hospital Care Conference, Santa Barbara, CA, June 23, 1986.

"Missile Medicine", Aerospace Medicine Primary Course, Brooks AFB, TX, July 22, 1986, Oct 18, 1986, Feb 8, 1987, Aug 21, 1987, Oct 5, 1987, March 17, 1988, July 27, 1988, Oct 13, 1988, March 20, 1989, Aug 1, 1989, Feb 14, 1990, August 1, 1990, March 21, 1991, Aug 15, 1991, Oct 15, 1991 and March 12, 92.

"Sexually Transmitted Diseases and Military Preventive Medicine", to Aerospace Medicine Primary Course, Brooks AFB, 6 Aug 1987, Oct 15, 1987, March 11, 1988, 5 Aug, 1988, Oct 11, 1988, March 20, 1989, July 27, 1989, Oct 6, 1989, Feb 15, 1990, August 2, 1990, Oct 4, 1990, March 13, 1991, August 16, 1991, Oct 4, 1991 and March 27, 1992.

"Role of the Flight Surgeon" (lecture) presented to AMP, Brooks AFB, Oct 2, 1987, March 7, 1988, 25 July 88, 4 Oct 88, 4 Mar 89, 24 Jul 89, 3 Oct 89, 12 Feb 90, 30 July 90, 2 Oct 90, 11 Mar 91, 28 Jul 91, 3 Oct 91, 9 Mar 92; Bioenvironmental Engineering Course, 2 Feb 89, 22 Aug 89, 26 Jan 90, 22 August 90, 1 Feb 91, 21 Aug 91, 7 Feb 92; Environmental Health Officer's Course, 5 July 89, 3 Oct 89, 26 Jan 90; Health Professions Scholarship Program, 5 June & 3 July 90, 4 June & 1 July 91.

"Introduction to Toxicology" (lecture) presented to Aerospace Medicine Primary Course, Brooks Air Force Base, Oct 6, 1987, March 10, 1988, 2 Aug 88, 26 Jul 89, 16 Feb 90, 2 Aug 90, 10 Oct 90, 15 Mar 91, 20 Aug 91, 8 Oct 91, 31 Mar 92, 1 Nov 93, 16 Mar 94, 16 Aug 94, 28 Oct 94, 18 Mar 95, 16 Aug 95, 20 Oct 95, 14 Aug 96, 16 Oct 96, 2 Apr 97.

"Fuels and Propellants" (lecture) presented to AMP, Brooks AFB, Oct 5, 1987, March 17, 1988, 28 July 88, 13 Oct 88, March 20, 1989, Aug 1, 1989, Feb 16, 1990, August 2, 1990, Oct 10, 1990, March 21, 1991, August 20, 1991, Oct 8, 1991, March 12, 1992, November 1, 1993, March 16, 1994, Aug 16, 1994, Oct 28, 1994, March 18, 1995, August 14, 1995, Oct 20, 1995, Aug 14, 1996, Oct 16, 1996, April 2, 1997 and Wright State University on Nov 18, 1988, University of Texas School of Public Health at Houston on April 10, 1989 and April 16, 1990, AAMIMO on April 18, 1988, Jan 19, 1989 Jan 18, 1990 and April 1, 1991 and RAM on Sept 14, 1989.

"Human Factors in Aircraft Accident Prevention", Aerospace Medicine Supervisor Course 1988, Brooks AFB, May 27, 1988 and Aerospace Medicine Primary Course, 10 Aug 88, 19 Oct 88, March 27, 1989, August 7, 1989, Oct 18, 1989, April 4, 1990, August 10, 1990, Oct 16, 1990, April 3, 1991, August 1, 1991, Oct 17, 1991, March 13, 1992 and Embry Riddle University Extension, Randolph AFB Human Factors

Course, Oct 11, 1989, August 22, 1990 and Aerospace Physiologists Course, 18 July 1989.

"Flight Surgeon Operations" (lecture), Battlefield Medical Operations Course, Brooks AFB, July 12, 1989 and Aerospace Physiologists course, July 18, 1989.

"Adjuncts to Airway and Ventillation" (lecture), Advanced Cardiac Life Support Course, Brooks AFB, July 19, 1989.

"Industrial Operations" (lecture) Environmental Health Officers Course, July 5, 1989; Aerospace Medicine Primary Course July 26, 1989, Oct 5, 1989, Feb 14, 1990, August 3, 1990, Oct 10, 1990, March 15, 1991, August 20, 1991, Oct 8, 1991, March 31, 1992 and Flight Surgeon Course, Defense and Civil Institute of Environmental Medicine, Toronto, Ontario, Nov 6, 1989.

"Medical Terminology" (lecture) Bioenvironmental Engineers Course, August 23, 1989.

"Human Physiology for Engineers" (8 hours of lecture) Bioenvironmental Engineers Course, August 24 & 25, 1989, Jan 26 & 27, 1990, August 23 & 24, 1990, Feb 4 & 5, 1991, August 22 & 23, 1991.

"Medical Readiness and Disaster Response" (lecture) Environmental Health Officers Course, Sept 14, 1989.

"Mishap Investigation" (lecture), Advanced Medical Standards Course, Sept 19, 1989.

"Crash Survival" (lecture), AMP Course, Oct 18, 1989, April 4, August 10, 1990, April 5, 1991, August 1, 1991, October 17, 1991, March 13, 1992.

"Myocardial Infarction" (lecture), Advanced Cardiac Life Support Course, Brooks AFB, Jan 17, 1990.

"Senior Flight Surgeon Examination Review Seminar", Operational Aeromedical Problems Course, Brooks AFB, Jan 24, 1990.

"Disaster Management Seminar", Operational Aeromedical Problems Course, Jan 25, 1990.

"Aeromedical Problems of Tactical Air Operations", Health Professions Scholarship Program, June 6 & July 5, 1990, June 5 & July 3, 1991.

"Aeromedical Problems of Strategic and Airlift Operations", Health Professions

Scholarship Program, June 7 & July 5, 1990, June 5 & July 3, 1991.

"Aeromedical Problems of Training Programs and Reconaissance Operations", Health Professions Scholarship Program, June 8 & July 6, 1990, June 6 & July 24, 1991.

"Monitoring and Dysrhythmias" Advanced Cardiac Life Support Course, Brooks AFB, July 9, 1990.

"Preparing for the Senior Flight Surgeons' Exam", Association of Military Surgeons of the United States 97th Annual Meeting, Nashville, Tennessee, November 15, 1990.

"Impact Acceleration", Aerospace Physiologist Course, Brooks AFB, July 9, 1991, University of Kansas Department of Preventive Medicine Grand Rounds, Feb. 20, 1992.

"Disaster Planning, Management and Medical Response", Lancaster County Civil Defense/Airshow Planning, Lincoln, Nebraska, August 27, 1991.

"Aeromedical Medicine", Grand Round at University of Utah School of Medicine, Salt Lake City Utah, Nov. 6, 1991.

"Human Factors in Air Force Helicopter Mishaps", 1st Coast Guard Aeromedical Problems Course, CGS Mobile, Alabama, Feb 28, 1992.

"Space Shuttle Contingency Operations", 1st Coast Guard Aeromedical Problems Course, CGS Mobile, Alabama, Feb 28, 1992.

"History of Aerospace Medicine", Residency in Aerospace Medicine, Brooks AFB, TX, July 1, 1992 and Advanced Aerospace Medicine for International Medical Officers, Brooks AFB, TX, Jan 26, 1993.

"Occupational Arthritis and Rheumatologic Problems", The Rheumatology Center, Kansas City, MO, Jan 16, 1993.

"AIDS and Buisness: Impact on the Workplace" St. Luke's Outreach, Kansas City, MO, May 12 & July 29, 1993.

"Basic Statistics", OB-GYN Grand Rounds, St. Luke's Hospital, Kansas City, MO, Sept 24, 1993.

"Drugs and Alcohol", Aviation Medical Seminar/Federal Aviation Administration, Chicago, IL, June 25, 1994, May 11, 1995, Memphis, TN, Aug 27, 1995.

"Aviation Toxicology", Aviation Medical Seminar/Federal Aviation Administration,

Chicago, IL, June 26, 1994, Anaheim, CA, May 12, 1995, Memphis, TN, Aug 27, 1995.

"Transport by Air of the Ill and Injured", Chicago, IL, June 26, 1994, Anaheim, CA, May 12, 1995, Memphis, TN, Aug 27, 1995.

"Aviation Physiology", Basic Aviation Medical Examiners Seminar, Civil Aeromedical Institute, Mike Monroney Aeronautical Center, Oklahoma City, OK, Nov 14, 1994, April 4, 1995, Sept 16, 1996, June 2, 1997.

"Biomedical Factors in Accident Prevention: Part I-Altitude Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 4, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part II-Acceleration Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 4, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part III-Perception in Flight", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 21, 1995, Sept 28, 1995, Jan 24, 1996, June 5, 1996, Oct 1, 1996, Jan 8, 1997, April 8, 1997.

"Biomedical Factors in Accident Prevention: Part IV-Environmental Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 9, 1997, April 9, 1997.

"Biomedical Factors in Accident Prevention: Part V-Self-Imposed Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 9, 1997, April 9, 1997.

"Biomedical Factors in Accident Prevention: Part VI-Drugs, Alcohol and Health Issues", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, June 22, 1995, Sept 29, 1995, Jan 25, 1996, June 5, 1996, Oct 2, 1996, Jan 8, 1997, April 9, 1997.

"Human Factors-Theme and Objectives" Aviation Medical Seminar/Federal Aviation Administration: Tampa, FL, Dec 2, 1995; Denver CO, Mar 8, 1996; Minneapolis, MN, Aug 3, 1996; Dallas, TX, Oct 18, 1996 Washington, DC, Apr 4, 1997.

"Human Performance" Aviation Medical Seminar/Federal Aviation Administration: Tampa, FL, Dec 3, 1995; Denver, CO, Mar 9, 1996; Minneapolis, MN, Aug 4, 1996: Dallas, TX, Oct 18, 1996, Washington, DC, Apr 5, 1997.

"Crashworthiness/Survival" Aviation Medical Seminar/
Federal Aviation Administration: Tampa, FL, Dec 3, 1995; Denver, CO, Mar 9, 1996; Minneapolis, MN, Aug 4, 1996: Dallas, TX, Oct 18, 1996, Washington, DC, Apr 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part I-Altitude Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part II-Acceleration Physiology", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part III-Perception in Flight", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 11, 1995, June 4, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part IV-Environmental Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part V-Self-Imposed Stress", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part VI-Drugs, Alcohol and Health Issues", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

"Biomedical Factors in Aircraft Accident Investigation: Part VII-Medical Forsenics and the Crash Scene-Hazards seen and unseen.", Aviation Safety Program of the Institute of Safety and Systems Management, University of Southern California, Los Angeles, CA, Dec 12, 1995, June 5, 1997.

# Attachment 6

## Resume, Medical Monitor

Curriculum Vitae - Dr. Mary E. Brothers

MARY ELIZABETH (CENTNER) BROTHERS, M.D., FACOEM, FAADEP

PII Redacted

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**Office Address:** dba, **Midwest Occupational Medicine®**, Owner
3037 Main Street, Suite 201
Kansas City, Missouri 64108-3323

**Office Phone/FAX:** (816) 561-3480 (answering machine after hours)
(816) 561-4043 - Fax

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**Education:** Bishop Miege High School, Mission, Kansas; College Prep Program, 1963-1967
Saint Mary College, Leavenworth, Kansas; BA in Biology, with Honors, 1971

**Medical Education:**

**1971-1974** University of Kansas School of Medicine, Kansas City, Kansas
M.D. in September, 1974; 3 year curriculum ('74 B)

**Post-Graduate Medical Education:**

Sept - Dec, 1974 KU: electives in emergency medicine, radiology and anesthesiology

Jan - June, 1975 Externship in General Surgery and Orthopedics, Eisenhower VA Medical Center, Leavenworth, Kansas

June '95 - July 28, 1979 Four year Residency in General Surgery, Eisenhower VA Medical Center; Chief Resident 1978-1979. (Former Program Chief - Mary P. McAnaw, MD, FACS

1982-1984 "Mini" Residency in Occupational Medicine, University of Cincinnati, Cincinnati, Ohio; (144 hours); Sidney Lerner, MD, FACOM, Director (deceased)

September 1994 Began graduate program for MPH, University of Kansas

Medical Center. 1st year, 1994-1995 (epidemiology, biostatistics, public health policy/admin., Environmental health). Anticipate completion of course work in Spring of 1998 and degree by Fall, 1999.

**Medical Licensure:**

| | |
|---|---|
| **04/18/77** | National Board of Medical Examiners |
| **12/07/77** | **Kansas** # 017191 (currently "exempt" status) |
| **04/13/79** | **Missouri** # MD R9252 |

**Medical Boards/Fellowship:**

| | |
|---|---|
| 05/05/87 | **Fellow,** ACOEM (formerly American Occupational Medical Association.) - **FACOEM** |
| Nov 1989 | **Fellow,** American Academy of Disability Evaluating Physicians - **FAADEP** |
| Feb 1997 | **Board Certified, Preventive Medicine/Occupational Medicine** 01/20/97 - examinee # 23833 |

**Summary of Medical Practice:**

| | |
|---|---|
| 07/31/79 - Present | Entered into practice of industrial injury with Paul J. Centner, MD, FACS, (father) at 2727 Main Street, Kansas City, Missouri. [Part-time until 1983, then full-time] |

**In addition:**

| | |
|---|---|
| 1980-07/15/81 | Medical Director for Midwest Grain, Inc., (formerly Midwest Solvents), Atchison, Kansas. Helped to establish company wellness and Occ Med programs. On courtesy staff, Atchison Community Hospital from 12/19/79-01/21/82. |
| 05/80-06/81 | Part-time staff and instructor in general surgery, Eisenhower VAMC, Leavenworth, Kansas. |
| 07/82-03/83 | Assisted as locum tenens in Occupational Medicine for Dr. James Hall, Landmark Medical Clinic, Kansas City, Missouri. On staff at Liberty Hospital, Liberty, Missouri during this period. |

| | |
|---|---|
| 1988-1992 | Purchased practice from Dr. Centner; practice incorporates Occupational Medicine and Disability Evaluation; practice name changed to **Midwest Occupational Medicine®** 1991-1992, at time of relocation to Union Hill Commons. |

**Hospital Staff Appointments:**

| | |
|---|---|
| 1979-1989 | St. Mary Hospital, Kansas City, Missouri (ceased to exist 1989 at purchase by Trinity Lutheran); active staff in general surgery. |
| 05/80-06/81 | Eisenhower VA, Leavenworth, Kansas, part-time staff surgeon. |
| 12/79-01/82 | Atchison Community Hospital, courtesy staff in general surgery. |
| 07/82-03/83 | Liberty Hospital, Liberty, Missouri, courtesy staff. |
| 1989-present | Trinity Lutheran Hospital, Kansas City, Missouri; active staff, department of Family Practice, sub-section of Occupational Medicine. |
| 1989-06/25/97 | Baptist Medical Center, Kansas City, Missouri. Adjunct staff in General Surgery. Resigned, 06/25/97. |
| 1992-1996 | Menorah Medical Center, Kansas City, Missouri; active staff, department of Family Practice/Section of Occupational Medicine. (Resigned when Hospital moved to Kansas, 1996.) |
| 1997 | North Kansas City Hospital - application pending. |

**Professional Memberships/Offices Held:**

**American College of Occupational/Environmental Medicine:**
**(Great Plains COEM - local chapter)**

| | |
|---|---|
| 1979-present | Membership |
| 1981-1982 | Secretary-treasurer |
| 1982-1983 | Second Vice-president |
| 1983-1984 | First Vice-president |
| 1984-1985 | President-elect |
| 1985-1986 | President |

| | |
|---|---|
| 1986-1987 | Past-president |
| 1989-1992 | Delegate to ACOEM |
| 1992-1995 | Second term as delegate to ACOEM |
| 1996-1999 | Alternate delegate to ACOEM |
| 1987-1991 | Member, Committee on Ethical Practice |
| 1990-1992 | Editor, Newsletter of the Section on Work Fitness/Disability Evaluation |
| 1992 | Alternate for election to three year term on the ACOEM Board of Directors |

**American Academy of Occupational Medicine - elected a member 11/87**

**American Medical Women's Association**

| | |
|---|---|
| Present | Life member |
| 1984-1986 | Secretary-treasurer, Kansas City |
| 1986-1988 | Vice-president and President-elect |
| 1988-1990 | President |
| 1985 | Faculty, Regional conference on Women in Medicine, Kansas City, Missouri |
| 1989 | First Legislative Conference on Politics of Women's Medicine, Washington, D.C. |

**American Medical Association**

| | |
|---|---|
| 1979-present | Member except for Jan-August 1992, due to practice relocation expenses. Rejoined August, 1992. |

**Metropolitan Medical Society of Kansas City (formerly Jackson County Medical Society)**

| | |
|---|---|
| 1980-present | Member |
| 1984 | Election Committee Chairperson |
| 1985-1988 | Public Relations Committee; Chairperson 1986-1988 (concerned with public complaints about physicians) |

| | |
|---|---|
| 1988-1990 | Medico-legal Liaison Committee Chairperson (dealt with liaison between physicians and bar association) |
| 11/17/88 | Attended local leadership conference, Kansas City, Missouri |

**Missouri State Medical Society**

| | |
|---|---|
| 1980-1991 | Member |

**Kansas State Medical Society**

| | |
|---|---|
| 1980-1982 | Member during practice in Kansas |

**Kansas City Surgical Society**

| | |
|---|---|
| 09/15/83-1991 | Member; resigned end of 1991 to devote full-time practice to Occupational Medicine CME activity |

**Teaching Appointments:**

| | |
|---|---|
| Spring, 1975 | Faculty, Saint Mary College, Leavenworth, Kansas; Histology and Micro technique. |
| 1980-06/10/81 | Part-time instructor in General Surgery, Eisenhower VA Medical Center. |
| 1987-present | Preceptor in Occupational Medicine; Trinity Lutheran Hospital Family Medicine Residency (formerly St. Mary's Hospital Family Medicine.) Scott Thompson, MD, Director. |

**Directorships:**

| | |
|---|---|
| Late 1980's | Co-Director, (with Dr. Centner), SHARE Program for Occupational Health Nursing, St. Mary's Hospital, Kansas City, Missouri. |
| 10/1992-12/31/93 | Co-Director, MedWorks Managed Occupational Health Network, Menorah Medical Center, Kansas City, Missouri. |
| 1994-1995 | MedWorks Director/Advisor; Mariner Rehabilitation (formerly Pinnacle Rehabilitation). |

**Curriculum Vitae - Dr. Mary E. Brothers**

**Consultant:**

| | |
|---|---|
| 10/01/92-10/1995 | Contract Occupational Physician Consultant, Federal Occupational Health-US Public Health Service, Region VII. |
| Fall, 1997 | Pending application to resume consulting position for Region VII, Public Health Service. |

**Hospital Committee Work:**

| | |
|---|---|
| St. Mary's Hospital | By-laws<br>Medical Records & Audit Chairperson, 1983-1986<br>Tissue Sub-committee, 1984-1988<br>ER/Outpatient Committee<br>Developed the Ambulatory Surgery Unit with Sr. Susan Scholl, SSM |
| Trinity Lutheran Hospital | By-laws, 1989-present<br>ER/Outpatient Committee, 1989-1996<br>Physician's Health Committee, 1997-present |

**Lectures:**

| | |
|---|---|
| 09/27-29/75 | Chairperson, panel on ER Medical Care, AMWA Regional Conference, Kansas City, Missouri |
| 07/09/80 | High Pressure Injection Injury; Leavenworth CME circuit Eisenhower VAMC |
| 07/27/89 & 10/26/89 | Two-part lecture on "Permanent Partial Disability Determination Within the Workers' Compensation System", for staff of OHS, Dr. Ed Kinports, Director |
| 11/02/89 | Rating Workers' Compensation Injuries - the Physician's Role; Fourth Annual Missouri Work Comp Seminar (Mo. Bar/UMKC Law School), Allis Plaza, Kansas City |
| 04/30/90 | Confidentiality of Company Medical Records-The Private Practice Experience; ACOEM Post-grad seminar in Ethics; American Occupational Health Conference, Houston, Texas |
| 04/28/91 | Committing Truth - The Occupational Physician on the Firing Line; ACOEM Post-grad seminar in Ethics; |

| | |
|---|---|
| | American Occupational Health Conference, San Francisco, California |
| 07/28/92 | Lecture on Disability Evaluation and Workers' Compensation; Physical therapy-orthopedic study group, Trinity Lutheran Hospital |
| 03/10/94 | Organophosphate Pesticide Poisoning, Kansas City, E.P.A. |
| 02/01/95 | Cumulative Trauma Disorders, Praxair Surface Technologies, Inc., Kansas City, Missouri |

**Publications:**

| | |
|---|---|
| 1971 | (Unpublished) Honors research paper on Chemoattractants in Fasciola hepatica and snail hosts; Saint Mary College, Leavenworth, Kansas |
| 1971 | An Analysis of Particulate Matter in the Lungs and Air Sacs of Columba livia; section of NSF-SOS Report on "Air and Water Pollution in Atchison, Kansas". Benedictine College Research Grant |
| 1990 | "You're Just the Company Doctor"; issue of the Kansas City Health Journal, in conjunction with Baptist Medical Center |

**Awards:**

| | |
|---|---|
| 1977; 1978 | Outstanding Young Women of America |

**Political Experience:**

See addendum "A"

**Continuing Medical Education:**

| | |
|---|---|
| 07/16/79-present | Physician's Recognition Award of the AMA |

See Addendum "B"

**Other:**

| | |
|---|---|
| 07/13/80-present | Aviation Medical Examiner for the FAA; completed the |

Senior Examiner's Seminar, Oklahoma City, in October, 1985.

August, 1990 - update seminar, Kansas City, Missouri

February, 1995 - update seminar, Savannah, Georgia

Fall, 1993 - Present

Appointed to serve as Committee member, Mid-America Coalition on Health Care Committee on Workers' Compensation, Kansas City, Missouri; background work on Robert Wood Johnson Grant applications project. Various presentations to KCMO business community, 1995-1996.

**Personal Information:**

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**Personal Memberships**

American Horticulture Society
The Audubon Society
The Nature Conservancy
Nash Car Club of America/Historic Trails Region
Smithsonian Institution

**Curriculum Vitae - Dr. Mary E. Brothers**

**Addendum "A" - Political Experience**

In August of 1980, after returning to the general surgical staff of the Eisenhower VA Medical Center on a part-time basis, I became aware of the existence of a questionable drug research study then ongoing in the Center. The study was being performed by the former Chief of Psychiatry (now deceased), and my opinion of it was requested by the former Chief of Surgery, Mary P. McAnaw, MD, FACS.

After examining a portion of the study records and research memos I was concerned that there was evidence of impropriety and I subsequently established contact with the VA's Inspector General to request a further investigation. I was also requesting an investigation by the IG into the proposed and ongoing attempt to remove the Chief of Surgery from her position at the Leavenworth VAMC. The two of us, in the company of a former staff psychologist, undertook the role of "whistle-blowers" to effect a complete investigation.

As a result of our combined activities in this matter the former Chief of Surgery was demoted and transferred to her present position at the VAMC, Kansas City, Missouri, where she has advanced to the position of Assistant Chief of Surgery. Both she and I sued the VA, and the Center Chief of Staff, and (former) Center Director in the Federal Court in Topeka, Kansas. Dr. McAnaw ultimately lost her suit in her position as a full-time federal employee. My suit was ongoing between 1982 and 1989; my contention was that I had been terminated from part-time employment and denied a full-time staff surgeon position because of retaliation for "whistle-blowing". In January of 1989, a jury in Topeka awarded over $ 90,000 in wage loss and $ 100,000 in punitive damages against the VA in my suit. However the suit had been filed and argued using a "Biven's" defense; the damage awards were a precedent at the time and were subsequently overturned by the U.S. District Appeals Court, Denver, Colorado, in October 1989 and remanded to the Office of Special Counsel (OSC). The case and verdict were under scrutiny by the attorneys of the Government Accountability project (GAP) in Washington through 1991.

During the "whistle-blower" period I was involved with the local staffs of both Senators Dole and Kassebaum, and of former Kansas Representative Jim Jeffries. The FDA ultimately supported all of the allegations, and also identified improprieties in a prior drug study by the same investigator, resulting in his signed agreement to do no further drug research. The situation received wide coverage in the media, including the Kansas City Times, Federal Times, WNEV-TV, Boston, and the case was featured in the book "The Whistleblowers" by Myron & Penina Glazer (Basic Books, NY, c. 1989). In May of 1989 I lectured to Dr. Glazer's sociology class at Smith College on the case.

As result of this case I participated in Representative Pat Schroeder's House Hearings on the OSC in 1985 and testified for Senators Pryor, Levin & Grassley in July

1987 at hearings for the "Whistleblower Protection Act". In November of 1991 I testified at oversight hearings on whistleblowing in the VA for Representative Ted Weiss, and appeared live on "Crier and Company", via Atlanta.

## Addendum "B" - Continuing Medical Education:

### Occupational Medicine:

| | |
|---|---|
| 1980-present | Attendance at local meetings of Great Plains College of Occupational & Environmental Medicine, and the annual "Hungate" Seminar. In 1986, I served as the Hungate Conference Chairperson.<br>Hungate Planning Committee Member, 1996; 1997 |
| April, 1985 | AOMA - American Occupational Health Conference, Kansas City. Post-graduate planning committee for this AOHC. |
| 4/27-05/01/86 | AOHC; Denver, Colorado |
| 04/23-29/87 | AOHC; New Orleans, Louisiana |
| 10/24-28/87 | Fall State of the Art Conference, San Antonio, Texas. AOMA and Academy merge to form the ACOM. |
| 04/27-05/02/88 | AOHC; Philadelphia, Pennsylvania (Obtain Fellowship) |
| 04/29-05/05/89 | AOHC; Boston, Massachusetts |
| 10/30-11/03/89 | Fall State of the Art Conference, Baltimore, Maryland |
| January 1990 | Medical Review Officer Training (MRO), Chicago, Illinois |
| 04/30-05/04/90 | AOHC; Houston, Texas |
| 10/08-12/90 | Fall State of the Art Conference, Pittsburgh, Pennsylvania |
| 04/26-05/03/91 | AOHC; San Francisco, California |
| 10/25-31/91 | Fall State of the Art Conference, and 2nd MRO training seminar, St. Louis, Missouri |
| 05/02-08/92 | ACOEM (name change) AOHC; Washington, D.C. |
| 04/26-30/93 | AOHC; Atlanta, Georgia; course on Medical Surveillance ASPHS Regional meeting, Atlanta. |

| | |
|---|---|
| 10/93 | Fall State of the Art; core course in Environmental Medicine; Dallas, Texas. |
| 04/18-22/94 | AOHC; Chicago, Illinois. |
| 10/94 | Fall State of the Art Conference; Denver, Colorado. |
| 04/29-05/03/96 | AOHC; San Antonio, Texas. |
| 03/1996 | Epidemiology and Prevention of Vaccine-Preventable Diseases; CDC Telecommunications Course, Kansas City, Missouri |
| 08/24-28/96 | 1996 Preventive Medicine Review Course, (ACPM), Washington, D.C. |
| 11/04/96 | Board Exam, Preventive/Occupational medicine, Chicago, Illinois. |

**Workers' Compensation & Disability Evaluation:**

| | |
|---|---|
| 05/16/84 | Satellite Video-teleconference; CTD's and Ergonomics, Kansas City, Missouri. |
| 06/07-08/84 | AMA Conference on Introduction to the Guides to the Evaluation of Impairment & Disability, 2nd Ed., Chicago, Illinois. |
| 10/27-29/86 | Impairment Evaluation & Disability Considerations, Department of Orthopedic Hand Surgery, University of Michigan, Ann Arbor. |
| 06/09-13/86 | Principles & Practice of Industrial Toxicology, 26th Annual course, Wayne State University, Detroit, Michigan. |
| 09/26/86 | 1st Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 10/15-16/87 | UMKC Heartland Labor & Employment Law Institute, Kansas City, Missouri. |
| 11/20/87 | 2nd Annual Missouri Work Comp Seminar, Kansas City, Missouri. |

| | |
|---|---|
| 11/18/88 | 3rd Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 04/08-09/89 | AADEP Clinical Overview Course, Chicago, Illinois. |
| 04/12/89 | NIOSH Spirometry Training Course, Research Medical Center, Kansas City, Missouri. |
| 08/07-09/89 | Current Topics in Occupational Safety, "Prevention of Upper Limb Injuries", University of Michigan School of Engineering, Ann Arbor, Michigan. |
| 09/20-21/89 | AADEP Clinical Training Conference, Chicago, Illinois. |
| 11/02/89 | 4th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 07/1990 | Seminar on Workers' Compensation & Occupational Medicine, Hyannis, Massachusetts. |
| 11/02-03/90 | Annual AADEP Scientific Session & Symposium, Las Vegas, Nevada. |
| 11/07/90 | 5th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 10/22/91 | 6th Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 11/14-16/91 | Annual AADEP Conference, Kansas City, Missouri. |
| 04/16/93 | Rehabilitation of the Injured Worker, Kansas City, Missouri. |
| 05/11/93 | Maternity Issues in the Workplace, Kansas City, Missouri. |
| 05/14/93 | Hungate Seminar in Occupational Medicine, Kansas City, Missouri. |
| 09/22-24/93 | Impact Hearing Course on Occupational Hearing Loss and Hearing Conservation/CAOHC certified for five years (09/24/93); certificate # 35543. |
| 11/93 | Annual AADEP Conference, San Diego, California. |

| | |
|---|---|
| 05/13-14/94 | AADEP Conference on IMEs, Kansas City, Missouri. |
| 05/20-21/94 | Hungate Seminar in Occupational Medicine, Overland Park, Kansas. |
| 06/24-25/94 | DATTI Conference-Breath Alcohol Analysis, Charlotte, North Carolina. |
| 04/22/95 | Hungate Seminar in Occupational Medicine, Kansas City, Missouri. |
| 06/09-12/95 | ACOEM Seminar-Fundamentals of and Advanced IME Exams, Atlanta, Georgia. |
| 11/02-24/95 | Annual AADEP Scientific Session & Symposium, Washington, D.C. |
| 04/1996 | Annual Missouri Work Comp Seminar, Kansas City, Missouri. |
| 02/26/97 | Impaired Physician - Richard Irons, MD - Trinity Lutheran Hospital, Kansas City, Missouri. |
| 03/07-08/97 | Hungate Seminar in Occupational Medicine, Overland Park, Kansas. |
| 04/01/97 | Evaluating Disability Under Social Security, St. Joseph Health Center, Kansas City, Missouri. |

**FAA Training Seminars:**

| | |
|---|---|
| 1980 | Initial Appointment, Memphis, Tennessee. |
| 1985 | Senior Examiner Seminar, Oklahoma City, Oklahoma. |
| 1990 | Kansas City Update. |
| 1995 | Savannah Update. |

**General Surgery CME Activity:**

| | |
|---|---|
| 05/18-20/77 | Symposium on "Hernia", Creighton University, Omaha, Nebraska. |

| | |
|---|---|
| 05/17-18/79 | "Pitfalls in Surgery" |
| 02/1980 | "SESAP III" surgery review (155 hours) - self assessment. |
| 09/13-14/80 | Kansas ACS Chapter Meeting, Wichita, Kansas. |
| 1983 | "SESAP IV" surgery review - self assessment. |
| 10/02-14/83 | Cook County Specialty Review Course in general Surgery, Chicago, Illinois. |
| 09/15/83-1991 | Member, Kansas City Surgical Society - attended most conferences during this time. |

**Other CME:**

| | |
|---|---|
| 09/20-21/84 | Interqual: Quality Controls-Tools for Assuring Effective Care, Kansas City, Missouri. |
| 03/13-15/88 | National Conference on Health Fraud, co-sponsored by the FDA and St. Mary's Hospital (Dr. John Renner), Allis Plaza, Kansas City, Missouri. |
| 12/06/90 | Kansas City Bar Conference on Tort Cases, Liability Actions and "Applied Kinesiology", Lance Welch Conference Center, Kansas City, Missouri. |
| 06/1992 | Second Annual Family Medicine Update, Trinity Lutheran Hospital, Kansas City, Missouri. |
| 04/23/93 | Maxillo-facial Seminar, Trinity Lutheran Hospital, Kansas City, Missouri. |
| 10/07/93 | American Heart Association BLS Training, Menorah Medical Center, Kansas City, Missouri. |
| 06/08/94 | Kansas City Coalition on Health Care-Symposium on Preventive Medicine and Self-Care. |
| 1990-present | CME Conferences sponsored by Trinity Lutheran Hospital, variety of topics. |
| | 1996-1997 Topics: include Violence in Society/Workplace, Travel Medicine - A.J. Parmet, M.D., |

| | |
|---|---|
| | Update on H. Pylori - Barry Marshall, M.D., Medical Humanities - Marjorie Sirridge, M.D. |
| 09/12/97 | Red Cross Health Care Providers BLS training, Midwest Occupational Medicine® (through St. Mary's Blue Springs), Kansas City, Missouri. |

**Special Projects:**

| | |
|---|---|
| 1993-1995 | Medical Consultant, cumulative trauma prevention research project, Smith Orthopedic Company, Topeka, Kansas - and MAMTC. |
| 1993-present | Kansas City Coalition on Health Care - Workers Compensation Draft Proposal; physician team member. (Robert Wood Johnson Grant proposal). Pilot project funded 1996. |

**Misc. Award: (update) -**

| | |
|---|---|
| 04/01/93-04/01/96 | PRA Award of the American Medical Association. |

# Attachment 7

# Adverse Event Report Form

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

# MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ___ of ___

Mfr report #

UF/Dist report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

## A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ___ lbs or ___ kgs

## B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

## C. SUSPECT PRODUCT(S)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

## D. SUSPECT MEDICAL DEVICE

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. Expiration date (mo/day/yr)
6. model # ___
   catalog # ___
   serial # ___
   lot # ___
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

## E. REPORTER INFORMATION

1. Name, address & phone #
   phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

FDA Form 3500A (1/96)

**Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.**

# Medication and Device Experience Report
(continued)

Refer to guidelines for specific instructions

**Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

Page ____ of ____

FDA Use Only

1. Check one ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report ☐ initial ☐ follow-up # ____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual)
patient code ____ – ____ – ____
device code ____ – ____ – ____
11. Report sent to FDA? ☐ yes ____ (mo/day/yr) ☐ no
12. Location where event occurred ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: ____ specify ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. Report sent to manufacturer? ☐ yes ____ (mo/day/yr) ☐ no
14. Manufacturer name/address

1. Contact office – name/address (& mfring site for devices)
2. Phone number
3. Report source (check all that apply) ☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other: ____
4. Date received by manufacturer (mo/day/yr)
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply) ☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ initial ☐ follow-up # ____
8. Adverse event term(s)
9. Mfr. report number

1. Type of reportable event ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: ____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual)
method ____ – ____ – ____ – ____
results ____ – ____ – ____ – ____
conclusions ____ – ____ – ____ – ____
7. If remedial action initiated, check type ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/ adjustment
8. Usage of device ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data



Please do NOT return this form to either of these addresses.

MIDWEST RESEARCH INSTITUTE
425 Volker Boulevard
Kansas City, Missouri 64110
Telephone (816) 753-7600
Telefax (816) 753-8420

June 26, 2000

Ronald E. Clawson, Ph.D.
USAMMDA
Attn: MCMR-UMP
622 Neiman Street
Fort Detrick, MD 21702-5009

Re: Contract DAMD17-97-C-7070; MRI Project No. 104863

Dear Dr. Clawson:

Enclosed is a copy of Amendment No. 1 to the protocol for Study 2 of our project "Individual Differences in Neurobehavioral Effects of Pyridostigmine". I am also furnishing copies to Ms. Cook in Regulatory Affairs, the chair of MRI's IRB, the project physician and the medical monitor. A copy of this letter will also be sent to Ms. Hackley, the contract specialist who is now dealing with this project. Please call me if you have any comments or questions.

Sincerely,

For Mary R. Cook, Ph.D.
Principal Investigator

cc: Ms. Cook
Ms. Hackley
Dr. Sastre
Dr. Parmet
Dr. Brothers
Dr. Podrebarac

# Midwest Research Institute
# Biobehavioral Sciences Section
# Protocol Amendment Number 1

| | |
|---|---|
| Title | Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 2 |
| Author | Mary R. Cook, Ph.D. and Antonio Sastre, Ph.D. |
| Contract No. | DAMD 17-97-C-7070 |
| MRI Project No. | 104863 |
| Study Director | Mary R. Cook, Ph.D. |
| Testing Facility Name | Midwest Research Institute<br>425 Volker Boulevard<br>Kansas City, Missouri 64110 |
| Sponsor Name | U.S. Army Medical Acquisition Agency |
| Project Physician | Allen J. Parmet, M.D. |
| Date of Amendment | June 23, 2000 |

**Approvals:**

Richard D. Brown — 6-23-00
Richard D. Brown — Date
Director, Life Sciences Division

Eugene G. Podrebarac — 6/23/00
Eugene G. Podrebarac, Ph.D. — Date
Manager Quality Assurance

R Sanchez for — 6.23.2000
Mary R. Cook, Ph.D. — Date
Study Director

Dr. Ronald E. Clawson — Date
Contracting Officer's Representative
USA MMDA

# Study Protocol: Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 2

## 1. Protocol Amendment No. 1

1. On the face page, change the anticipated start date to June 12, 2000, and the anticipated end date to December 29, 2000.

   Rationale: Delays in negotiation a contract modification and obtaining approval from the Human Subjects Research Review Board resulted in a delay in the start of Study 2.

2. Change the 3rd sentence, Synopsis, p. v, paragraph 2, to read: "Twenty-four volunteers will be randomly assigned to two test order groups, with approximately equal numbers of men and women in each group; at least 10 volunteers of each gender will participate."

   Rationale: Change in the Statement of Work deleted analysis by gender.

3. Change the next-to last sentence, Synopsis, p. v, paragraph 2, to delete butyrlcholinesterase (BuChE).

   Rationale: BuChE in Study 1 did not provide additional information beyond that provided by AchE, so to reduce costs BuChE assays were omitted and AchE assays retained.

4. Change the second study objective on page 3 to delete butyrlcholinesterase (BuChE).

   Rationale: See item 3.

5. In Section 3.1, Study Design, replace the 6th sentence with "During this time period, blood for baseline determination of PH, THMP, and AchE will be obtained between 1100 and 1130 hours, and each volunteer will be asked to hold his/her breath for as long as possible."

   Rationale: See item 3 for rationale for omitting BuChE. Time of voluntary breath hold has been used as a measure of an individual's willingness to endure discomfort. In Study 1, symptoms during the placebo week were the best predictor of symptoms during the pyridostigmine bromide week. If this occurs, again, this measure will prove to be a valuable covariate, and can be obtained with no additional cost to the project.

6. Change the third sentence, Section 3.2.2, Recruitment and Inclusion Criteria, to read "A sufficient number of volunteers will be recruited to complete the evaluation on approximately 24 people, with at least 10 persons of each gender."

   Rationale: Analysis by gender was omitted from the Statement of Work, and it is not necessary to have equal numbers of men and women.

7. Change the 5th bullet under Section 3.2.2, Recruitment and Inclusion Criteria, to read "Willing to abstain from alcohol and illicit drugs during the drug administration and testing phases of the program, and to inform the investigators of any medications used."

   Rationale: Protocol as written did not match the final approved consent form.

8. Add to inclusion criteria, Section 3.2.2, Recruitment and Inclusion Criteria: normal color vision, and between 121 and 231 pounds.

   Rationale: In accordance with the revised Statement of Work, we have added the Stroop Color-Word Test with negative priming as an additional measure of central nervous system functioning. Color blind people have great difficulty with this test. Limitations on the weight of subjects were inadvertently omitted from the protocol. Smaller people appear to metabolize pyridostigmine bromide differently, and heavier people require longer exposure to heat to reach equilibrium.

9. Change the sentence in the last paragraph of section 4.4, Data Collection, that begins "Before the first dose" to delete reference to BuChE.

   Rationale: see item 3.

10. Change the last sentence of Section 4.4.2, Subjective Effects, to read, "After each test battery, the volunteer will complete computerized subjective fatigue and workload scales, and a symptom checklist that refers to experiences while in the temperature chamber."

    Rationale: Additional data about symptoms while exposed to heat, and how they compare to symptoms experienced during testing at room temperature, could prove to be of value in interpreting the physiological and performance data.

11. Delete the first sentence of the second paragraph in Section 4.4.4, Blood Processing.

    Rationale: To reduce costs; see item 3.

12. Delete the last sentence of Section 4.4.4, Blood Processing

    Rationale: The genetic analysis of samples from Study 2 was deleted from the Statement of Work.

13. Change the second paragraph, Section 4.4.6, "Quantification of Plasma and Red Blood Cell Cholinesterase to delete collection of plasma from the heading and the text, and to delete details of quantification of BuChE.

    Rationale: See item 3 above.

14. Change the first paragraph, Section 4.4.7 "Test Battery", to delete BuChE.

    Rationale: See item 3 above

15. Change Section 4.4.7, Test Battery, to delete the Grip Strength Test, and to add the Stroop Color-Word Test.

    Rationale: Further data analysis indicated that there were not pyridostigmine bromide-related effects on grip strength. As discussed above, the Stroop was added to provide an additional measure that might be altered were pyridostigmine bromide to cross the blood-brain barrier.

16. Replace Attachment 4, Symptom Check List, with Attachments 4A and 4B enclosed herein.

    Rationale: Minor changes to the symptom check list were made for data tracking purposes. Also, a second version was made that asks the volunteer about symptoms while he or she was in the testing chamber. This will allow us to determine whether the subjective sensations associated with heat are different when a volunteer is taking pyridostigmine bromide than when taking placebo.

MRI

# Individual Differences in Neurobehavioral Effects of Pyridostigmine Bromide

## Final Report

## Volume 3—Appendix 16
## Sections 16.1.2 to 16.2.8

MRI Project No. 104863.1.004.03

May 2, 2001

Midwest Research Institute

425 Volker Boulevard
Kansas City, Missouri
64110-2299
(816) 753-7600

*solutions through science and technology*

## 16. **APPENDICES**

### 16.1 Study Information

16.1.1 Protocol and protocol amendments, Study 1 and Study 2

16.1.2 Sample case report form (unique pages only), Study 1 and Study 2

16.1.3 List of IEC's or IRB's (plus the name of the committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms.

16.1.3.1 Study 1 consent form
16.1.3.2 Study 2 consent form

16.1.4 List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study.

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.

16.1.6 N/A, Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.

16.1.7 Randomization schemes

16.1.8 N/A, Audit certificates

16.1.9 N/A, Documentation of statistical methods.

16.1.10 N/A, Documentation of inter-laboratory standardization methods and quality assurance procedures if used.

16.1.11 N/A, Publications based on the study.

16.1.12 N/A, Important publications referenced in the report.

### 16.2 Patient Data Listings

16.1.2 Discontinued patients. See tables 9.3 and 9.4, Disposition of subjects

16.2.2 Protocol deviations. See section 10.2.

16.2.3 N/A, Patients excluded from the efficacy analysis.

16.2.4 Demographic data, Study 1 and Study 2

16.2.5 Drug concentration data.

16.2.5.1 Plasma PB, Study 1
16.2.5.2 Plasma THMP, Study 1
16.2.5.3 Corrected Urinary THMP, Study 1
16.2.5.4 Urinary THMP, Study 1
16.2.5.5 Corrected Urinary PB, Study 1
16.2.5.6 Urinary PB, Study 1
16.2.5.7 Plasma PB, Study 2
16.2.5.8 Plasma THMP, Study 2

16.2.6 N/A, Individual efficacy response data.

16.2.7 Adverse event listings. See Table 12.1, Table of Adverse Events.

16.2.8 Individualized laboratory measurements.

16.2.8.1 AChE, Study 1
16.2.8.2 BuChE, Study 1
16.2.8.3 AChE, Study 2
16.2.8.4 Side effects scores, Study 1
16.2.8.5 Side effects scores, Study 2

4863PP
Version 3
Effective 9/30/98

CALL #_____
Screener_____
Date:___/___/___

| | |
|---|---|
| Data Entry 1st_____ | 2nd_____ |
| Reviewed by _____ | Date_____ |
| PI Review: _____ | Date_____ |

## VOLUNTEER POOL—PRE-SCREENING FORM

Name: _____

Phone( h)_____ (w) _____

Address_____

Age____ **(If S is older than 35, end interview)** Birthdate ____/___/____ Gender: M F

What is your ethnicity? Are you: **(Read choices to subject.)**

1.___ American Indian or Alaskan Native, 4.___ Hispanic

2.____ Asian or Pacific Islander, 5.___ White, not of Hispanic background

3.___ Black, not of Hispanic background, 6.___ Other

Referral Source_____

How much do you currently weigh?_____ Lbs. **(If S weighs ≤ 121 lbs., end interview)**

Do you: Read English? yes no **(If no, end interview)**
Write English? yes no **(If no, end interview)**

What is the last year of school that you completed?

K-6 7-9 10-12 13-16 >17

**(If S is female ask)** Are you currently pregnant, or do you plan to become pregnant in the near future?
yes no **(If yes, end interview)**

Have you ever taken Pyridostigmine for any reason? yes no **(If yes, end interview)**

Have you ever been in the Military? yes no

Were you in the Gulf War? yes no

Were you ever in the Persian Gulf during the Gulf War? yes no

(If yes) Where were you located?_____**(If S was in the Persian Gulf, end interview)**

Have you ever participated in any other research studies? yes no

(If yes) What were the studies you participated in?_____

_____

CALL #_____
Screener_____
Date:___/___/___

(If yes) When did you participate in these studies? _____

_____

Do you expect to be in the metropolitan area for the next two months? yes no

If no) When will you be in the metropolitan area for two consecutive months?_____

_____

Do you plan to be out of town for any period of time for the next two months? yes no

(If yes) When do you plan to be out of town?_____

(If yes) How long do you plan to be out of town?_____

You will need to be able to come to MRI at a variety of times for the study. Do you have transportation to get to and from MRI? yes no **(If no, end interview)**

We will schedule the times that you come to MRI in advance. Do you have any times already set up that you know about now, that you could not come to MRI, such as for classes? yes no

(If yes) What are the times that you **cannot** come to MRI in the next two months?

**(RECORD DATES SUBJECT CANNOT COME TO MRI)**

| DAYS OF THE WEEK | DAY / MONTH/ YEAR , TIME<br>DAYS AND TIMES NOT AVAILABLE TO COME TO MRI |
|---|---|
| MONDAY | |
| TUESDAY | |
| WEDNESDAY | |
| THURSDAY | |
| FRIDAY | |
| SATURDAY | |
| SUNDAY | |

Do you currently smoke cigarettes? yes no

(If yes) How many cigarettes do you smoke in one day?_____

Have you ever been diagnosed with any of the following conditions?

| | | |
|---|---|---|
| yes | no | Myasthenia Gravis |
| yes | no | Asthma |
| yes | no | High Blood Pressure |
| yes | no | Diabetes |
| yes | no | Heart Disease |

**(If yes to any of these conditions, end interview)**

CALL #_____
Screener_____
Date:___/___/___

Have you ever been diagnosed with liver or kidney disease? yes no

(If yes) Explain_____

_____

Have you ever been diagnosed with chronic bladder disease or urine problems? yes no

(If yes) Explain _____

_____

Have you ever had any seizures or been diagnosed with a seizure disorder? yes no
**(If yes, end interview)**

Have you ever been diagnosed with any other chronic illnesses? yes no

(If yes) Explain _____

_____

Have you ever had problems with your eyes? yes no

(If yes) Explain_____

_____

Is your vision normal or corrected to normal? yes no **(If no, end interview)**

Have you ever had problems with your hearing? yes no

(If yes) Explain _____

_____

Do you wear hearing aides? yes no **(If yes, end interview)**

Is your hearing normal? yes no **(If no, end interview)**

Have you had any acute illness within the last month that has required bed rest? yes no

**(If yes)** When were you ill? _____

How long did your illness last? _____

**(If yes, wait one month past illness to schedule subject for study.)**

Have you or any family members ever experienced a severe reaction to a dental procedure or anesthetic? yes no

(If yes) Explain_____

Has any member of your family died a sudden or unexpected death, other than accident or injury?
yes no

(If yes) Explain_____

CALL #_____
Screener_____
Date:___/___/___

Are you currently taking any prescription medications, (**If female add:**) birth control pills or have a birth control implant? yes no

(**If yes**) List medications_____

_____

Do you regularly take any over-the-counter medications, including vitamins, minerals, or health supplements? yes no

(**If yes**) List _____

_____

Do you regularly drink any herbal teas or drinks, or take any herbal supplements?
yes no

(**If yes**) List _____

_____

Have you ever experienced any difficulties when having your blood drawn? yes no

(**If yes**) Explain_____

_____

Have you ever worked for a company that manufactured, used, or applied pesticides?
yes no

(**If yes**) When did you work there? _____

How long did/have you work/ed there? _____

What did/do you do for this company?_____

What pesticides were/are used or applied there? _____

Do you work with any pesticides at school? yes no
(**If yes**) What are the pesticides? _____

_____

Are you allergic to Latex? yes no

Have you ever worked at a job where you were exposed to extreme heat? yes no

(If yes) Where was that? _____

When did you work there? _____

What did you do there? _____

CALL #_____
Screener_____
Date:___/___/___

If you are selected for our study, we must ask that you abstain from using any alcohol, illicit drugs, or over-the-counter drugs other than vitamins, during the activity days of the study. Are you willing to abstain from these things on those days?
yes no **(If no, end interview)**

In case we are unable to reach you at your home or work, may I have the name and phone number of one person who will know how to reach you? _____

_____

Accept_____Reject _____ S Refusal _____ Reviewed by _____on ___/___/___

Consent Session appointment: DATE ___ / ___ / ___, TIME _____

If subject refuses to participate, state reason:_____

_____

_____

If not selected for the study, state reason:_____

_____

_____

Best time to call respondent:_____

**Deviations and Observations**

863PP

# SUBJECT APPOINTMENT CALENDAR

NAME:_____

**ENTRANCE BLOOD DRAW AT MRI: DATE ___ / ___ / ___, TIME _____**
**ENTRANCE MEDICAL EXAMINATION, DR. PARMET: DATE ___ / ___ / ___ , TIME _____** CALL # _____
**EXIT MEDICAL EXAMINATION, DR. PARMET:DATE ___ / ___ / ___ , TIME _____**

**TRAINING WEEK:☐ DOSING & BATTERY A; ☐ BATTERY B SESSION 1;☐ BATTERY B SESSION 2; ☐ BATTERY B FINAL**

| SUN | MON | TUES | WED | THURS | FRI | SAT |
|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐REMINDER CALL |

**Please remember to refrain from alcoholic beverages during each study phase.)** **REFRESHER TRAINING: DATE ___ / ___ / ___, TIME _____**

| SUN | MON | TUES | WED | THURS | FRI | SAT |
|---|---|---|---|---|---|---|
| ☐ **ENTER FOOD AND DRINK INTO 1ST DAILY FOOD DIARY FOR PHASE I** | ☐_____Dose, Brkfst _____ 11:30 Blood, Lunch, Battery _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 11:30 Blood, Urine, Lunch, Battery _____16:00 Dose _____24:00 Dose | ☐_____Dose, Brkfst _____ 11:30 Blood, Urine, Lunch, Battery | ☐ |
| ☐ | ☐ _____ 11:30 Blood, Daily Log Phase I Payment | ☐ | ☐ | ☐ _____ Pregnancy Test Blood Draw **(If Female )** | ☐ | ☐ **REMINDER CALL** |
| ☐ **ENTER FOOD AND DRINK INTO 1ST DAILY FOOD DIARY FOR PHASE II** | ☐_____Dose, Brkfst _____ 11:30 Blood, Lunch, Battery _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 16:00 Dose _____ 24:00 Dose | ☐_____Dose, Brkfst _____ 11:30 Blood, Urine, Lunch, Battery _____16:00 Dose _____24:00 Dose | ☐_____Dose, Brkfst _____ 11:30 Blood, Urine, Lunch, Battery | ☐ |
| ☐ | ☐ _____ 11:30 Blood, Daily Log, Phase II Payment | ☐ | ☐ | ☐ | ☐ | ☐ |

**If you have questions regarding your appointment times, please call: (816) 753-7600, ext. 1610**

4863PP **SBJID#**_____

## BASELINE DATA SHEET

**For Entrance or Exit Medical Examinations:** Dr. Allen Parmet: ofc: 561-3480; pgr: 860-2278
**For Interim Referral Examinations:** Dr. Mary Brothers: ofc: 561-3480; pgr: 727-6168

**BATTERY RUN ORDER:** ABA BAB

**BATTERY B COMPONENT ORDER:** ANAM/NES2 NES2/ANAM

**BATTERY B-DOMINANT HAND TO USE COMPUTER MOUSE:** Right Left

**BASELINE PULSE RATE:** Training pulse 1. _____ 2. _____

**Baseline pulse** _____ (Lowest Pulse Rate from the 2 training rates and Monday, Day 1, Phz 1.)

**TONOMETRY CUFF SIZE:**

**Large** **Small**

**SENSOR HOOK-UP:**

_____ Nasion to Inion, _____ Left to Right Preauricular Points

**HAND STEADINESS TEST:**

**Dominant Hand:** Right Hand Left Hand

**GRIP STRENGTH (HAND DYNAMOMETER) TEST:**

_____ Hand Grip Measurement **(Set Hand Grip according to Hand Dynamometer procedures.)**

**BREAKFAST/LUNCH:**
Breakfast choice: _____
Lunch choice:_____
**(Record breakfast and lunch choices from Informed Consent Session Checklist.)**

4863PP
Revision: 0
Effective: 10/14/98

SBJID _____
DATE ____ / ____ / ____
DAY 1 2 3 4 5
Experimenter _____

Data Entry 1st _____ 2nd
Reviewed by: _____ Date
PI Review _____ Date

# TRAINING CHECKLIST

## BATTERY A

**PRE SESSION PREPARATIONS:**

➡ **HOOK-UP ROOM**

- ☐ GOLD CUP SENSOR TAIL
- ☐ EC2 CREAM
- ☐ WAX PENCIL
- ☐ CRF (CASE REPORT FILE)
- ☐ Q-TIPS
- ☐ GAUZE PADS
- ☐ SKIN PREP GEL
- ☐ ECG PADS
- ☐ TAPE MEASURE
- ☐ SURGICAL TAPE
- ☐ SCRUB TOP

➡ **TONOMETRY**

- ☐ ATTACH ECG ELECTRODES TO TONOMETRY UNIT
- ☐ TURN ON COLIN UNIT AND LAPTOP
- ☐ SELECT: **PP ACQUISITION**
- ☐ SELECT: **ACQUIRE**, ENTER FILE NAME **PP##*PD*T**
- ☐ COLLECT 4 SECONDS OF CALIBRATION
- ☐ PRESS: **ENTER** TO PAUSE COLLECTION

➡ **CONTROL ROOM D:**

➡ **NEUROSCAN SET-UP**

- ☐ POWER ON TO MONITOR
- ☐ POWER ON TO SYNAMPS

✶**(Wait for SCSI to show before powering up SCAN and STIM)**

- ☐ DISCONNECT NETWORK CABLE TO SCAN
- ☐ POWER ON TO SCAN AND STIM
- ☐ POWER ON TO TALK-A-PHONE
- ☐ POWER ON TO LIGHTS AND VIDEO
- ☐ POWER ON TO VIDEO MONITOR
- ☐ POWER ON TO FAN

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

➡ **CHAMBER D:**

- ☐ CFF CONTROL BOX IN POSITION (**Flash intensity set to 1 and flashes to repeat**)
- ☐ STROBE LIGHT PLUGGED IN
- ☐ PUT EARPLUGS ON EARPHONES

➡ **CONTROL ROOM A:**

- ☐ **OPTEC :** POWER ON; ORANGE AND GREEN LIGHTS ON, FOREHEAD PAD IN PLACE
- ☐ **HAND STEADINESS TEST**
- ☐ **GRIP STRENGTH:** PERCEIVED EXERTION SCALE
- ☐ **MARI & WORKLOAD:** POWER ON TO COMPUTER, TYPE <PP>

**TRAINING, BATTERY A:**

- ☐ SUBJECT ARRIVAL TIME _____

➡ **SHOW SUBJECT TO HOOK-UP ROOM**

- ☐ ASK SUBJECT TO PUT ON SCRUB TOP (**Leave room. SUBJECT will open door when changed.**)
- ☐ TAKE BASELINE HEIGHT _____ In.
- ☐ TAKE BASELINE WEIGHT _____ Lbs.(**Scales #G-6324**)

➡ **COMPLETE ECG AND TONOMETRY HOOK-UP**

- ☐ ATTACH ECG ELECTRODES:
  - **LL (Red)--LEFT RIB**
  - **LA(Black)--LEFT CLAVICLE**
  - **RA(White)--RIGHT CLAVICLE**
- ☐ ATTACH BP CUFF TO RIGHT ARM

➡ **BLOOD PRESSURE MEASUREMENT (Tonometry Unit # 012567)**

✶**(Subject will lie down for a total of 8 minutes. Subject will stand for a total of 8 minutes.)**

- ☐ INSTRUCT SUBJECT TO LIE DOWN
  - ☐ CIRCLE CUFF SIZE IF OTHER THAN ADULT:
    **Large** **Small**
  - ☐ TURN ON TONOMETRY UNIT AND SET CUFF INTERVAL TO 2 (**Press cuff start/stop button 2X to start and press enter on laptop to start tonometry collection. Click event marker at beginning of first cuff inflation.**)
  - ☐ **RECORD BEGINNING BP** _____/_____
  - ☐ **RECORD BP** _____/_____ **(At 2 minutes)**
  - ☐ **RECORD BP** _____/_____ **(At 4 minutes)**
  - ☐ **RECORD BP** _____/_____ **(At 6 minutes)**

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

☐ INSTRUCT SUBJECT TO STAND WHEN CUFF BEGINS TO INFLATE **(Click event marker.)**

- ☐ **RECORD BP** _____/_____ **(At 8 minutes)**
- ☐ **RECORD BP** _____/_____ **(At 10 minutes)**
- ☐ **RECORD BP** _____/_____ **(At 12 minutes)**
- ☐ **RECORD BP** _____/_____ **(At 14 minutes)**
- ☐ **RECORD BP** _____/_____ **(At 16 minutes) (Click event marker.)**

➡ **COMPLETE SENSOR HOOK UP (Record hook-up measurements for baseline data sheet.)**

NASION TO INION _____ , LEFT TO RIGHT PREAURICULAR POINTS _____

☐ CHECK RESISTANCE **(Record resistance measurements. Resistance ≤ 3)**

Forehead (ground) _____, CZ _____, Oz _____, Rt. Mastoid _____, Lft. Mastoid ____

➡ **SUBJECT TO CHAMBER D**

- ☐ ADJUST PILLOW ON CHAIR TO SUPPORT NECK. ASSURE SUBJECT'S RELAXATION.
- ☐ PLUG IN ELECTRODE TAIL
- ☐ DEMONSTRATE HOW EARPLUGS WORK / CLIP EARPHONES ONTO SCRUB
- ☐ PULL MONITOR FORWARD UNTIL IT TOUCHES CHAIR LEGS **(65cm from nasion to middle of monitor screen)**
- ☐ CLOSE BOTH DOORS
- ☐ CHECK INTERCOM

➡ **CHECKERBOARD TASK (VEP) ( Neuroscan #9302040)**

Set Headbox

- ☐ INSERT PINS 13 AND 14 INTO REFERENCE
- ☐ INSERT SHORTING PLUG

Calibrate SCAN (start with **Acquire** icon)

- ☐ Menu: **Setup | Select ... PPvep.ast**
- ☐ Menu: **Acquisition | Calibrate** - Sine wave clean and value between 0.99 and 1.10

Check EEG Quality

- ☐ HEADBOX: REMOVE SHORTING PLUG
- ☐ SCAN: green ▷ speed button
- ☐ ENTER FILE NAME: **PP##*PD*V**

Set STIM

- ☐ STIM: press **V** **(but not ↵)**

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

☐ MONITOR BOX: SUBJECT (STIM monitor screen will go black)

Set SCAN

☐ SCAN: **SAVE** speed button

☐ ENTER FILE NAME: **PP##*PD*V**

Start Collection

☐ INSTRUCT SUBJECT: *Look directly at blue dot in the middle of the screen. Try not to blink. Sit Still.*

☐ CHAMBER LIGHTS OFF

☐ STIM: press ↵ Note developing Waveform and accumulation of Accepted Sweeps.

Finish Collection - after **Accepted Sweeps = 200**

☐ SCAN: **STOP** icon

☐ STIM: **ESC** x2

☐ EXIT ACQUIRE

☐ CHAMBER LIGHTS ON

☐ MONITOR BOX: **E**

☐ CHAMBER MONITOR OFF (Power strip beside SynAmps)

☐ INSTRUCT SUBJECT: *Insert earplugs and prepare for Click Task.*

➡ **CLICK TASK (BAEP) ( Neuroscan #9302040)**

Set Headbox

☐ INSERT PINS 13 AND 14 INTO HOLES 29 AND 30; RESPECTIVELY

☐ INSERT SHORTING PLUG

Calibrate SCAN (starts with **Acquire** icon)

☐ Menu: **Setup | Select ... PPbaep.ast**

☐ Menu: **Acquisition | Calibrate** - Sine wave clean and values between 1.10 and 1.20

Check EEG Quality

☐ HEADBOX: REMOVE SHORTING PLUG

☐ SCAN: green ▷ speed button

Set STIM

☐ STIM: press **B (but not** ↵**)**

Set SCAN

☐ SCAN: **SAVE** speed button

☐ ENTER FILE NAME: **PP##*PD*B1**

☐ INSTRUCT SUBJECT: *Close eyes ... Relax jaw ... Ok to doze ... Just listen to clicks ... Hold still.*

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

☐ CHAMBER LIGHTS **OFF**

Start Collection ONE

☐ STIM: press ↵ Note developing Waveforms and accumulation of Accepted Sweeps.

☐ SCAN: **STOP** icon when Accepted Sweeps=2000 and Fsp≥4; or Accepted Sweeps=4000 and Fsp≥2

Start Collection TWO

☐ SCAN: green ▷ speed button

☐ SCAN: **SAVE** speed button

☐ ENTER FILE NAME: **PP##*PD*B2**

Note developing Waveform and accumulation of Accepted Sweeps.

☐ SCAN: **STOP** icon when Accepted Sweeps=2000 and Fsp≥4; or Accepted Sweeps=4000 and Fsp≥2

☐ STIM: **ESC**

☐ EXIT ACQUIRE

☐ CHAMBER LIGHTS ON

☐ INSTRUCT SUBJECT: *Open eyes... Remove headphone... Put earplugs in labeled Baggie... Be careful to leave white plastic piece in blue tube!*

☐ TURN SUBJECT MONITOR ON FOR NEXT RUN

➡ **CFF (STROBE LIGHT TASK) (CFF #8834)**

☐ SEAT SUBJECT IN STRAIGHT BACK CHAIR

☐ POSITION STROBE LIGHT (**Light at eye level/ string from S's nasion to strobe light.**)

☐ CFF CONTROL BOX, POWER TO ON

☐ CFF CONTROL BOX, FLASH SWITCH TO REPEAT

☐ BEGINNING TIME: _____

☐ AS STROBE IS SOLID, SUBJECT TURNS DIAL UNTIL LIGHT BLINKS, AND VICE VERSA. RECORD NUMBER WHERE SUBJECT STOPS. EXPERIMENTER, TURN DIAL TO 60 THEN 1

| | |
|---|---|
| PRACTICE AT 60. . . . . _____ | PRACTICE AT 1 . . . . . _____ |
| 1. START AT 60. . . . . _____ | 2. START AT 1. . . . . _____ |
| 3. START AT 60. . . . . _____ | 4. START AT 1. . . . . _____ |
| 5. START AT 60. . . . . _____ | 6. START AT 1. . . . . _____ |

☐ ENDING TIME: _____

☐ TURN CFF OFF

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

➡SUBJECT TO CONTROL ROOM A

➡**OPTEC TEST (OPTEC #011037)**

☐ INSTRUCTIONS TO THE SUBJECT

☐ TEAR SHEET FROM OPTEC PAPER PAD

☐ ADJUST THE OPTEC UP OR DOWN TO COMFORT LEVEL

☐ PRESS FOREHEAD AGAINST HEADREST PAD

➡ **FAR VISION TEST**

☐ SET NEAR/FAR BUTTON TO FAR (YELLOW)

☐ (F-1 VERTICAL PHORIA)
TURN DIAL INDICATOR TO 1 (YELLOW)

SAY: "LOOK INTO THE OPTEC. DO YOU SEE A RED DOTTED LINE? IS IT CROSSING A ROW OF STAIR STEPS? WHICH STEP IS THE DOTTED LINE AT THE CLOSEST LEVEL WITH?" **(Circle Subject's score.)**

1 2 3 4 5 6 7 8 9

☐ (F-2 LATERAL PHORIA)

TURN DIAL INDICATOR TO 2 (YELLOW)

SAY: "WHAT NUMBER DOES THE ARROW POINT TO?"

**(Circle Subject's score.)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

☐ (F-3 ACUITY)

TURN DIAL INDICATOR TO 3 (YELLOW)

SAY "IN THE BIG SIGN AT THE TOP, THE #1 SIGN, DO YOU SEE A LARGE BLACK CHECKERBOARD ON YOUR RIGHT? I WANT YOU TO GO THROUGH EACH NUMBER AND TELL ME WHERE THE CHECKERBOARD IS IN EACH BOX, RIGHT, LEFT, TOP, OR BOTTOM."

**(Circle Subject's score.)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R | L | T | L | B | L | T | B | T | R | B | R |

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

☐ (F-6 DEPTH)

TURN DIAL INDICATOR TO 6 (YELLOW)

SAY, "YOU SHOULD SEE SOME RINGS. TELL ME WHICH RING SEEMS TO BE 3-D OR FLOATING ABOVE THE OTHERS, EITHER TOP, BOTTOM, RIGHT, OR LEFT."

**(Circle Subject's score.)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| B | L | B | T | T | L | R | L | R |

➡ **NEAR VISION TEST**

☐ SET NEAR /FAR BUTTON TO NEAR (BLUE)

☐ (N-8 ACUITY)

TURN DIAL INDICATOR TO 8 (BLUE)

SAY "ONCE AGAIN, PLEASE GO THROUGH AND TELL ME WHAT POSITION THE CHECKERBOARD IS IN."

**(Circle Subject's score.)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T | T | R | T | R | T | L | T | R | L | R | B |

☐ (N-11 VERTICAL PHORIA) (BLUE)

TURN DIAL INDICATOR TO 11

SAY: "WHICH STEP IS AT THE CLOSEST LEVEL TO THE DOTTED LINE?"

**(Circle Subject's score.)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

☐ (N-12 LATERAL PHORIA) (BLUE)

TURN DIAL INDICATOR TO 12

SAY: "WHAT NUMBER IS THE ARROW POINTING TO?"

**(Circle Subject's score.)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

➡ **HAND STEADINESS TEST**(USE DOMINANT HAND ONLY.)
**(Hand Steadiness tester #32011)**

☐ RECORD DOMINANT HAND: RIGHT_____ LEFT_____

**(RECORD DOMINANT HAND ON BASELINE DATA SHEET )**

☐ SUBJECT WILL PRACTICE USING LARGE HOLES, TOP ROW **(DO NOT RECORD)** TEST IN SMALL HOLES, BOTTOM ROW **(RECORD INDIVIDUAL MEASUREMENT FROM EACH HOLE.)** RESET AND INSTRUCT SUBJECT TO INSERT STYLUS, SAY "STEADY-GO" FOR EACH HOLE.

HOLE 1 _____, HOLE 2 _____, HOLE 3 _____, HOLE 4 _____, HOLE 5 ____

➡ **GRIP STRENGTH TEST (DETERMINE HAND GRIP MEASUREMENT, RECORD ON BASELINE DATA SHEET)**

**(Hand Dynamometer #G-6268)**

☐ RECORD HAND GRIP MEASUREMENT _____

☐ GRIP STRENGTH ☐ PERCEIVED EXERTION RATE

| | | | |
|---|---|---|---|
| **1.** DOMINANT | _____ | **2.** | _____ |
| **3.** NON DOMINANT | _____ | **4.** | _____ |
| **5.** DOMINANT | _____ | **6.** | _____ |
| **7.** NON DOMINANT | _____ | **8.** | _____ |
| **9.** DOMINANT | _____ | **10.** | _____ |
| **11.** NON DOMINANT | _____ | **12.** | _____ |

➡ **MARI AND OVERALL WORKLOAD TESTS**

☐ TYPE: **PP**
☐ TYPE: **DP ##**
☐ OVERALL WORKLOAD: THIS IS A ONE-LINE TEST ASKING HOW DIFFICULT YOU FEEL THE ENTIRE BATTERY OF TESTS HAVE BEEN FOR YOU TODAY. ANSWER THE QUESTION AND CLICK DONE.
☐ MARI: THIS TEST ASKS HOW YOU FEEL **RIGHT NOW**. ANSWER ALL THE QUESTIONS AND CLICK DONE WHEN YOU ARE FINISHED WITH EACH PAGE.

➡ **DAILY DEBRIEFING WHILE REMOVING SENSORS**

☐ SUBJECT TO HOOK UP ROOM: REMOVE SENSORS
☐ DOES THE SUBJECT HAVE ANY QUESTIONS?
☐ DID ANYTHING MAKE HIM/HER UNCOMFORTABLE?
☐ REMIND SUBJECT TO COMPLETE FOOD DIARY

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
Experimenter _____

- ☐ REMIND SUBJECT TO FOLLOW APPOINTMENT CALENDAR
- ☐ REMIND SUBJECT TO RETURN FOR NEXT DAILY DOSE AT _____(TIME)
- ☐ IF LAST TRAINING SESSION, PAY SUBJECT AND HAVE SUBJECT SIGN RECEIPT
- ☐ ENDING TIME _____
- ☐ ESCORT SUBJECT OUT OF BUILDING

**POST SESSION CLEAN-UP**

- ☐ CLEAN SENSORS
- ☐ BACK UP, TONOMETRY, VEP, BAEP, AND WORKLOAD/MARI
- ☐ TURN OFF NEUROSCAN EQUIPMENT
- ☐ TURN OFF CONTROL ROOM A EQUIPMENT
- ☐ CHECK ALL DATA FOR APPROPRIATE ID (**S # and session date/time**)
- ☐ RETURN EAR PLUGS TO POCKET IN CRF NOTEBOOK
- ☐ TRANSFER THE FOLLOWING TO BASELINE DATA SHEET
  - ☐ TONOMETRY CUFF SIZE IF OTHER THAN ADULT
  - ☐ NASION TO INION MEASUREMENT
  - ☐ LEFT TO RIGHT PREAURICULAR POINTS
  - ☐ DOMINANT HAND
  - ☐ HAND GRIP MEASUREMENT
- ☐ IF LAST TRAINING SESSION, FILE SUBJECT PAYMENT RECEIPT
- ☐ SUBJECT'S CRF RETURNED TO FILE AREA FOR DATA MANAGER

SBJID _____
DATE ____ / ____ / ____
DAY 1 2 3 4 5
Experimenter _____

## DEVIATIONS AND OBSERVATIONS

4863PP
Revision: 2
Effective: 9/25/98

SBJID#_____
Date:____/____/____
Day 1 2 3 4 5
Experimenter:_____

Data Entry_____ 1st, _____2nd
Reviewed by_____ Date:_____
PI Review_____ Date:_____

# DOSE SESSION
# TRAINING CHECKLIST

## PRE SESSION PREPARATIONS

☐ **CONTROL ROOM E**

- ☐ SUBJECT's CRF
- ☐ BLOOD PRESSURE EQUIPMENT
- ☐ STETHOSCOPE
- ☐ THERMOMETER\THERMOMETER PROBE COVERS
- ☐ TRAINING SCRIPT
- ☐ PRACTICE FOOD DIARY & SCRIPT
- ☐ **(If Dose Training occurs on Friday)** BEGINNING SUNDAY FOOD DIARY
- ☐ GENERAL RESPONSE QUESTIONNAIRE (GRQ) & SCRIPT
- ☐ GENERAL RESPONSE QUESTIONNAIRE (GRQ) & SCRIPT
- ☐ DAILY LOG
- ☐ GLOBAL RATING FORM
- ☐ SUBJECT ID # **(If Dose Session Training occurs on the first day of training)**
  - ☐ SBJID TAG
  - ☐ SBJID CARD

☐ **BIO PREP ROOM**

- ☐ URINE CUP WITH LABELED LID **(First name and SBJID#)**

SBJID#_____
Date:____/____/____
Day 1 2 3 4 5
Experimenter:_____

## DOSING & MORNING SESSION TRAINING:

☐ SUBJECT TO CONTROL ROOM E

- ☐ ARRIVAL TIME _____

☐ **(If Dose Session Training occurs on first training day)** GIVE SUBJECT, SBJID #

- ☐ SBJID TAG
- ☐ SBJID CARD
- ☐ BASELINE URINE SAMPLE **(RECORD TIME)** _____
- ☐ GIVE SUBJECT CUP WITH LABELED LID TO COLLECT URINE SAMPLE

☐ **SUBJECT TO BIO PREP ROOM**

- ☐ BASELINE BLOOD DRAW **(RECORD TIME)**_____
  - ☐ PREGNANCY BLOOD DRAW FOR ALL FEMALES

☐ DEMONSTRATE FOOD DIARY

- ☐ GIVE SUBJECT PRACTICE FOOD DIARY

☐ ORAL TEMPERATURE _____**(If Temp. ≥ 99.6 , inform PI)**

- ☐ **RECORD THERMOMETER #G-631**

☐ BLOOD PRESSURE_____ / _____ **(If DBP is outside 50-90 mm/Hg, inform PI)**

- ☐ **CIRCLE BP CUFF IF OTHER THAN ADULT #G-6322 SIZE**

  Large# G-6321 Child# G-6323
- ☐ STETHOSCOPE # G-6327

☐ 1ST PULSE RATE _____**(If < 50 bpm, inform PI)**

☐ DEMONSTRATE DAILY LOG

- ☐ SUBJECT COMPLETES BASELINE DAILY LOG **(Check Daily Log and follow criteria for continuation of session as indicated in Daily Log procedures.)**

☐ EXPLAIN THE GLOBAL RATING FORM

☐ DEMONSTRATE GRQ

SBJID#_____
Date:____/____/____
Day 1 2 3 4 5
Experimenter:_____

☐ SUBJECT COMPLETES GRQ (**Check GRQ and follow criteria for continuation of session as indicated in GRQ procedures**)

☐ 2ND PULSE RATE _____ **(If < 50 bpm, inform PI)**

☐ REMIND SUBJECT TO COMPLETE PRACTICE FOOD DIARY

☐ REMIND SUBJECT TO FOLLOW APPOINTMENT CALENDAR

☐ REMIND SUBJECT TO RETURN FOR NEXT TRAINING SESSION ON

_____

☐ **(If Dose Training occurs on Friday)** GIVE SUBJECT A FOOD DIARY TO FILL OUT ON SUNDAY

☐ CONTINUE TO BATTERY TRAINING

**POST SESSION CLEAN UP:**

☐ RETURN DAILY LOG, GRQ, AND GLOBAL RATING FORM TO CRF AFTER SCORING.

☐ RECORD TRAINING PULSE ONE AND TWO ON BASELINE DATA SHEET.

**DEVIATIONS AND OBSERVATIONS**

SBJID#_____
Date____/____/____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date_____ |
| PI Review _____ | Date _____ |

# BATTERY B TRAINING CHECKLIST
## ANAM

**PRE SESSION PREPARATIONS**
**CONTROL ROOM B:**

☐ ANAM COMPUTER ON
☐ PRINTER ONLINE AND SET TO NEW PAGE
☐ DISKETTE IN COMPUTER TO VERIFY TRAINING DATA
☐ CHECK COMPUTER FOR CORRECT DATE/TIME
☐ CLIPBOARD WITH GRQ AND PENS
☐ PRACTICE GRQ AND GRQ KEY
☐ SUBJECT ID # **(If ANAM training occurs first, on the first day of training)**
  ☐ SBJID TAG
  ☐ SBJID CARD

**ANAM TRAINING:**

☐ SUBJECT ARRIVAL TIME _____
☐ CLOSE DOOR TO CONTROL ROOM B
☐ GIVE SBJID# **(If ANAM training occurs first, on first day of training)**
☐ GRQ **(Check GRQ as indicated in GRQ procedures)**
☐ EXPLAIN THE ANAM TASKS AND THEIR RELEVANCE TO THE STUDY
  ☐ Complex tasks that measure reaction time, memory, attention, reasoning
  ☐ Importance of getting consistent performance scores
  ☐ Meeting criteria
☐ DETERMINE IF SUBJECT GUIDES THE MOUSE WITH RIGHT OR LEFT HAND AND ENTER ON BASELINE DATA SHEET RIGHT LEFT

☐ **ENTER START TIME** _____
☐ RUN DEMO PROGRAM TO FAMILIARIZE SUBJECTWITH TASKS AND PROCEDURES **(ENTER <DEMO(space)SBJ ##>)** e.g. for subject 10 enter <DEMO 10>

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

☐ ENTER START TIME _____

☐ HAVE SUBJECT PERFORM ALL TRIALS IN EACH BATTERY. **(Subject can take breaks if he/she feels it's needed.)**

☐ TO RUN, ENTER <T1>SPACE<##> e.g. for subject 10 enter <T1 10>

**NOTE:** TASKS CAN BE ABORTED/RE-STARTED BY USING THE INTERRUPT MENU (ALT-F1 KEYS.)

**NOTE INTERRUPTS IN CHECKLIST DEVIATIONS.**

| TASK | TRIALS | CRITERIA | CRITERIA MET? | # OF RE-RUNS ≤ 3 | CRITERIA MET? |
|---|---|---|---|---|---|
| RUNNING MEMORY TASK | 4 | Twice w/mean RT ≤ 800ms<br>accuracy ≥ 90% | YES NO | | YES NO |
| SIMPLE REACTION TIME | 4 | Twice w/mean RT ≤ 400ms<br>accuracy ≥ 90% | YES NO | | YES NO |
| UNSTABLE TRACKING TASK | 5 | Twice in a row<br>w/overall RMS tracking error ≤ 20<br>control losses ≤ 3 | YES NO | | YES NO |
| STERNBERG MEMORY TASK SET SIZE 4 | 4 | Twice w/mean<br>RT correct ≤ 700ms<br>errors ≤ 4 | YES NO | | YES NO |
| STERNBERG MEMORY TASK SET SIZE 6 | 4 | Twice in a row w/mean<br>RT correct ≤ 900ms<br>errors ≤ 5 | YES NO | | YES NO |

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

| TASK | TRIALS | CRITERIA | CRITERIA MET? | # OF RE-RUNS ≤ 3 | CRITERIA MET? |
|---|---|---|---|---|---|
| 2 CHOICE REACTION TIME TASK | 4 | Twice w/mean<br>RT correct ≤ 500ms<br>% correct ≥ 90% | YES NO | | YES NO |
| DUAL TRACKING/ STERNBERG SET-SIZE 4 | 5 | Twice in a row<br>% correct ≥ 80%<br>mean RT correct ≤ 1000<br>control losses ≤ 6<br>RMS error ≤ 25 | YES NO | | YES NO |
| MATH PROCESSING TASK | 4 | Twice w/mean<br>RT correct ≤ 3500ms<br>% correct ≥ 80% | YES NO | | YES NO |
| DUAL TRACKING/ STERNBERG SET-SIZE 6 | 5 | Twice in a row<br>% correct ≥ 80%<br>mean RT correct ≤ 1300ms<br>control losses ≤ 6<br>RMS error ≤ 25 | YES NO | | YES NO |

NOTE: TASKS CAN BE ABORTED/RE-STARTED BY USING THE INTERRUPT MENU (ALT-F1 KEYS.) **NOTE INTERRUPTS IN CHECKLIST DEVIATIONS.**

☐ S COMPLETES MARI/WORKLOAD QUESTIONNAIRE

☐ DID YOU NOTICE THAT YOUR STRATEGY CHANGED ON HOW YOU PERFORMED THE TASKS FROM THE FIRST TIME YOU DID THEM IN TRAINING, UNTIL NOW?

YES NO **(If YES, describe under Observations)**

☐ REVIEW ANAM DATA TO DETERMINE IF SUBJECT MEETS CRITERIA **(red titles indicate subject didn't meet criteria. Blue titles indicate that subject met criteria.)**

IF MORE THAN ONE SUBJECT IS TRAINING, EXIT THE CONTROL ROOM TO DISCUSS SCORES

☐ RE-RUN SINGLE TASKS IF APPLICABLE

ENTER: <T1>SPACE<##>SPACE<START TASK#>SPACE<ENDTASK #>
(e.g., to re-run task 5 for subject 3 enter: <T1 03 5 5>

☐ BATTERY END TIME _____

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

☐ IF CRITERIA WAS NOT MET, PRINT SCORES AND SEND TO BATTERY B REVIEWER (**labeled "For Performance Stability Review Only"**)

☐ BATTERY B REVIEWER:

- ☐ STABLE, NO RE-RUNS_____
- ☐ UNSTABLE, RE-RUN THE FOLLOWING TASKS_____
  WITH THE FOLLOWING NUMBER OF TRIALS_____
- ☐ UNSTABLE, REMOVE FROM STUDY_____
- ☐ BATTERY B REVIEWER INITIAL AND DATE_____

☐ **RE-RUNS COMPLETE**
YES NO NA **(If NO, explain in observations)**

**POST SESSION PROCEDURES:**

☐ TURN OFF POWER STRIP
☐ CHECK FORMS FOR PROPER ID
☐ STAPLE PRINTOUT TO CHECKLIST IN CRF
☐ BACKUP DATA TO LAN:

- **Copy training data to F:\study\pp\data\training\anam**

**TO DATA MANAGER:**

☐ TRAINING CHECKLIST
☐ PERFORMANCE PRINTOUT **(Signed and dated by Experimenter)**
☐ BATTERY B REVIEWER PRINTOUT (if subject didn't meet criteria)

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

## CHECKLIST DEVIATIONS OR OBSERVATIONS

4863PP
Revision: 3
Effective: 11/3/98

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date_____ |
| PI Review _____ | Date _____ |

# BATTERY B TRAINING CHECKLIST
## NES2

**PRE SESSION PREPARATIONS**
**CONTROL ROOM B:**

☐ NES2 COMPUTER ON
☐ PRINTER ONLINE AND SET TO NEW PAGE
☐ DISKETTE IN COMPUTER TO VERIFY TRAINING DATA
☐ CHECK COMPUTER FOR CORRECT DATE/TIME
☐ CLIPBOARD WITH GRQ AND PENS
☐ PRACTICE GRQ AND GRQ KEY
☐ SUBJECT ID # **(If NES2 training occurs first, on the first day of training)**
  ☐ SBJID TAG
  ☐ SBJID CARD

**NES2 TRAINING:**

☐ SUBJECT'S ARRIVAL TIME _____
☐ CLOSE DOOR TO CONTROL ROOM B
☐ GIVE SBJID# **(If NES2 training occurs first, on first day of training)**
☐ GRQ **(Check GRQ as indicated in GRQ procedures)**
☐ EXPLAIN THE NES2 TASKS AND THEIR RELEVANCE TO THE STUDY
  ☐ Complex tasks that measure reaction time, memory, attention, reasoning
  ☐ Importance of getting consistent performance scores
  ☐ Meeting criteria
☐ DETERMINE THE HAND WITH WHICH SUBJECT GUIDES THE MOUSE AND ENTER ON BASELINE DATA SHEET RIGHT LEFT

☐ **ENTER START TIME** _____

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

☐ RUN DEMO PROGRAM TO FAMILIARIZE SUBJECT WITH TASKS, PROCEDURES, AND PROPER KEYBOARD OPERATION
**(ENTER <DEMO(space)SBJ ##>) e.g. for subject 10 enter <DEMO 10>**

☐ **ENTER START TIME** _____

☐ HAVE SUBJECT PERFORM ALL TRIALS IN EACH BATTERY. (Subject can take breaks if he/she feels it's needed.)
☐ TO RUN ENTER: <T1> SPACE <##> e.g. for subject 10 enter <T1 10>

**NOTE**: TASKS CAN BE ABORTED/RE-STARTED BY USING THE INTERRUPT MENU (**F1-F8** AND CONTROL-C KEYS.) **NOTE INTERRUPTIONS IN CHECKLIST DEVIATIONS.**

| TASK | TRIALS | CRITERIA | CRITERIA MET? | # OF RE-RUNS ≤ 3 | CRITERIA MET? |
|---|---|---|---|---|---|
| PATTERN MEMORY TASK | 3 | Twice w/ ≤ 3 errors mean RT ≤ 7sec | YES NO | | YES NO |
| SYMBOL DIGIT SUBSTITUTION TASK | 4 | Twice w/ ≤ 5 errors mean RT ≤ 4sec | YES NO | | YES NO |
| SWITCHED ATTENTION TASK | 4 | Twice w/ # of errors in 3rd "switching" block ≤ 5 mean RT ≤ 800ms | YES NO | | YES NO |
| GRAMMATICAL REASONING TASK | 4 | Twice w/ ≤ 8 errors mean RT ≤ 5sec | YES NO | | YES NO |

☐ S PERFORMS MARI/WORKLOAD QUESTIONNAIRE
☐ DID YOU NOTICE THAT YOUR STRATEGY CHANGED ON HOW YOU PERFORMED THE TASKS FROM THE FIRST TIME YOU DID THEM IN THE TRAINING, UNTIL NOW? YES NO **(If YES, describe under Observations)**
☐ REVIEW NES2 DATA TO DETERMINE IF SUBJECT MEETS CRITERIA **(red titles indicate subject didn't meet criteria. Blue titles indicate that subject met criteria.)**

IF MORE THAN ONE SUBJECT IS TRAINING, EXIT THE CONTROL ROOM TO DISCUSS SCORES

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

☐ RE-RUN SINGLE TASKS IF APPLICABLE
ENTER: <T1>SPACE<##>SPACE<START TASK#>SPACE<ENDTASK #>
(e.g., to re-run task 5 for subject 3 enter: <T1 03 5 5>

☐ BATTERY END TIME_____

☐ IF CRITERIA WAS NOT MET, PRINT SCORES AND SEND TO BATTERY B REVIEWER (**labeled "For Performance Stability Review Only"**)

☐ **BATTERY B REVIEWER:**

- ☐ STABLE, NO RE-RUNS_____
- ☐ UNSTABLE, RE-RUN THE FOLLOWING TASKS_____
  WITH THE FOLLOWING NUMBER OF TRIALS_____
- ☐ UNSTABLE, REMOVE FROM STUDY_____
- ☐ BATTERY B REVIEWER INITIAL AND DATE_____

☐ **RE-RUNS COMPLETE**
YES NO NA **(If NO, explain in observations)**

**POST SESSION PROCEDURES:**

☐ TURN OFF POWER STRIP
☐ CHECK FORMS FOR PROPER ID
☐ STAPLE PRINTOUT TO CHECKLIST IN CRF
☐ BACKUP DATA TO LAN:

- **Copy training data to F:\study\pp\data\training\nes2**

**TO DATA MANAGER:**

☐ TRAINING CHECKLIST
☐ PERFORMANCE PRINTOUT **(Signed and dated by experimenter.)**
☐ BATTERY B REVIEWER PRINTOUT (if subject didn't meet criteria)

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

## CHECKLIST DEVIATIONS OR OBSERVATIONS

4863PP
Revision: 4
Effective: 11/3/98

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date_____ |
| PI Review _____ | Date _____ |

# BATTERY B TRAINING CHECKLIST
# FINAL TRAINING

## PRE SESSION PREPARATIONS
## CONTROL ROOM B:

☐ TURN COMPUTERS ON
☐ PRINTERS ONLINE AND SET TO NEW PAGE
☐ DISKETTES IN COMPUTERS TO VERIFY DATA
☐ CHECK COMPUTER FOR CORRECT DATE/TIME
☐ CLIPBOARD WITH GRQ AND PENS
☐ PRACTICE GRQ AND GRQ KEY
☐ DETERMINE ORDER OF TASKS **(indicated in baseline data sheet)**
☐ FOOD DIARY **(If Battery B Final Training occurs on Friday)**

## BATTERY B FINAL TRAINING:

☐ SUBJECT ARRIVAL TIME _____
☐ CLOSE DOOR TO CONTROL ROOM B
☐ GRQ **(Check GRQ as indicated in GRQ procedures)**
☐ EXPLAIN WHAT SESSION TWO INCLUDES:
- ☐ ONE TRIAL OF EACH TASK
- ☐ SESSION INCLUDES ANAM AND NES2 **(order is specified in header, and noted on baseline data sheet)**

☐ RUN DEMO PROGRAM TO FAMILIARIZE SUBJECT WITH TASKS AND PROCEDURES
**(ENTER <DEMO(SPACE)SBJ##>)** e.g., FOR SUBJECT 10 ENTER <DEMO 10>

☐ **ENTER START TIME** _____
☐ TO BEGIN ENTER <T2 ##> e.g. for subject 10 enter <T2 10>

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

NOTE: TASKS CAN BE ABORTED/RESTARTED BY USING THE INTERRUPT MENU (F1-F8; CONTROL-C KEYS). NOTE ALL INTERRUPTS IN CHECKLIST DEVIATIONS

☐ SUBJECT COMPLETES ALL TASKS: ANAM NES2

☐ S COMPLETES MARI/WORKLOAD ANAM NES2

☐ DETERMINE IF S MET CRITERIA

☐ DID YOU NOTICE THAT YOUR STRATEGY CHANGED ON HOW YOU PERFORMED THE TASKS FROM THE FIRST TIME YOU DID THEM IN THE TRAINING, UNTIL NOW? YES NO **(If YES, describe under Observations)**

☐ GIVE S A FOOD DIARY TO FILL OUT ON SUNDAY **(If Battery B Training occurs on Friday)**

☐ IF THIS IS FINAL TRAINING SESSION, PAY SUBJECT AND HAVE SUBJECT SIGN RECEIPT

☐ **END TIME** _____

**POST SESSION PROCEDURES:**

☐ IF CRITERIA WAS NOT MET, PRINT SCORES AND SEND TO BATTERY B REVIEWER **(labeled "For Performance Stability Review Only")**

☐ **BATTERY B REVIEWER**

- ☐ STABLE, NO RE-RUNS _____
- ☐ UNSTABLE, RE-RUN THE FOLLOWING TASKS _____
  WITH THE FOLLOWING NUMBER OF TRIALS _____
- ☐ UNSTABLE, REMOVE FROM STUDY _____
- ☐ BATTERY B REVIEWER INITIAL AND DATE _____

☐ **RE-RUNS COMPLETE**
YES NO NA **(If NO, explain in Observations)**

☐ TURN OFF COMPUTERS/PRINTERS

☐ CHECK FORMS FOR PROPER ID

☐ IF THIS IS FINAL TRAINING SESSION, FILE PAYMENT RECEIPT

☐ BACKUP DATA TO LAN:

- **Copy training data to training ANAM or NES2 file in F:\study\pp\data\training**

4863PP
Revision: 4
Effective: 11/3/98

SBJID#_____
Date_____/_____/_____
TRNG DAY 1 2 3 4 5
Experimenter_____
Training Order: NES2/ANAM
ANAM/NES2

☐ RETURN SUBJECT'S CRF NOTEBOOK TO FILE AREA FOR DATA MANAGER

## CHECKLIST DEVIATIONS OR OBSERVATIONS

4863 pp
Revision 1
Effective: 8/12/98

SBJID# _____
DATE ____ / ____ / ____
DAY 1 2 3 4 5
PHASE I PHASE II
Experimenter _____

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date _____ |
| PI Review _____ | Date _____ |

# AM DOSING CHECKLIST

## PRE SESSION PREPARATIONS:

☐ **CONTROL ROOM E:**

- ☐ S's CRF
- ☐ BLOOD PRESSURE EQUIPMENT
- ☐ STETHOSCOPE
- ☐ THERMOMETER/THERMOMETER PROBE COVERS
- ☐ FOOD DIARY & SCRIPT
- ☐ GENERAL RESPONSE QUESTIONNAIRE (GRQ) & GRQ KEY
- ☐ DAILY LOG
- ☐ SUBJECT APPOINTMENT CALENDAR
- ☐ PILLS (Mon=01, Tues=04, Wed=07, Thur=10, Fri=13)
- ☐ WATER & CUPS
- ☐ ENTER S's BREAKFAST CHOICE FROM BASELINE DATA SHEET _____

## AM DOSING SESSION:

☐ SUBJECT TO CONTROL ROOM E.
- ☐ TIME S ARRIVED _____

☐ FOOD DIARY FROM PREVIOUS DAY (**Check Food Diary. Retrieve missing information from S.**)

- ☐ GIVE S NEW FOOD DIARY FOR CURRENT DAY. (**Experimenter will instruct the S to record all food and drink consumed before S's arrival at MRI that day, as well as all food and drink consumed while at MRI.) (S will not receive a Food Diary on Day 5, Friday**)

☐ ORAL TEMPERATURE _____ ( **If Temp. ≥ 99.6°, refer to medical monitor**)
- ☐ **RECORD THERMOMETER # G-631**

☐ BLOOD PRESSURE ____/____ (**If DBP is outside 50-90 mm/Hg, refer to medical monitor**)
- ☐ **CIRCLE BP CUFF SIZE IF OTHER THAN ADULT #G-6322**
  Large# G-6321 Child# G-6323
- ☐ STETHOSCOPE # G-6327

☐ PULSE RATE _____ (**If ≥ 20% below baseline pulse rate on Baseline Data Sheet, or < 50 bpm, refer to medical monitor**)

SBJID# _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II
Experimenter _____

☐ S REFERRED TO PHYSICIAN YES NO

☐ SERVE S BREAKFAST (**While eating breakfast, S will complete the following:**)

☐ DAILY LOG (**Check Daily Log and follow criteria for continuation of session as indicated in Daily Log procedures.**)

☐ DAILY LOG RESPONSES REFERRED TO PI YES NO

☐ GENERAL RESPONSE QUESTIONNAIRE (**Check GRQ and follow criteria for continuation of session as indicated in GRQ procedures.**)

☐ S REFERRED TO PHYSICIAN YES NO

☐ MORNING DOSE, TIME _____ (**Experimenter will watch as S swallows pill.**)

☐ REMIND S OF RETURN TIME _____ (**Check the S's Appointment Calendar for return time.**)

☐ DEPARTURE TIME _____

## POST SESSION CLEAN UP:

☐ DISPOSE OF EMPTY BLISTER PACKS
☐ IF DOSE IS NOT TAKEN, RETURN UNUSED DOSE TO REFRIGERATOR
☐ NOTE DEVIATION ON CHECKLIST AND INFORM PI
☐ DISPOSE OF BREAKFAST WASTE
☐ RETURN S'S CRF NOTEBOOK TO FILE AREA FOR DATA MANAGER

**DEVIATIONS / OBSERVATIONS:**

SBJID#_____
Date___/___/____
Day 1 2 3 4 5
Dose: 16:00 24:00
Phase I Phase II
Experimentor_____

Data Entry 1st_____, 2nd_____
Reviewed by_____ Date_____
PI Review_____ Date_____

# DOSING—16:00, 24:00 CHECKLIST

**PRE-SESSION PREPARATIONS:**

☐ **CONTROL ROOM E:**

- ☐ SUBJECT'S CRF NOTEBOOK
- ☐ PILLS (Mon=02, 03; Tues=05, 06; Wed=08, 09; Thurs=11, 12)
- ☐ WATER & CUPS

☐ 16:00 DOSE, SUBJECT TO CONTROL ROOM E.

☐ 24:00 DOSE, VOLKER ENTRANCE RECEPTION AREA

☐ ARRIVAL TIME_____

☐ **(IF SUBJECT COMPLAINS OF FEELING ILL, TAKE VITAL SIGNS AND GRQ)**

- ☐ VITAL SIGNS
  - ☐ ORAL TEMPERATURE _____ **(IF TEMP. ≥ 99.6°, REFER TO PHYSICIAN.)**

    **RECORD THERMOMETER #G-631**
  - ☐ BLOOD PRESSURE _____ **(IF DBP IS OUTSIDE 50-90 mm/Hg, REFER TO PHYSICIAN.)**
    - ☐ **(CIRCLE BP CUFF SIZE IF OTHER THAN ADULT# G-6322**

      Large# G-6321 Child# G-6323
    - ☐ STETHOSCOPE # G-6327
    - ☐ PULSE RATE _____ **(IF < 50 BPM, REFER TO PHYSICIAN OR ≥ 20% BELOW BASELINE PULSE RATE-SEE BASELINE DATA SHEET)**

☐ SUBJECT REFERRED TO PHYSICIAN YES NO

SBJID#_____
Date___/___/___
Day 1 2 3 4 5
Dose: 16:00 24:00
Phase I Phase II
Experimentor_____

☐ GRQ (**CHECK GRQ AND FOLLOW CRITERIA FOR CONTINUATION OF SESSION AS INDICATED IN GRQ PROCEDURES.**)

☐ SUBJECT REFERRED TO PHYSICIAN YES NO

☐ (**If yes**) LEAVE VOICE MAIL INFORMING PI OF INTERIM REFERRAL.

☐ DOSE, TIME _____ (**EXPERIMENTER WILL WATCH AS SUBJECT SWALLOWS PILL.**)

☐ REMIND SUBJECT OF RETURN TIME _____ (**CHECK THE SUBJECT's APPOINTMENT CALENDAR FOR RETURN TIME.**)

☐ SUBJECT DEPARTURE TIME_____

**POST SESSION ACTIVITIES:**

☐ RETURN SUBJECT'S CRF NOTEBOOK TO FILE AREA FOR DATA MANAGER

☐ DISPOSE OF EMPTY BLISTER PACK AND CUP

☐ IF INTERIM REFERRAL IS MADE, NOTE DEVIATION ON CHECKLIST AND INFORM PI

## DEVIATIONS / OBSERVATIONS

4863PP
Revision 1
Effective 7/10/98

SBJID # _____
DATE _____ / _____ / _____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

Date Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# GENERAL RESPONSE QUESTIONNAIRE

**INSTRUCTIONS:** Below, is a list of the kind of symptoms that people sometimes report to their doctor. Please read each symptom carefully. Put an **X** in the box that best describes each symptom: **IF THE SYMPTOM HAS OCCURRED IN THE LAST 24 HOURS, PUT AN X IN THE BOX THAT BEST HOW MUCH YOU WERE BOTHERED OR DISTRESSED BY EACH SYMPTOM.** Check only one selection for each symptom and do not skip any items. If you change your mind, mark one line through your first answer, initial and date it, then put an **X** on your new choice.

**In the last 24 hours, how much were you distressed or bothered by:**

| DESCRIPTION: | Did Not Occur | A Little | Somewhat | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 1. Weakness | | | | | | | |
| 2. Trouble speaking | | | | | | | |
| 3. Chills | | | | | | | |
| 4. Blind spots in eyes | | | | | | | |
| 5. Temper outbursts | | | | | | | |
| 6. Chest pain | | | | | | | |
| 7. Excessive thirst | | | | | | | |
| 8. Nausea | | | | | | | |
| 9. Skin rash | | | | | | | |
| 10. Numbness | | | | | | | |
| 11. Headaches | | | | | | | |
| 12. Stiff neck | | | | | | | |
| 13. Night sweats | | | | | | | |
| 14. Depression | | | | | | | |
| 15. Nose bleeds | | | | | | | |
| 16. Unusual belching | | | | | | | |
| 17. Trouble swallowing | | | | | | | |
| 18. Blurred/double vision | | | | | | | |
| 19. Body aches | | | | | | | |

# GENERAL RESPONSE QUESTIONNAIRE (CONTINUED)

4863PP
Revision 1
Effective 7/10/98

SBJID # _____
DATE _____ / _____ / _____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

| DESCRIPTION: | Did Not Occur | A Little | Somewhat | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 20. Swollen lymph nodes | | | | | | | |
| 21. Urination problem | | | | | | | |
| 22. Shortness of breath | | | | | | | |
| 23. Bloating | | | | | | | |
| 24. Fainting | | | | | | | |
| 25. Dizziness | | | | | | | |
| 26. Memory impairment | | | | | | | |
| 27. Sore tongue | | | | | | | |
| 28. Vomiting | | | | | | | |
| 29. Heartburn | | | | | | | |
| 30. Bleeding gums | | | | | | | |
| 31. Fearfulness/anxiety | | | | | | | |
| 32. Diarrhea | | | | | | | |
| 33. Heart palpitations | | | | | | | |
| 34. Ringing in ears | | | | | | | |
| 35. Flatulence/passing gas | | | | | | | |
| 36. Hand tremors/shaking | | | | | | | |
| 37. Persistent cough | | | | | | | |
| 38. Skin itching | | | | | | | |
| 39. Fever | | | | | | | |
| 40. Nervousness | | | | | | | |
| 41. Abdominal pain | | | | | | | |
| 42. Sleep disturbance | | | | | | | |
| 43. Dark or bloody urine | | | | | | | |
| 44. Fatigue | | | | | | | |
| 45. Constipation | | | | | | | |

4863PP
Revision 2
Effective 11/3/98

SBJID # _____
DATE ____/____/_____
DAY 1 2 3 4 5 8
Phase I Phase II Training
Experimenter _____

Date Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# DAILY LOG

Please complete the following questionnaire. We are concerned only with the **last 24 hour period** so answer the questions for that time period only. If you want to change any of your answers, please clearly mark through your first answer, write your initial and the current date next to the mark, and then circle or write your new answer. If you have any questions, please ask for assistance.

1. Have you used or applied any insecticide, that is, chemicals used to kill insects, within the last twenty-four hours? YES NO

   If yes, please list the names of the chemicals you used: _____
   _____

2. Have you taken any of the following within the last twenty-four hours?

   a. **Prescription medications** YES NO
   If yes, please list medications: _____
   _____

   b. **Over-the-counter-medications** YES NO
   If yes, please list medications: _____
   _____

   c. **Vitamins or minerals** YES NO
   If yes, please list: _____
   _____

   d. **Health supplements** YES NO
   If yes, please list: _____
   _____

3. Have you consumed any herbal teas or drinks, or taken any herbal supplements within the last twenty-four hours? YES NO

   If yes, please list: _____
   _____

4863PP
Revision 1
Effective 7/10/98

SBJID # _____
DATE _____ / _____ / _____
Phase I Phase II Training
Experimenter _____

Date Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

## GLOBAL-RATING FORM

Please answer the following questions about the study phase you just completed.

1. IN YOUR JUDGMENT, WHICH PILLS DID YOU RECEIVE THIS PAST WEEK.
   1. _____ PYRIDOSTIGMINE
   2. _____ PLACEBO

2. HOW CONFIDENT ARE YOU OF THIS JUDGMENT? **(Circle one)**

   **1** **2** **3** **4** **5**
   **(Not at all confident)** **(Totally confident)**

3. WHAT ARE YOU BASING THIS JUDGMENT ON?

   _____
   _____
   _____
   _____

4. OVER THE PAST WEEK, HAVE YOU NOTICED ANY CHANGES IN YOUR:

   **(1)** PHYSICAL COORDINATION YES NO **(If Yes, Describe)** _____
   _____
   _____

   **(2)** VISUAL PERCEPTION YES NO **(If Yes, Describe)** _____
   _____
   _____

   **(3)** MEMORY YES NO **(If Yes, Describe)** _____
   _____
   _____

   **(4)** ATTENTION SPAN YES NO **(If Yes, Describe)** _____
   _____
   _____

   **(5)** SENSE OF TIME YES NO **(If Yes, Describe)** _____
   _____
   _____

4863(PP) Revision 1 (8/17/98)

Reviewed by _____ Date _____
PI Review _____ Date _____

SBJID#_____
PHASE: 1 2 Training
DATE: ___ / ___ / ___

# FOOD DIARY

**FOOD DIARY FOR: Sun. ___ Mon. ___ Tues. ___ Wed. ___ Thur. ___**

| | FOOD EATEN | | BEVERAGES | |
|---|---|---|---|---|
| | **DESCRIPTION** (Any foods: Meat, beans, rice, vegetables, fruit, breads, potatoes, candy, etc.) ( Please describe fully.) | **TIME** | **DESCRIPTION** (Any drinks: Milk, water, soft drinks, juice, coffee, or tea, black or with cream or sugar, etc.) ( Please describe fully.) | **TIME** |
| **Breakfast** 1 | | | | |
| **Snacks** 2 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Lunch** 3 | | | | |
| **Snacks** 4 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Dinner** 5 | | | | |
| **Before Bed Snacks** 6 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Midnight Snacks** 7 | (Any food eaten between meals) | | (Any beverages between meals) | |

4863PP
Revision:4
Effective: 11/3/98

SBJID#_____
Date:____/____/____
DAY 1 4 5
Phase I Phase II
Experimenter _____
Battery Order: ANAM/NES2
NES2/ANAM

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date_____ |
| PI Review _____ | Date_____ |

## BATTERY B EXPERIMENTAL CHECKLIST

### PRE SESSION PREPARATIONS:

☐ TURN COMPUTERS ON
☐ PRINTERS ONLINE AND SET TO NEW PAGE
☐ DISKETTES IN COMPUTERS TO RECORD DATA FILES
☐ CHECK COMPUTERS FOR CORRECT DATE/TIME
☐ DETERMINE ORDER OF TASKS **(indicated in baseline data sheet)**
☐ BIO PREP ROOM: URINE CUP WITH LABELED LID **(For days 4 and 5 only)**
☐ RECORD LUNCH CHOICE FROM BASELINE DATA SHEET_____

### RUNNING BATTERY B:

☐ SUBJECT ARRIVAL TIME _____
☐ URINE SAMPLE **(DAYS 4 AND 5 ONLY)**
**(RECORD TIME)**_____
- ☐ SHOW SUBJECT TO BIO PREP ROOM
- ☐ GIVE SUBJECT CUP WITH LABELED LID AND TOWELETTE
  - ☐ INSTRUCT SUBJECT TO FILL CUP, PLACE LID LIGHTLY ON CONTAINER
  - ☐ INSTRUCT SUBJECT TO BRING URINE SPECIMEN BACK TO BIO PREP ROOM
  - ☐ LEAVE SAMPLE WITH LAB TECH IN BIO PREP ROOM

☐ BLOOD DRAW **(DAYS 1, 4, AND 5)**
**(RECORD TIME)**_____
☐ SERVE SUBJECT LUNCH **(IN CONTROL ROOM E)**
☐ CLOSE DOOR TO CONTROL ROOM B

4863PP
Revision:4
Effective: 11/3/98

SBJID#_____
Date:____/____/____
DAY 1 4 5
Phase I Phase II
Experimenter _____
Battery Order: ANAM/NES2
NES2/ANAM

☐ REVIEW GENERAL PROCEDURES FOR PERFORMING TASK BATTERY

☐ RUN DEMO PROGRAM TO FAMILIARIZE SUBJECT WITH TASKS AND PROCEDURES
**(ENTER <DEMO(space)SBJ##>)** e.g., for subject 10 enter <DEMO 10>

☐ **ENTER START TIME** _____

☐ HAVE SUBJECT PERFORM ENTIRE BATTERY **(includes one trial of each task)**
COMMANDS FOR ANAM/NES2 OR NES2/ANAM (## is the sbjid):

**PHASE I:**

☐ MONDAY: <M1>SPACE<##>
☐ THURSDAY: <R1>SPACE<##>
☐ FRIDAY: <F1>SPACE<##>

**PHASE II:**

☐ MONDAY: <M2>SPACE<##>
☐ THURSDAY: <R2>SPACE<##>
☐ FRIDAY: <F2>SPACE<##>

**(THE EXPERIMENTER WILL TRY TO BE AS QUIET AS POSSIBLE DURING TESTING)**
☐ S COMPLETES MARI/WORKLOAD NES2/ANAM
☐ DID YOU NOTICE THAT YOUR STRATEGY CHANGED ON HOW YOU PERFORMED THE TASKS, FROM THE FIRST TIME YOU DID THEM, UNTIL NOW?
YES NO **(IF YES, DESCRIBE IN DEVIATIONS AND OBSERVATIONS SECTION, PG. 3)**
☐ **ENTER ENDING TIME** _____

**POST SESSION PROCEDURES:**
☐ TURN OFF COMPUTERS/PRINTERS
☐ CHECK FORMS FOR PROPER ID
☐ BACKUP DATA TO LAN:

- **Copy experimental data to experimental ANAM or NES2 file in F:\study\pp\data\experim**
- **Convert eforms to notepad. Move the updated txt file to F:\study\pp\data\transfer**

**TO DATA MANAGER**
☐ EXPERIMENTAL CHECKLIST

4863PP
Revision:4
Effective: 11/3/98

SBJID#_____
Date:____/____/____
DAY 1 4 5
Phase I Phase II
Experimenter _____
Battery Order: ANAM/NES2
NES2/ANAM

## DEVIATIONS OR OBSERVATIONS

4863PP
Revision: 1
Effective: 4/9/99

Data Entry _____1st, _____2nd
Reviewed by _____ Date
PI Review _____ Date

SBJID _____
DATE ___ / ___ / ___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

# BATTERY A CHECKLIST

## PRE SESSION PREPARATIONS:

### ➡ HOOK-UP ROOM

- ☐ GOLD CUP SENSOR TAIL
- ☐ EC2 CREAM
- ☐ WAX PENCIL
- ☐ CRF (Case Report File)
- ☐ Q-TIPS
- ☐ GAUZE PADS
- ☐ SKIN PREP GEL
- ☐ ECG PADS
- ☐ TAPE MEASURE
- ☐ SURGICAL TAPE
- ☐ SCRUB TOP
- ☐ CHECK BASSELINE DATA SHEET FOR CUFF SIZE AND MARK ON PAGE 3 IF OTHER THAN ADULT
- ☐ RECORD NASION TO INION AND LEFT TO RIGHT PREAURICULAR POINTS ON PG. 3 OF CHECKLIST FROM BASELINE DATA SHEET
- ☐ RECORD DOMINANT HAND ON PG. 8 OF CHECKLIST FROM BASELINE DATA SHEET
- ☐ RECORD HAND GRIP MEASUREMENT ON PG. 9 OF CHECKLIST FROM BASELINE DATA SHEET
- ☐ RECORD TIME OF NEXT DOSE ON PG. 9 OF CHECKLIST
- ☐ RECORD LUNCH CHOICE FROM BASELINE DATA SHEET _____

### ➡ TONOMETRY

- ☐ ATTACH ECG ELECTRODES TO TONOMETRY UNIT
- ☐ TURN ON COLIN UNIT AND LAPTOP
- ☐ SELECT: **PP ACQUISITION**
- ☐ SELECT: **ACQUIRE**, ENTER FILE NAME **PP##*PDT***
- ☐ COLLECT 4 SECONDS OF CALIBRATION
- ☐ PRESS: **ENTER** TO PAUSE COLLECTION

### ➡ CONTROL ROOM D:

#### ➡ NEUROSCAN SET-UP

- ☐ POWER ON TO MONITOR
- ☐ POWER ON TO SYNAMPS

*** (Wait for SCSI to show before powering up SCAN and STIM)**

SBJID _____
DATE ___ / ___ / ___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

- ☐ DISCONNECT NETWORK CABLE TO SCAN
- ☐ POWER ON TO SCAN AND STIM
- ☐ POWER ON TO TALK-A-PHONE
- ☐ POWER ON TO LIGHTS AND VIDEO
- ☐ POWER ON TO VIDEO MONITOR
- ☐ POWER ON TO FAN

➡ **CHAMBER D:**

- ☐ CFF CONTROL BOX IN POSITION **(Flash intensity set to 1 and flashes to repeat)**
- ☐ STROBE LIGHT PLUGGED IN
- ☐ PUT EARPLUGS ON EARPHONES

➡ **CONTROL ROOM A:**

- ☐ **OPTEC:** POWER ON; ORANGE AND GREEN LIGHTS ON, FOREHEAD PAD IN PLACE
- ☐ **HAND STEADINESS TEST:**
- ☐ **GRIP STRENGTH:** SET HAND GRIP FOR S's MEASUREMENT SHOWN ON BASE LINE DATA SHEET
- ☐ **MARI & WORKLOAD:** POWER ON TO COMPUTER, TYPE <PP>

➡ **BIO PREP ROOM**

- ☐ URINE CUP WITH LABELED LID **(First name, SBJID, and Time. Days 4 and 5 only)**

**BATTERY A:**

- ☐ SUBJECT ARRIVAL TIME _____
- ☐ URINE SAMPLE **(Days 4 and 5 only, approx. 11:25 am)**
  **(RECORD TIME)** _____
- ☐ GIVE SUBJECT CUP WITH LABELED LID AND TOWELETTE TO COLLECT URINE SAMPLE
  **(Days 4 and 5 only)**

➡ **SUBJECT TO BIO PREP ROOM**

- ☐ BLOOD DRAW **(Days 1, 4, and 5) (Approx. 11:30 am.) (RECORD TIME)** _____

➡ **SUBJECT TO CONTROL ROOM E**

- ☐ SERVE SUBJECT LUNCH **(ON DAY 5 ONLY: Collect Thursday's food diary and have Subject record Friday's food on back.)**

➡ **SHOW SUBJECT TO HOOK-UP ROOM**

- ☐ ASK SUBJECT TO PUT ON SCRUB TOP **(Leave room. Subject will open door when changed.)**
- ☐ TAKE WEIGHT. _____ Lbs. **(Scales #G-6324)**

SBJID _____
DATE ___ / ___ / ___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

➡ **COMPLETE ECG AND TONOMETRY HOOK UP**

☐ ATTACH ECG ELECTRODES:

**LL (Red)--LEFT RIB**
**LA(Black)--LEFT CLAVICLE**
**RA(White)--RIGHT CLAVICLE**

☐ ATTACH BP CUFF TO RIGHT ARM

➡ **BLOOD PRESSURE MEASUREMENT (Tonometry Unit #012567)**

✶**(Subject will lie down for a total of 8 minutes. Subject will stand for a total of 8 minutes.)**

☐ INSTRUCT SUBJECT TO LIE DOWN

☐ CIRCLE CUFF SIZE IF OTHER THAN ADULT:
**Large** **Small**

☐ TURN ON TONOMETRY UNIT AND SET CUFF INTERVAL TO 2 **(Press cuff start/stop button 2X to start and press enter on laptop to start tonometry collection. Click event marker at beginning of first cuff inflation.)**

☐ **RECORD BEGINNING BP** _____/_____
☐ **RECORD BP** _____/_____ **(At 2 minutes)**
☐ **RECORD BP** _____/_____ **(At 4 minutes)**
☐ **RECORD BP** _____/_____ **(At 6 minutes)**

☐ INSTRUCT SUBJECT TO STAND WHEN CUFF BEGINS TO INFLATE **(Click event marker.)**
☐ **RECORD BP** _____/_____ **(At 8 minutes)**
☐ **RECORD BP** _____/_____ **(At 10 minutes)**
☐ **RECORD BP** _____/_____ **(At 12 minutes)**
☐ **RECORD BP** _____/_____ **(At 14 minutes)**
☐ **RECORD BP** _____/_____ **(At 16 minutes) (Click event marker.)**

➡ **COMPLETE SENSOR HOOK UP (Use hook-up measurements from baseline data sheet)**

NASION TO INION _____ LEFT TO RIGHT PREAURICULAR POINTS _____

☐ CHECK RESISTANCES **(Record resistance measurements. Resistance ≤ 3.)**

Forehead (ground) _____, Cz _____, Oz _____, Rt. Mastoid _____; Lft. Mastoid _____

SBJID _____
DATE ___ / ___ / ___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

➡ **SUBJECT TO CHAMBER D**

- ☐ ADJUST PILLOW ON CHAIR TO SUPPORT NECK. ASSURE SUBJECT's RELAXATION.
- ☐ PLUG IN ELECTRODE TAIL
- ☐ CLIP EARPHONES ONTO SCRUB
- ☐ PULL MONITOR FORWARD UNTIL IT TOUCHES CHAIR LEGS **(65cm from nasion to middle of monitor screen)**
- ☐ CLOSE BOTH DOORS
- ☐ CHECK INTERCOM

➡ **CHECKERBOARD TASK (VEP) ( Neuroscan #9302040)**

Set Headbox

- ☐ INSERT PINS 13 AND 14 INTO REFERENCE
- ☐ INSERT SHORTING PLUG

Calibrate SCAN (start with **Acquire** icon)

- ☐ Menu: **Setup | Select ... PPvep.ast**
- ☐ Menu: **Acquisition | Calibrate** - Sine wave clean and value between 0.99 and 1.10

Check EEG Quality

- ☐ HEADBOX: REMOVE SHORTING PLUG
- ☐ SCAN: green ▷ speed button
- ☐ ENTER FILE NAME: **PP##*PD*V**

Set STIM

- ☐ STIM: press **V (but not ↵)**
- ☐ MONITOR BOX: **S** (STIM monitor screen will go black)

Set SCAN

- ☐ SCAN: **SAVE** speed button
- ☐ ENTER FILE NAME: **PP##*PD*V**

Start Collection

- ☐ INSTRUCT SUBJECT: *Look directly at blue dot in the middle of the screen. Try not to blink. Sit Still.*
- ☐ CHAMBER LIGHTS OFF
- ☐ STIM: press ↵ Note developing Waveform and accumulation of Accepted Sweeps.

SBJID _____
DATE ___/___/___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

Finish Collection - after **Accepted Sweeps = 200**

- ☐ SCAN: **STOP** icon
- ☐ STIM: **ESC** x2
- ☐ EXIT ACQUIRE
- ☐ CHAMBER LIGHTS ON
- ☐ MONITOR BOX: **E**
- ☐ CHAMBER MONITOR OFF (Power strip beside SynAmps)
- ☐ INSTRUCT SUBJECT: *Insert Earplugs and Prepare for Click Task.*

➡ **CLICK TASK (BAEP) ( Neuroscan #9302040)**

Set Headbox

- ☐ INSERT PINS 13 AND 14 INTO HOLES 29 AND 30; RESPECTIVELY
- ☐ INSERT SHORTING PLUG

Calibrate SCAN (starts with **Acquire** icon)

- ☐ Menu: **Setup | Select ... PPbaep.ast**
- ☐ Menu: **Acquisition | Calibrate** - Sine wave clean and values between 1.10 and 1.20

Check EEG Quality

- ☐ HEADBOX: REMOVE SHORTING PLUG
- ☐ SCAN: green ▷ speed button

Set STIM

- ☐ STIM: press **B (but not ↵)**

Set SCAN

- ☐ SCAN: **SAVE** speed button
- ☐ ENTER FILE NAME: **PP##*PD*B1**

☐ INSTRUCT S: *Close eyes ... Relax jaw ... Ok to doze ... Just listen to clicks ... Hold still.*

☐ CHAMBER LIGHTS **OFF**

Start Collection ONE

- ☐ STIM: press ↵ Note developing Waveforms and accumulation of Accepted Sweeps.
- ☐ SCAN: **STOP** icon when Accepted Sweeps=2000 and Fsp≥4; or Accepted Sweeps=4000 and Fsp≥2

Start Collection TWO

- ☐ SCAN: green ▷ speed button
- ☐ SCAN: **SAVE** speed button
- ☐ ENTER FILE NAME: **PP##*PD*B2**

Note developing Waveform and accumulation of Accepted Sweeps.

SBJID _____
DATE ___/___/___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

☐ SCAN: **STOP** icon when Accepted Sweeps=2000 and Fsp≥4; or Accepted Sweeps=4000 and Fsp≥2
☐ STIM: **ESC**
☐ EXIT ACQUIRE

☐ CHAMBER LIGHTS ON
☐ INSTRUCT SUBJECT: *Open eyes... Remove earplugs from ear... Relax...*
☐ TURN SUBJECT MONITOR ON FOR NEXT RUN

➡ **CFF (STROBE LIGHT TASK) (CFF #8834)**

☐ SEAT SUBJECT IN STRAIGHT BACK CHAIR
☐ POSITION STROBE LIGHT **(Light at eye level/ string from Subject's nasion to strobe light.)**
☐ CFF CONTROL BOX, POWER TO ON
☐ CFF CONTROL BOX, FLASH SWITCH TO REPEAT
☐ BEGINNING TIME: _____

☐ AS STROBE IS SOLID, SUBJECT TURNS DIAL UNTIL LIGHT BLINKS, AND VICE VERSA. RECORD NUMBER WHERE S STOPS. EXPERIMENTER, TURN DIAL TO 60 THEN 1

| | |
|---|---|
| PRACTICE AT 60. . . . . _____ | PRACTICE AT 1 . . . . . _____ |
| 1. START AT 60. . . . . _____ | 2. START AT 1. . . . . _____ |
| 3. START AT 60. . . . . _____ | 4. START AT 1. . . . . _____ |
| 5. START AT 60. . . . . _____ | 6. START AT 1. . . . . _____ |

☐ ENDING TIME: _____

☐ TURN CFF OFF

➡ **SUBJECT TO CONTROL ROOM A**

➡ **OPTEC TEST (OPTEC #011037)**

☐ INSTRUCTIONS TO THE SUBJECT
☐ TEAR SHEET FROM OPTEC PAPER PAD
☐ ADJUST THE OPTEC UP OR DOWN TO COMFORT LEVEL
☐ PRESS FOREHEAD AGAINST HEADREST PAD

SBJID _____
DATE ___/___/___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

## ➡ FAR VISION TEST

☐ SET NEAR/FAR BUTTON TO FAR (YELLOW)

☐ (F-1 VERTICAL PHORIA)
TURN DIAL INDICATOR TO 1 (YELLOW)

SAY: "LOOK INTO THE OPTEC. DO YOU SEE A RED DOTTED LINE? IS IT CROSSING A ROW OF STAIR STEPS? WHICH STEP IS THE DOTTED LINE AT THE CLOSEST LEVEL WITH?" **(Circle Subject's score)**

1 2 3 4 5 6 7 8 9

☐ (F-2 LATERAL PHORIA)
TURN DIAL INDICATOR TO 2 (YELLOW)

SAY: "WHAT NUMBER DOES THE ARROW POINT TO?"
**(Circle Subject's score)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

☐ (F-3 ACUITY)
TURN DIAL INDICATOR TO 3 (YELLOW)

SAY "IN THE BIG SIGN AT THE TOP, THE #1 SIGN, DO YOU SEE A LARGE BLACK CHECKERBOARD ON YOUR RIGHT? I WANT YOU TO GO THROUGH EACH NUMBER AND TELL ME WHERE THE CHECKERBOARD IS IN EACH BOX, RIGHT, LEFT, TOP, OR BOTTOM."
**(Circle Subject's score)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R | L | T | L | B | L | T | B | T | R | B | R |

☐ (F-6 DEPTH)
TURN DIAL INDICATOR TO 6 (YELLOW)

SAY, "YOU SHOULD SEE SOME RINGS. TELL ME WHICH RING SEEMS TO BE 3-D OR FLOATING ABOVE THE OTHERS, EITHER TOP, BOTTOM, RIGHT, OR LEFT." **(Circle Subject's score)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| B | L | B | T | T | L | R | L | R |

SBJID _____
DATE ___/___/___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

➡ **NEAR VISION TEST**

☐ SET NEAR/FAR BUTTON TO NEAR (BLUE)

☐ (N-8 ACUITY)
TURN DIAL INDICATOR TO 8 (BLUE)

SAY "ONCE AGAIN, PLEASE GO THROUGH AND TELL ME WHAT POSITION THE CHECKERBOARD IS IN."
**(Circle Subject's score)**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T | T | R | T | R | T | L | T | R | L | R | B |

☐ (N-11 VERTICAL PHORIA) (BLUE)
TURN DIAL INDICATOR TO 11

SAY "WHICH STEP IS AT THE CLOSEST LEVEL TO THE DOTTED LINE?"
**(Circle Subject's score)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

☐ (N-12 LATERAL PHORIA) (BLUE)
TURN DIAL INDICATOR TO 12

SAY "WHAT NUMBER IS THE ARROW POINTING TO?"
**(Circle Subject's score)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

➡ **HAND STEADINESS TEST** (USE DOMINANT HAND ONLY.)
**(Hand Steadiness tester #32011)**

☐ RECORD DOMINANT HAND: RIGHT _____, LEFT_____
**(RECORD DOMINANT HAND FROM BASELINE DATA SHEET )**

➡ $1^{ST}$ - $5^{TH}$ HOLE, BOTTOM ROW
☐ RESET: "INSERT STYLUS, STEADY-GO," PUSH START ( INSERT STYLUS, SAY "STEADY-GO" FOR EACH HOLE. DO NOT PUSH RESET EACH TIME.)

☐ RECORD TOTAL HAND STEADINESS MEASUREMENT _____

SBJID _____
DATE ___ / ___ / ___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

➡ **GRIP STRENGTH TEST (DETERMINE HAND GRIP MEASUREMENT, RECORD FROM BASELINE DATA SHEET)**
**(Hand Dynamometer #G-6268)**

☐ RECORD HAND GRIP MEASUREMENT

☐ GRIP STRENGTH ☐ PERCEIVED EXERTION RATE

| | |
|---|---|
| 1. DOMINANT _____ | 2. _____ |
| 3. NON DOMINANT _____ | 4. _____ |
| 5. DOMINANT _____ | 6. _____ |
| 7. NON DOMINANT _____ | 8. _____ |
| 9. DOMINANT _____ | 10. _____ |
| 11. NON DOMINANT _____ | 12. _____ |

➡ **MARI AND OVERALL WORKLOAD TESTS**

☐ TYPE: **PP**
☐ TYPE: **DP ##**
☐ OVERALL WORKLOAD: THIS IS A ONE-LINE TEST ASKING HOW DIFFICULT YOU FEEL THE ENTIRE BATTERY OF TESTS HAVE BEEN FOR YOU TODAY. ANSWER THE QUESTION AND CLICK DONE.
☐ MARI: THIS TEST ASKS HOW YOU FEEL **RIGHT NOW**. ANSWER ALL THE QUESTIONS AND CLICK DONE WHEN YOU ARE FINISHED WITH EACH PAGE.

➡ **DAILY DEBRIEFING WHILE REMOVING SENSORS**

☐ SUBJECT TO HOOK UP ROOM: REMOVE SENSORS
☐ DOES THE SUBJECT HAVE ANY QUESTIONS?
☐ DID ANYTHING MAKE HIM/HER UNCOMFORTABLE?
☐ REMIND SUBJECT TO COMPLETE FOOD DIARY
☐ REMIND SUBJECT TO FOLLOW APPOINTMENT CALENDAR
☐ REMIND SUBJECT TO RETURN FOR NEXT DAILY DOSE AT _____(TIME)
☐ ENDING TIME _____
☐ ESCORT SUBJECT OUT OF BUILDING

SBJID _____
DATE ___/___/___
DAY 1 4 5
PHASE I PHASE II
Experimenter _____

**POST SESSION CLEAN-UP**

- ☐ CLEAN SENSORS
- ☐ BACK UP, TONOMETRY, VEP, BAEP, AND WORKLOAD/MARI
- ☐ TURN OFF NEUROSCAN EQUIPMENT
- ☐ TURN OFF CONTROL ROOM A EQUIPMENT
- ☐ CHECK ALL DATA FOR APPROPRIATE ID **(Subject # and session date/time)**
- ☐ RETURN EAR PLUGS TO POCKET IN CRF NOTEBOOK
- ☐ SUBJECT'S CRF RETURNED TO FILE AREA FOR DATA MANAGER

---

**DEVIATIONS AND OBSERVATIONS**

MRI

NAME:_____
CALL#:_____
Experimenter's Initials:_____

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600

Data Entry 1st _____ 2nd _____
Reviewed by_____ Date_____
PI Review _____ Date_____

## Medical Examination Referral

**Referral to:** **Allen J. Parmet, M.D.**
**Union Hill Commons**
**3037 Main, Suite 201**
**Kansas City, Mo. 64108-3323**
**Telephone: 561-3480**
**FAX: 561-4043**

**Appointment Date: ___/___/____** **Time:_____**

| *Medical examination referral* | *For doctor's use only* | *Doctor's signature* |
|---|---|---|
| Entrance Medical Exam____ | Criteria met: YES NO | |
| Exit Medical Exam_____ | Changes noted: YES NO | |

*Doctor's Comments:*

INSTRUCTIONS TO DOCTOR

**For all referrals:**

- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

**Entrance Medical Exam:**

- Mark whether criteria have been met for inclusion in the study.
- Call MRI to state whether or not the subject has been approved for the study: **753-7600, ext. 1610**

**For Exit Medical Exam:**

- Mark whether changes have been noted compared to Entrance Medical exam.

MRI

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600

NAME:_____
SBJID:_____
Experimenter's Initials:_____

Data Entry 1st_____ 2nd_____
Reviewed by_____ Date_____
PI Review_____ Date_____

# Interim Referral

**Referral to:** **Mary Brothers, M.D.**
**Union Hill Commons**
**3037 Main, Suite 201**
**Kansas City, Mo. 64108-3323**
**Telephone: 561-3480**
**FAX: 561-4043**

**Appointment Date:**___/___/___ **Time:**_____

| *Interim referral* | *For doctor's use only* | *Doctor's signature* |
|---|---|---|
| Referral due to Vital Signs___<br><br>Referral due to General Response Questionnaire ____ | Medically approved to remain in study:<br>YES NO<br>Subject took pills:<br>YES NO | |

| **If subject will not return to study, schedule Exit Examination with Dr. Parmet** | Date | Time |
|---|---|---|

***Doctor's comments:***

**Instructions to Doctor:**
- Mark whether or not the subject is approved to remain in the study.
- If approved to remain in study, **watch the subject swallow pill. If not, return the pill to MRI.**
- If subject is approved to remain in study but wishes to quit, indicate this in Doctor's Comments.
- If subject will not return to study, schedule an Exit Examination. Enter Date and Time on form.
- Call MRI to state whether or not the subject remains in the study: **753-7600, ext. 1610**
- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

MRI

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600, ext 1610

NAME:_____
SBJID:_____
Experimenter's initials:_____

Data Entry 1st _____ 2nd _____
Reviewed by_____ Date_____
PI Review _____ Date_____

## Follow-up Referral

**Referral to:** Mary Brothers, M.D.
Union Hill Commons
3037 Main, Suite 201
Kansas City, Mo. 64108-3323
Telephone: 561-3480
FAX: 561-4043

**Appointment Date:**____/____/____ **Time:**_____

| *Follow-up Referral* | *For doctor's use only* | *Doctor's signature* |
|---|---|---|
| 3 mo. after study _____<br>6 mo. after study_____<br>12 mo. after study_____ | Symptoms related to study<br>YES NO<br>Requires Doctor's Follow-up<br>YES NO | |

***Doctor's Comments:***

**Instructions to Doctor:**
- Mark whether or not the subject's symptoms are related to the study.
- Mark whether or not the subject requires doctor's follow-up for symptoms.
- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

SBJID#_____
Date____/____/____
Phase I Phase II
Experimentor_____

Data Entry 1st_____, 2nd_____
Reviewed by_____ Date_____
PI Review_____ Date_____

# CHECKLIST
# BLOOD DRAW—MONDAY, DAY 8

## PRE SESSION PREPARATIONS:

☐ CONTROL ROOM E

- ☐ DAILY LOG
- ☐ GLOBAL RATING FORM
- ☐ PHYSICIAN REFERRAL FORM **(FOR EXIT EXAM, PHASE II ONLY)**
- ☐ APPOINTMENT CARD **(FOR EXIT EXAM, PHASE II ONLY)**
- ☐ RECEIPT FORM FOR PHASE I
  - ☐ $225.00 COMPLETION PAYMENT
- ☐ RECEIPT FORM FOR PHASE II
  - ☐ $225.00 COMPLETION PAYMENT
  - ☐ FOLLOW-UP TELEPHONE NUMBER **(AT PHASE II, GET TELEPHONE NUMBER WHERE SUBJECT CAN BE REACHED IN 3 MONTHS FOR FOLLOW-UP INTERVIEW)**
  - ☐ RECORD TELEPHONE # _____**(Enter into Scheduler)**

## MONDAY—DAY 8 SESSION:

☐ ARRIVAL TIME _____

☐ BLOOD DRAW

- ☐ SHOW SUBJECT TO BIO PREP ROOM
- ☐ TIME _____ (APPROXIMATELY 11:30AM)

SBJID#_____
Date____/____/____
Phase I Phase II
Experimentor_____

☐ DAILY LOG
☐ GLOBAL RATING FORM
☐ **COMPLETION PAYMENT**
- ☐ $225.00 PHASE I, RECEIPT SIGNED YES NO
- ☐ $225.00 PHASE II, RECEIPT SIGNED YES NO

☐ **PHASE I ONLY**
- ☐ GIVE SUBJECT FOOD DIARY FOR THE SUNDAY BEFORE PHASE II BEGINS
- ☐ **(If Female)** CONFIRM APPOINTMENT ON SUBJECT CALENDAR FOR PREGNANCY BLOOD DRAW

☐ **PHASE II ONLY:** CONFIRM EXIT MEDICAL EXAMINATION APPOINTMENT ON SUBJECT CALENDAR
- ☐ RECORD APPOINTMENT DATE ____ / ____ /____
- ☐ RECORD APPOINTMENT TIME_____
- ☐ COMPLETE PHYSICIAN REFERRAL FORM
- ☐ PHYSICIAN APPOINTMENT CARD TO SUBJECT
- ☐ INFORM SUBJECT: WHEN RESULTS OF EXIT EXAM ARE RECEIVED AT MRI, EXPERIMENTER WILL CALL THE SUBJECT TO SCHEDULE $100 EXIT EXAM BONUS PAYMENT.
- ☐ REMIND SUBJECT OF FOLLOW-UP CALLS AT 3, 6, AND 12 MONTHS

☐ DEPARTURE TIME_____

☐ POST SESSION CLEAN-UP
- ☐ FILE SIGNED PAYMENT RECEIPT IN LOCKED FILE CABINET.
- ☐ SUBJECT'S CRF RETURNED TO FILE AREA FOR DATA MANAGER
- ☐ **(For Subject about to begin Phase II)** CHECK SCHEDULER TO CONFIRM THAT PREGNANCY BLOOD DRAW **(if female)**, AND SUNDAY FOOD DIARY REMINDER CALL ARE ENTERED INTO THE SCHEDULER
- ☐ **(For Phase II Only)** FAX REFERRAL FORM TO PHYSICIAN
- ☐ **(For Phase II Only)** PUT 3-, 6-, AND 12-MONTH TELEPHONE FOLLOW-UP APPOINTMENTS ON SCHEDULER

SBJID#_____
Date____/____/____
Phase I Phase II
Experimentor_____

# DEVIATIONS AND OBSERVATIONS

4863PP
Revision: 1
Effective 8/14/98

SBJID#_____
DATE ____/____/____
DAY 1 2 3 4 5 8
Phase I Phase II Training
Experimenter _____

Data Entry 1st _____ ,2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

**EARLY EXIT CHECKLIST**

☐ REASON FOR EARLY EXIT:

- ☐ INTERIM REFERRAL, PHYSICIAN'S RECOMMENDATION YES NO
- ☐ SUBJECT DROP YES NO
- ☐ OTHER YES NO **(If YES)** EXPLAIN_____

_____

IF S EXITS DURING TRAINING:

- ☐ NUMBER OF TRAINING HOURS COMPLETED_____
- ☐ AMOUNT OF TRAINING PAYMENT_____
- ☐ DID SUBJECT RECEIVE $5.00 PER HOUR FOR TRAINING COMPLETED? YES NO
  **(If NO, explain)** _____
  _____
- ☐ RECEIPT SIGNED YES NO

IF S EXITS DURING PHASE I:

- ☐ NUMBER OF DAYS COMPLETED DURING PHASE I _____
- ☐ AMOUNT OF PHASE I PAYMENT_____
- ☐ DID SUBJECT RECEIVE $25.00 PER DAY FOR PARTIAL COMPLETION OF PHASE I? YES NO **(If NO, explain)** _____
  _____
- ☐ RECEIPT SIGNED YES NO

IF S EXITS DURING PHASE II:

☐ NUMBER OF DAYS COMPLETED DURING PHASE II _____

- ☐ AMOUNT OF PHASE II PAYMENT_____
- ☐ DID SUBJECT RECEIVE $25.00 PER DAY FOR PARTIAL COMPLETION OF PHASE II? YES NO **(If NO, explain)** _____
  _____
- ☐ RECEIPT SIGNED YES NO

SBJID#_____
DATE ____ / ____ / _____
DAY 1 2 3 4 5 8
Phase I Phase II Training
Experimenter _____

☐ SCHEDULE EXIT MEDICAL EXAMINATION
- ☐ RECORD APPOINTMENT DATE ___ / ___ / ____
  APPOINTMENT TIME _____
- ☐ COMPLETE MEDICAL EXAMINATION REFERRAL FORM
- ☐ GIVE S A PHYSICIAN APPOINTMENT CARD
- ☐ INFORM S: WHEN RESULTS OF EXIT EXAM ARE RECEIVED AT MRI, EXPERIMENTER WILL CALL S TO ARRANGE $100 BONUS PAYMENT
- ☐ DEPARTURE TIME _____

☐ POST SESSION CLEAN-UP
- ☐ S's CRF RETURNED TO FILE AREA FOR DATA MANAGER
- ☐ FAX MEDICAL EXAMINATION REFERRAL FORM TO PROJECT PHYSICIAN

**DEVIATIONS AND OBSERVATIONS**

4863PP

# PAYMENT RECEIPT

SBJID_____

## TRAINING SESSION RECEIPT

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED **$ 50.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

4863pp

**PAYMENT RECEIPT**

SBJID_____

**COMPLETION OF PHASE I RECEIPT**

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED **$ 225.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE

SIGNATURE:_____

4863PP

# PAYMENT RECEIPT

SBJID_____

## COMPLETION OF PHASE II RECEIPT

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF **$225.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

4863PP

**PAYMENT RECEIPT**

SBJID_____

**COMPLETION OF EXIT MEDICAL EXAMINATION**

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF **$100.00** AS COMPLETION PAYMENT FOR COMPLETING A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

4863PP

**PAYMENT RECEIPT**
**EARLY EXIT**

SBJID_____

**PHASE I/PHASE II PARTIAL PARTICIPATION RECEIPT**

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF $_____ FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE, ON THE FOLLOWING DAYS, AT $25.00 PER DAY:

**PHASE I:** MON ___, TUES ___, WED ___, THUR ___, FRI ___, MON ___

**PHASE II:** MON ___, TUES ___, WED ___, THUR ___, FRI ___, MON ___

SIGNATURE:_____

4863PP

**PAYMENT RECEIPT**
**EARLY EXIT**

SBJID_____

**TRAINING PARTIAL PARTICIPATION RECEIPT**

THIS IS TO CERTIFY THAT ON __ /__ /__ , I RECEIVED A TOTAL OF $_____
FOR _____ HOURS OF TRAINING TO PARTICIPATE IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE, AT $5.00 PER HOUR.

SIGNATURE:_____

SBJID#_____
Date___/___/___
Month: 3 6 12
Date of Last Contact_____
Experimenter_____

Data Entry 1st_____, 2nd_____
Reviewed by_____ Date_____
PI Review_____ Date_____

---

## FOLLOW-UP TELEPHONE INTERVIEW

Hello, ___Subject___ this is ___Experimenter___ with Midwest Research Institute. I'm calling because you participated in a study with us **3, 6, 12** months ago, and we'd like to see how you are doing. As a routine part of our study, we want to ask you some follow-up questions about your health and well-being at 3 months, 6 months, and 12 months since the end of the study. Let me begin by asking you about your over-all health.

HOW HAVE YOU BEEN FEELING SINCE THE STUDY ENDED **3, 6, 12** MONTHS AGO?

---

---

---

DID SUBJECT REPORT COMPLAINT? YES NO
**(If subject reports complaints, ask next question.)**

WOULD YOU ATTRIBUTE **Complaint** TO YOUR PARTICIPATION IN THE STUDY? YES NO

Now I want to read a list of symptoms to you that people who returned from the Gulf War said they sometimes experienced. We don't think that you will experience these symptoms because of this study, but the Army wants us to ask everyone who participates in the project about these symptoms.

SBJID#_____
Date___/___/____
Month: 3 6 12
Date of Last Contact_____
Experimenter_____

SINCE THE LAST TIME WE TALKED TO YOU, WOULD YOU SAY THAT YOU HAVE BEEN BOTHERED OR DISTRESSED BY ANY OF THE FOLLOWING THINGS?

**(Read each symptom to the subject. For each yes answer, ask:)**
IS THIS AN UNUSUAL PROBLEM FOR YOU?
HAVE YOU SEEN A DOCTOR FOR **SYMPTOM** ? (If yes) WHEN?

| | SYMPTOM | | UNUSUAL SYMPTOM | | VISITED DOCTOR | | DATE OF DOCTOR VISIT |
|---|---|---|---|---|---|---|---|
| | YES | NO | YES | NO | YES | NO | MO/DY/YR |
| 1. JOINT OR MUSCLE PAIN | | | | | | | |
| 2. VERTIGO OR DIZZINESS | | | | | | | |
| 3. PROBLEMS WITH YOUR ATTENTION SPAN | | | | | | | |
| 4. SKIN RASHES | | | | | | | |
| 5. UNINTENTIONAL WEIGHT LOSS | | | | | | | |
| 6. FEVERS | | | | | | | |
| 7. PERSISTENT COUGH | | | | | | | |
| 8. DAYTIME SLEEPINESS | | | | | | | |
| 9. SEVERE HEADACHES | | | | | | | |
| 10. IMPOTENCE (Ask Males Only) | | | | | | | |
| 11. INSOMNIA OR TROUBLE SLEEPING | | | | | | | |
| 12. DEPRESSION | | | | | | | |
| 13. MEMORY PROBLEMS | | | | | | | |
| 14. MUSCLE FATIGUE | | | | | | | |
| 15. LUMPS OR CYSTS IN BREASTS (Ask Females Only) | | | | | | | |
| 16. DIFFICULTY REASONING | | | | | | | |
| 17. SLURRED SPEECH | | | | | | | |
| 18. SHORTNESS OF BREATH | | | | | | | |
| 19. CHEST PAIN | | | | | | | |
| 20. DIARRHEA | | | | | | | |
| 21. VISION OR EYE PROBLEMS | | | | | | | |
| 22. GYNECOLOGICAL PROBLEMS (Ask Females Only) | | | | | | | |

SBJID#_____
Date___/___/___
Month: 3 6 12
Date of Last Contact_____
Experimenter_____

**(If 3 or 6 month interview)** Thank you ___SUBJECT__. Someone from our project will call you back around __Month/Year__ to speak with you again.

Will you be at the same telephone number months from now? YES NO
**(If no, Record new telephone number)** _____

We appreciate your help with this study. Have a nice day.

**(If 12 month interview)** Thank you _SUBJECT_. That is all of the questions I have for you. We really appreciate the help you have given us with this important study. Thank you again, and have a nice day.

**POST - PHONE CALL:**
Should Interim referral be made? YES NO

**(Interim Referral should be made if the subject reports an unusual symptom for which medical evaluation has not been sought. The Interim Referral form should be completed according to Interim Referral procedures.)**

## DEVIATIONS AND OBSERVATIONS

# Sample Record Form

Project 4863
Subject ID:_____
Male/Female:_____
Start Date:_____
Labeling Key: Subject #/Phase/Day

Regularly Drink Coffee? Yes or No

**Blood Samples**

| | Training | Phase 1 | | | |
|---|---|---|---|---|---|
| | Predose | Monday Day 1 | Thursday Day 4 | Friday Day 5 | Monday Day 8 |
| Collection Date: | | | | | |
| Collection Time: | | | | | |
| Drawn by: (initials) | | | | | |
| ~ Amount Coffee in last 24 hrs (cups) | | | | | |
| Collection Tubes: | | | | | |
| SST Red Top (females only) | | | | | |
| ACD Yellow Top (prechilled) | | | | | |
| EDTA Purple Top (prechilled) | | | | | |
| Place yellow & purple top tubes into ice slurry | | | | | |
| Centifuge Tubes for 20 min ~ 2800 g at 5°C | | | | | |
| **Red Top:** (females only) | | | | | |
| Transfer serum x1 (#) | | | | | |
| Assay for HCG | | | | | |
| **Yellow Top (ACD):** | | | | | |
| Pipette 1.0 mL aliquots plasma x3 (#) | | | | | |
| Store all aliquots at ~ –80°C (time) | | | | | |
| Remove buffy coat x1 (time) | | Dispose | Dispose | Dispose | Dispose |
| Aliquot RBC sample for Dr. DR. (time) | | | | | |
| Mix RBC with buffer | | | | | |
| ~ 500 µL aliquots RBC x4 (#) | | | | | |
| Store RBC aliquots at ~ –80°C (time) | | | | | |
| **Purple Top (EDTA):** | | | | | |
| ~ 500 µL aliquots plasma x4 (#) | | | | | |
| Store plasma aliquots at ~ –20°C (time) | | | | | |
| Samples processed by: (initials) | | | | | |

**Urine Samples**

| | Training | Phase 1 | | | |
|---|---|---|---|---|---|
| | Predose | Monday Day 1 | Thursday Day 4 | Friday Day 5 | Monday Day 8 |
| Collection Date: | | | | | |
| Collection Time: | | | | | |
| Pipette 200 µL aliquots x3 (#) | | | | | |
| Store these aliquots at ~ –80°C (time) | | | | | |
| Pipette ~ 1000 µ aliquots x2 (#) | | | | | |
| Store these aliquots at ~ –20°C (time) | | | | | |
| Samples processed by: (initials) | | | | | |

# Sample Record Form (Continued)

Project 4863
Subject ID:_____
Male/Female:_____
Start Date:_____
Labeling Key: Subject #/Phase/Day

Regularly Drink Coffee? Yes or No

| | Refresher | Phase 2 | | | |
|---|---|---|---|---|---|
| **Blood Samples** | Females Only Pregnancy | Monday Day 1 | Thursday Day 4 | Friday Day 5 | Monday Day 8 |
| Collection Date: | | | | | |
| Collection Time: | | | | | |
| Drawn by: (initials) | | | | | |
| ~ Amount Coffee in last 24 hrs (cups) | | | | | |
| Collection Tubes: | | | | | |
| SST Red Top | | | | | |
| ACD Yellow Top (prechilled) | | | | | |
| EDTA Purple Top (prechilled) | | | | | |
| Place yellow & purple top tubes into ice slurry | | | | | |
| Centifuge Tubes for 20 min ~ 2800 g at 5°C | | | | | |
| **Red Top:** | | | | | |
| Transfer serum x1 (#) | | | | | |
| Assay for HCG | | | | | |
| **Yellow Top (ACD):** | | | | | |
| Pipette 1.0 mL aliquots plasma x3 (#) | | | | | |
| Store all aliquots at ~ –80°C (time) | | | | | |
| Remove buffy coat x1 (time) | | Dispose | Dispose | Dispose | Dispose |
| Aliquot RBC sample for Dr. DR (time) | | | | | |
| Mix RBC with buffer | | | | | |
| ~ 500 µL aliquots RBC x4 (#) | | | | | |
| Store RBC aliquots at ~ –80°C (time) | | | | | |
| **Purple Top (EDTA):** | | | | | |
| ~500µL aliquots plasma x4 (#) | | | | | |
| Store plasma aliquots at ~ –20°C (time) | | | | | |
| Samples processed by: (initials) | | | | | |

| | Refresher | Phase 2 | | | |
|---|---|---|---|---|---|
| **Urine Samples** | Predose | Monday Day 1 | Thursday Day 4 | Friday Day 5 | Monday Day 8 |
| Collection Date: | | | | | |
| Collection Time: | | | | | |
| Pipette 200 µL aliquots x3 (#) | | | | | |
| Store these aliquots at ~ –80°C (time) | | | | | |
| Pipette ~ 1000 µL aliquots x2 (#) | | | | | |
| Store these aliquots at ~ –20°C (time) | | | | | |
| Samples processed by: (initials) | | | | | |

# Sample Record Form (Continued)

Project 4863
Subject ID:_____
Male/Female:_____
Start Date:_____
Labeling Key: Subject #/Phase/Day

| **Interim Blood Samples** | **Phase ____/Day _____** |
|---|---|
| Collection Day: | |
| Collection Date: | |
| Collection Time: | |
| Drawn by: (initials) | |
| ~ Amount Coffee in last 24 hrs (cups) | |
| Collection Tubes: | |
| ACD Yellow Top (prechilled) | |
| EDTA Purple Top (prechilled) | |
| Place yellow & purple top tubes into ice slurry | |
| Centifuge Tubes for 20 min ~2800g at 5°C | |
| **Yellow Top (ACD):** | |
| Pipette 1.0 mL aliquots plasma x3 (#) | |
| Store all aliquots at ~ –80°C (time) | |
| Remove buffy coat x1 (time) | Dispose |
| Mix RBC with buffer | |
| ~ 500 µL aliquots RBC x4 (#) | |
| Store RBC aliquots at ~ –80°C (time) | |
| **Purple Top (EDTA):** | |
| ~ 500 µL aliquots plasma x4 (#) | |
| Store plasma aliquots at ~ –20°C (time) | |
| Samples processed by: (initials) | |

4863
Version 6
Effective 6/5/00

CALL #_____
Screener_____
Date:___/___/___

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date _____ |
| PI Review _____ | Date _____ |

## VOLUNTEER POOL PRE-SCREENING FORM

Name: _____

Phone (h) _____ (w) _____

Address _____

Age ____ **(If S is older than 35, end interview)** Birthdate ___/___/___ Gender M F

What is your race or ethnicity? Are you: (Read choices to subject. If more than one applies, choose number 7, other, and list all that apply.)

1. ____ **American Indian or Alaska Native** (Origins in any of the original peoples of North and South America, including Central America, and who maintains tribal affiliation or community attachment)
2. ____ **Asian** (Far East, Southeast Asia, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, Philippine Islands, Thailand, Vietnam)
3. ____ **Black or African American** (Origins in any of the black racial groups of Africa)
4. ____ **Hispanic or Latino** (Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin)
5. ____ **Native Hawaiian or Other Pacific Islander** (Hawaii, Guam, Samoa, Pacific Islands)
6. ____ **White** (Europe, Middle East, North Africa)
7. ____ **Other** (Includes multiple choices) _____

Referral Source _____

What is your height and weight _____ Ht. _____ Lbs. **(If S weighs < 121 lbs. or > 231 lbs., end interview)**

Do you: Read English? yes no **(If no, end interview)**
Write English? yes no **(If no, end interview)**

What is the last year of school that you completed?
K–6 7–9 10–12 13–16 >17

**(If S is female ask)** Are you currently pregnant, or do you plan to become pregnant in the near future?
yes no **(If yes, end interview)**

Have you ever taken Pyridostigmine for any reason? yes no **(If yes, end interview)**

Have you ever been in the Military? yes no

CALL #_____
Screener_____
Date:___/___/___

Were you in the Gulf War? yes no

Were you ever in the Persian Gulf during the Gulf War? yes no
Where were you located? _____ **(If S was in the Persian Gulf, end interview)**

Have you ever participated in any other research studies? yes no
**(If yes)** What were the studies you participated in?_____
_____
**(If yes)** When did you participate in these studies? _____
_____

Do you expect to be in the metropolitan area for the next two months? yes no
**(If no)** When will you be in the metropolitan area for two consecutive months? _____
_____

Do you plan to be out of town for any period of time for the next two months? yes no
**(If yes)** When do you plan to be out of town? _____
_____
**(If yes)** How long do you plan to be out of town? _____
_____

You will need to be able to come to MRI several times per day during the study. Do you have a way to get to and from MRI for that period of time? yes no **(If no, end interview)**

We will schedule the times that you come to MRI in advance. Do you have any times already set up that you know about now, that you could not come to MRI, such as for classes? yes no
**(If yes)** What are the times that you **can/cannot** come to MRI in the next two months?

**(RECORD DATES SUBJECT CAN/CANNOT COME TO MRI)**

| DAY | SCHEDULE |
|---|---|
| MONDAY | |
| TUESDAY | |
| WEDNESDAY | |
| THURSDAY | |
| FRIDAY | |
| SATURDAY | |
| SUNDAY | |

Do you currently smoke cigarettes? yes no
**(If yes)** How many cigarettes do you smoke in one day? _____

CALL #_____
Screener_____
Date:___/___/___

Have you ever been diagnosed with any of the following conditions?

yes no Myasthenia Gravis
yes no Asthma
yes no High Blood Pressure
yes no Diabetes
yes no Heart Disease

**(If yes to any of these conditions, end interview)**

Have you ever been diagnosed with liver or kidney disease? yes no
**(If yes)** Explain _____

Have you ever been diagnosed with chronic bladder disease or urine problems? yes no
**(If yes)** Explain _____

Have you ever had any seizures or been diagnosed with a seizure disorder? yes no **(If yes, end interview)**

Have you ever been diagnosed with any other chronic illnesses? yes no
**(If yes)** Explain _____

Have you ever had problems with your eyes? yes no
**(If yes)** Explain _____

Are you unable to see certain colors? yes no **(If yes, end interview)**

Is your vision normal or corrected to normal? yes no **(If no, end interview)**

Have you ever had problems with your hearing? yes no
**(If yes)** Explain _____

Do you wear hearing aides? yes no **(If yes, end interview)**

Is your hearing normal? yes no **(If no, end interview)**

Have you had any acute illnesses within the last month that has required bed rest? yes no
**(If yes)** When were you ill? _____
How long did your illness last? _____
**(If yes, wait ≥ one month past illness to schedule subject for study.)**

Have you or any family members ever experienced a severe reaction to a dental procedure or anesthetic? yes no
**(If yes)** Explain _____

Has any member of your family died a sudden or unexpected death, other than accident or injury? yes no
**(If yes)** Explain _____

CALL #_____
Screener_____
Date:___/___/___

Are you currently taking any prescription medications, (**If female add:**) birth control pills or have a birth control implant? yes no

**(If yes)** List medications _____

_____

Do you regularly take any over-the-counter medications, including vitamins, minerals, or health supplements?

yes no

**(If yes)** List _____

_____

Do you regularly drink any herbal teas or drinks, or take any herbal supplements? yes no

**(If yes)** List _____

_____

Have you ever experienced any difficulties when having your blood drawn? yes no

**(If yes)** Explain _____

_____

Have you ever worked for a company that manufactured, used, or applied pesticides? yes no

**(If yes)** When did you work there? _____

How long did/have you work/ed there? _____

What did/do you do for this company? _____

What pesticides were/are used or applied there?

Do you work with any pesticides at school? yes no

**(If yes)** What are the pesticides_____

_____

Are you allergic to Latex? yes no

Have you ever worked at a job where you were exposed to extreme heat? yes no

**(If yes)** Where was that? _____

When did you work there _____

What did you do there? _____

CALL #_____
Screener_____
Date:___/___/___

If you are selected for our study, we must ask that you abstain from using any alcohol, illicit drugs, or over-the-counter drugs other than vitamins, during the activity days of the study. Are you willing to abstain from these things on those days? yes no **(If no, end interview)**

In case we are unable to reach you at your home or work, may I have the name and phone number of one person who will know how to reach you?

_____

Accept _____ Reject _____ S Refusal _____ Reviewed by _____ on ___/___/___

Consent Session appointment: DATE ____/____/____, TIME _____

If subject refuses to participate, state reason: _____

_____

_____

If not selected for the study, state reason: _____

_____

_____

Best time to call respondent: _____

_____

**Deviations and Observations**

4863TT Study 2

**SUBJECT APPOINTMENT CALENDAR**

NAME:_____

**ENTRANCE BLOOD/URINE AT MRI: DATE ___ / ___ / ___, TIME _____**

**ENTRANCE MEDICAL EXAMINATION: DATE ___ / ___ / ___ , TIME _____**

CALL # _____

**EXIT MEDICAL EXAMINATION: DATE ___ / ___ / ___ , TIME _____**

**TRAINING WEEK: ☐ DOSING; ☐ PHYSIOLOGY; ☐ PERFORMANCE; ☐ FINAL TRAINING**

| SUN | MON | TUES | WED | THURS | FRI | SAT |
|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**(Please remember to refrain from alcoholic beverages during each study phase.) REFRESHER TRAINING: DATE ___ / ___ / ___, TIME _____**

| SUN | MON | TUES | WED | THURS | FRI | SAT |
|---|---|---|---|---|---|---|
| ☐ **ENTER FOOD AND DRINK INTO 1ST DAILY FOOD DIARY FOR PHASE I** | ☐ _____ Blood draw<br>_____Dose, brkfst<br>_____16:00 Dose<br>_____ 24:00 Dose | ☐ _____Dose, brkfst<br>_____16:00 Dose<br>_____ 24:00 Dose | ☐ _____Dose, brkfst<br>_____16:00 Dose<br>_____24:00 Dose | ☐ _____Dose, brkfst<br>_____ 11:30 Bld, Lunch, Battery<br>_____16:00 Dose<br>_____24:00 Dose | ☐ _____Dose, brkfst<br>_____ 11:30 Bld, Lunch, Battery | ☐ |
| ☐ **ENTER FOOD AND DRINK INTO 1ST DAILY FOOD DIARY FOR PHASE II** | ☐ _____ Blood draw<br>_____Dose, brkfst<br>_____ 16:00 Dose<br>_____ 24:00 Dose | ☐ _____Dose,brkfst<br>_____16:00 Dose<br>_____ 24:00 Dose | ☐ _____Dose, brkfst<br>_____16:00 Dose<br>_____24:00 Dose | ☐ _____Dose, brkfst<br>_____ 11:30 Bld, Lunch, Battery<br>_____16:00 Dose<br>_____24:00 Dose | ☐ _____Dose, brkfst<br>_____ 11:30 Bld, Lunch, Battery | ☐ |
| ☐ | ☐ _____ 11:30 Blood Draw, Phase II Payment | ☐ | ☐ | ☐ | ☐ | ☐ |

**If you have questions regarding your appointment times, please call: (816) 753-7600, ext. 1610**

MRI

NAME:_____
CALL#:_____
Experimenter's Initials:_____

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600

Data Entry 1st_____ 2nd_____
Reviewed by_____ Date_____
PI Review _____ Date_____

## Medical Examination Referral

**Referral to:** **Allen J. Parmet, M.D.**
**Union Hill Commons**
**3037 Main, Suite 201**
**Kansas City, Mo. 64108-3323**
**Telephone: 561-3480**
**FAX: 561-4043**

**Appointment Date: ___/___/____** **Time:_____**

| *Medical examination referral* | *For doctor's use only* | *Doctor's signature* |
|---|---|---|
| Entrance Medical Exam____ | Criteria met: YES NO | |
| Exit Medical Exam_____ | Changes noted: YES NO | |

***Doctor's Comments:***

INSTRUCTIONS TO DOCTOR

**For all referrals:**

- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

**Entrance Medical Exam:**

- Mark whether criteria have been met for inclusion in the study.
- Call MRI to state whether or not the subject has been approved for the study: 753-7600, **ext. 1610**

**For Exit Medical Exam:**

- Mark whether changes have been noted compared to Entrance Medical exam.

4863TT SBJID#_____

## BASELINE DATA SHEET

**For Entrance or Exit Medical Examinations:** Dr. Allen Parmet: off. 561-3480; pgr: 860-2278
**For Interim Referral Examinations:** Dr. Mary Brothers: off. 561-3480; pgr: 727-6168

**BASELINE HEIGHT** _____ inches

**BASELINE WEIGHT** _____ lbs.

**BASELINE PULSE RATE:** **Training pulse** 1. _____ 2. _____

**Baseline pulse** _____ (Lowest Pulse Rate from the 2 training rates and Monday, Day 1, Ph 1.)

**HAND STEADINESS TEST:**

**Dominant Hand:** Right Hand Left Hand

**HAJEK BREATH HOLD** _____ seconds

**TIME OF EQUILIBRATION** _____

**BREAKFAST/LUNCH:**

Breakfast choice: _____

Lunch choice:_____

4863 Study 2
Version: 4
Effective: 6/9/00

SBJID# _____
DATE ____ / ____ / ____
TRNG DAY 1 2 3 4 5
Experimenter _____

| | |
|---|---|
| Data Entry 1st | 2nd |
| Reviewed by | Date |
| PI Review | Date |

## PERFORMANCE TRAINING

**PRE SESSION PREPARATIONS:**

- ☐ COMPUTER ON
- ☐ GRQ AND GRQ KEY
- ☐ SUBJECT ID# **(If training occurs on the first day of training)**
- ☐ TRAINING SCRIPT

**TRAINING:**

- ☐ S ARRIVAL TIME _____
- ☐ CLOSE DOOR TO CONTROL ROOM
- ☐ GIVE SBJID# **(If training occurs on first day of training)**
- ☐ EXPLAIN AND ADMINISTER GRQ **(Check GRQ as indicated in GRQ procedures)**
- ☐ EXPLAIN THE TASKS AND THEIR RELEVANCE TO THE STUDY **(see script)**

- ☐ **ENTER START TIME** _____
- ☐ RUN DEMO, ENTER <DEMO ##> **(## is the subject ID number)**
- ☐ RUN TWO TRIALS OF EACH TASK. ENTER <T1 ##>

| TASK | Trials | CRITERIA MET? | MAX RE-RUNS | CRITERIA MET? | CRITERIA | ABORT KEYS |
|---|---|---|---|---|---|---|
| **RUNNING MEMORY** | 2 | YES NO | 2 | YES NO | **Twice** w/mean RT ≤ 650ms, accuracy ≥ 90% | **ALT-F1** |
| **UNSTABLE TRACKING** | 2 | YES NO | 3 | YES NO | **Twice in a row** w/RMS tracking error ≤ 20, control losses ≤ 3 | **ALT-F1** |
| **STERNBERG MEMORY: SET SIZE 6** | 2 | YES NO | 2 | YES NO | **Twice in a row** w/mean RT correct ≤ 900ms, errors ≤ 5 | **ALT-F1** |
| **SWITCHED ATTENTION** | 2 | YES NO | 2 | YES NO | **Twice** w/ # of errors in 3rd "switching" block ≤ 5, mean RT ≤ 800ms | **ESCAPE** |
| **DUAL TRACKING/ STERNBERG: SET-SIZE 6** | 2 | YES NO | 3 | YES NO | **Twice in a row** % correct ≥ 80%, mean RT correct ≤ 1300ms, control losses ≤ 6, RMS error ≤ 25 | **ALT-F1** |
| **STROOP** | 2 | YES | 0 | N/A | **Perform Twice** | **ESCAPE** |

- ☐ IF CRITERIA WERE NOT MET AFTER FIRST TWO TRIALS, RE-RUN SINGLE TASKS
- ☐ ENTER <ET##> FOR RERUNS **(do not exceed maximum re-run amount)**

SBJID# _____
DATE ____ / ____ / ____
TRNG DAY 1 2 3 4 5
Experimenter _____

□ S COMPLETES MARI/WORKLOAD QUESTIONNAIRE
ENTER <WM##>

□ **TRAINING END TIME** _____

□ IF CRITERIA WERE NOT MET, EVEN AFTER RUNNING THE MAXIMUM NUMBER OF TRIALS, SEND PRINTOUT TO PERFORMANCE TASK REVIEWER **(labeled "For Performance Stability Review Only")**

□ PERFORMANCE TASK REVIEWER COMMENTS:

_____

_____

_____

□ RE-RUN SINGLE TASKS PER PERFORMANCE TASK REVIEWER
ENTER <ET ##> TO BEGIN

| TASK | RE-RUNS | CRITERIA | CRITERIA MET? | ABORT KEYS |
|---|---|---|---|---|
| **RUNNING MEMORY** | | **Twice** w/mean RT ≤ 650ms, accuracy ≥ 90% | YES NO | **ALT-F1** |
| **UNSTABLE TRACKING** | | **Twice in a row** w/RMS tracking error ≤ 20, control losses ≤ 3 | YES NO | **ALT-F1** |
| **STERNBERG MEMORY TASK: SET SIZE 6** | | **Twice in a row** w/mean RT correct ≤ 900ms, errors ≤ 5 | YES NO | **ALT-F1** |
| **DUAL TRACKING/ STERNBERG: SET-SIZE 6** | | **Twice in a row** % correct ≥ 80%, mean RT correct ≤ 1300ms, control losses ≤ 6, RMS error ≤ 25 | YES NO | **ESCAPE** |
| **SWITCHED ATTENTION** | | **Twice** w/ # of errors in 3rd "switching" block ≤ 5, mean RT ≤ 800ms | YES NO | **ALT-F1** |

□ DETERMINE IF S MET CRITERIA

4863 Study 2
Version: 4
Effective: 6/9/00

SBJID# _____
DATE ____ / ____ / ____
TRNG DAY 1 2 3 4 5
Experimenter _____

**POST SESSION PROCEDURES:**

- ☐ CHECK FORMS FOR PROPER ID
- ☐ TURN OFF COMPUTER
- ☐ ATTACH PRINTOUT TO CHECKLIST
- ☐ RETURN CRF TO FILE AREA FOR DATA MANAGER

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**DEVIATIONS AND OBSERVATIONS**

SBJID#_____
Date:___/___/___
Day 1 2 3 4 5
Experimenter:_____

Data Entry 1st _____, 2nd _____
Reviewed by: _____ Date _____
PI Review _____ Date _____

# DOSE TRAINING CHECKLIST

## PRE SESSION PREPARATIONS:

☐ CONTROL ROOM:

- ☐ S'S CRF
- ☐ BLOOD PRESSURE EQUIPMENT
- ☐ STETHOSCOPE
- ☐ THERMOMETER AND PROBE COVERS
- ☐ TRAINING SCRIPT
- ☐ FOOD DIARY
- ☐ **(If Dose Training occurs on Friday)** BEGINNING SUNDAY FOOD DIARY
- ☐ GENERAL RESPONSE QUESTIONNAIRE (GRQ)
- ☐ DAILY LOG
- ☐ GLOBAL RATING FORM
- ☐ SUBJECT ID# AND TAG **(if Dose Training occurs on 1st day of training)**
- ☐ FOOD CHOICE MENU

☐ ARRIVAL TIME _____

- ☐GIVE SUBJECT ID# AND TAG **(if Dose Training occurs on 1st day of training)**

## DOSE TRAINING

☐SUBJECT TO BIOPREP ROOM
☐BASELINE BLOOD DRAW

☐SUBJECT TO CONTROL ROOM

- ☐DEMONSTRATE FOOD DIARY
- ☐GIVE SUBJECT PRACTICE FOOD DIARY

☐RECORD BASELINE VITAL SIGNS

- ☐ORAL TEMPERATURE _____(IF TEMP. ≥ 99.6, INFORM PI)
- ☐RECORD THERMOMETER #G-631

- ☐BLOOD PRESSURE _____ (IF DBP IS OUTSIDE 50-90 mm/Hg, INFORM PI)
- ☐CIRCLE BP CUFF SIZE IF OTHER THAN ADULT# G-6321 SIZE
  Large# G-6322 Child# G-6323

☐1ST PULSE RATE _____ (IF < 50 BPM, INFORM PI)

SBJID#_____
Date:___/___/___
Day 1 2 3 4 5
Experimenter:_____

☐DEMONSTRATE DAILY LOG AND HAVE SUBJECT COMPLETE **(Check Daily Log and follow criteria for continuation of session as indicated in procedures.)**
☐DEMONSTRATE GLOBAL RATING FORM AND HAVE SUBJECT COMPLETE
☐DEMONSTRATE GRQ AND HAVE SUBJECT COMPLETE **(Check GRQ and follow criteria for continuation of session as indicated in procedures.)**

☐2ND PULSE RATE _____ **(IF < 50 BPM, INFORM PI)**

☐ASK SUBJECT TO FILL OUT BREAKFAST AND LUNCH CHOICES FOR DOSE WEEKS
☐REMIND SUBJECT TO COMPLETE PRATICE FOOD DIARY AND BRING TO NEXT SESSION
☐REMIND SUBJECT TO RETURN FOR NEXT TRAINING SESSION ON _____
☐ **(If Dose Training occurs on Friday)** GIVE SUBJECT FOOD DIARY TO FILL OUT FOR SUNDAY

**POST SESSION:**
☐ RETURN DAILY LOG, GRQ, AND GLOBAL RATING FORM TO CRF AFTER SCORING.
☐ RECORD TRAINING PULSE ONE, TWO, AND FOOD CHOICES ON BASELINE DATA SHEET.

**DEVIATIONS / OBSERVATIONS**

4863 STUDY 2
Version: 0
Effective: 06/13/00

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

Data Entry _____1st, _____2nd
Reviewed by _____ Date _____
PI Review _____ Date _____

# PHYSIOLOGY TRAINING CHECKLIST

## PRE SESSION PREPARATIONS:

➡ **HOOK-UP ROOM**

- ☐ GRQ KEY
- ☐ CRF
- ☐ SCRUB TOP AND PILLOWCASE
- ☐ STOPWATCH
- ☐ ECG HOOK-UP SUPPLIES
- ☐ PPI HOOK-UP SUPPLIES

➡ **HOOK-UP ROOM:**

- ☐ DISCONNECT LAN HOOK-UP
- ☐ POWER TO GRASS
- ☐ POWER TO ACQ COMPUTER

**Acq computer: ECG Collection**

- ☐ DOUBLE CLICK "GRASS LINK 15" ICON
- ☐ SELECT "MODEL 15"
- ☐ CLICK "CONNECT", select "TTECG.set"
  **Wait for Channels to scroll through**
- ☐ CLICK "USE"
- ☐ MINIMIZE "LINK 15"
- ☐ DOUBLE CLICK "ECG" ICON
- ☐ CLICK "ACQUIRE"
- ☐ TYPE SESSION ID: tt##T1*e*.daq (##= sbjid, e=ECG collection)

**STOP HERE (Do not press enter until subject is ready.)**

## SUBJECT ARRIVES:

- ☐ SUBJECT ARRIVAL TIME _____

➡ **SHOW SUBJECT TO HOOK-UP ROOM**

- ☐ TAKE BASELINE WEIGHT _____ Lbs.(Scales #G-6324)
- ☐ TAKE BASELINE HEIGHT _____ inches.(Scales #G-6324)

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

➡ COMPLETE ECG HOOK-UP

☐ ASK SUBJECT TO PUT ON SCRUB TOP
☐ EXPLAIN HOOK-UP
☐ EXPLAIN PPI AND SHOW S SENSORS; **Explain that PPI will be done in last training session.**
☐ ATTACH LEADS AND PLUG IN TAIL

**(Black)--G1--LEFT RIB**
**(Green)--GROUND--LEFT CLAVICLE**
**(Red)--G2--RIGHT CLAVICLE**

## BEGIN BATTERY:

☐ **BATTERY START TIME** _____

➡ **HAJEK BREATH HOLD**

☐ STAND WITH S
☐ TELL S TO TAKE A DEEP BREATH AND HOLD IT AS LONG AS THEY CAN
**(Start stopwatch as S takes a breath and stop as S releases breath. Do NOT face S to a clock or allow them to watch the stopwatch)**
☐ RECORD TIME OF BREATH HOLD IN SECONDS _____

➡ **ECG MEASUREMENT**

✶**(Subject will lie down for a total of 8.5 minutes. Subject will stand for a total of 8.5 minutes.)**

☐ INSTRUCT SUBJECT TO LIE DOWN AND MOVE WIRES OUT OF WAY **(Instruct S to keep hands by side and don't cross feet. Remind S to lay very still, try not to talk, fidget, or sleep)**

**REMIND S THAT THE SIGNAL TO STAND WILL BE WHEN E TOUCHES SUBJECT'S ANKLE**

**Acq computer: ECG Collection**
☐ **CLICK "OK"** TO BEGIN COLLECTION
☐ CLICK ON THE TITLE BAR OF THE ACQUISITION PROGRAM AND CHECK RECORDING

☐ BEGIN **SUPINE** COLLECTION ***CLICK EVENT MARKER*** **(Use stopwatch to time 8.5 minutes)**
☐ WHEN **8.5 MINUTES** HAVE PASSED, TOUCH S ON ANKLE TO INSTRUCT S TO STAND **as quickly and as comfortably as possible *CLICK EVENT MARKER***
**(Use stopwatch to time additional 8.5 minutes)**
☐ WHEN **17 MINUTES** HAVE PASSED END COLLECTION ***CLICK EVENT MARKER***

☐ CLICK **STOP** @ ACQ COMPUTER
☐ CLICK **QUIT** @ ACQ COMPUTER
☐ REMOVE SENSORS AND PADS

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

➡ CONTROL ROOM A

HAND STEADINESS TEST (USE DOMINANT HAND ONLY.)
**(Hand Steadiness tester #32011)**

- ☐ RECORD DOMINANT HAND: RIGHT_____ LEFT_____
- ☐ SUBJECT WILL PRACTICE USING LARGE HOLES, TOP ROW **(DO NOT RECORD)**
- ☐ TEST IN SMALL HOLES, BOTTOM ROW **(RECORD INDIVIDUAL MEASUREMENT FOR EACH OF THE FIRST FOUR HOLES)**

**For each hole, press reset and instruct subject to insert stylus, say "steady-go".**

HOLE 1 _____, HOLE 2 _____, HOLE 3 _____, HOLE 4 _____

➡ MARI AND OVERALL WORKLOAD TESTS

- ☐ AT C:\TTPROG TYPE: **"T1 ##" ( ## is the subject number)**
- ☐ OVERALL WORKLOAD: THIS IS A ONE-LINE TEST ASKING HOW MUCH WORK YOU FEEL THE ENTIRE TEST BATTERY HAS BEEN FOR YOU TODAY. ANSWER THE QUESTION AND CLICK DONE.
- ☐ MARI: THIS TEST ASKS HOW YOU FEEL **RIGHT NOW**. ANSWER ALL THE QUESTIONS AND CLICK DONE WHEN YOU ARE FINISHED WITH EACH PAGE.

➡ TO HOOK UP ROOM

- ☐ GIVE S THE GRQ
- ☐ ALLOW S TO CHANGE CLOTHES
- ☐ DOES S HAVE ANY QUESTIONS?
- ☐ DID ANYTHING MAKE HIM/HER UNCOMFORTABLE?
- ☐ REMIND S TO COMPLETE FOOD DIARY IF APPLICABLE
- ☐ REMIND S TO FOLLOW APPOINTMENT CALENDAR
- ☐ REMIND S TO RETURN FOR NEXT APPOINTMENT AT _____(TIME)
- ☐ ENDING TIME _____
- ☐ ESCORT S OUT OF BUILDING

POST SESSION CLEAN-UP

- ☐ CHANGE PILLOW CASE IN HOOK-UP ROOM
- ☐ BACK UP ECG AND EFORMS
- ☐ TURN OFF EQUIPMENT
- ☐ CHECK ALL DATA FOR APPROPRIATE ID **(S # and session date/time)**
- ☐ TRANSFER HEIGHT, WEIGHT, HAJEK BREATH HOLD AND DOMINANT HAND INFO TO BASELINE DATA SHEET
- ☐ SUBJECT'S CRF RETURNED TO FILE AREA FOR DATA MANAGER

SBJID _____
DATE ___/___/___
DAY 1 2 3 4 5
Experimenter _____

## DEVIATIONS AND OBSERVATIONS

4863TT

# PAYMENT RECEIPT

SBJID_____

## TRAINING SESSION RECEIPT

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED **$ 50.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

## COMPLETION OF PHASE I RECEIPT

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED **$ 225.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE

SIGNATURE:_____

## COMPLETION OF PHASE II RECEIPT

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF **$225.00** AS PAYMENT FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

## COMPLETION OF EXIT MEDICAL EXAMINATION

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF **$100.00** AS COMPLETION PAYMENT FOR COMPLETING A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE.

SIGNATURE:_____

4863
Version: 2
Effective: 3/24/00

SBJID#_____
DATE_____/_____/_____
DAY 1 2 3 4 5
PHASE I PHASE II
EXPERIMENTER_____

Data Entry 1st _____ 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# AM DOSING CHECKLIST

PRE SESSION PREPARATIONS:

☐ CONTROL ROOM E:
- ☐ S's CRF
- ☐ BLOOD PRESSURE EQUIPMENT
- ☐ STETHOSCOPE
- ☐ THERMOMETER/THERMOMETER PROBE COVERS
- ☐ FOOD DIARY & SCRIPT
- ☐ GENERAL RESPONSE QUESTIONNAIRE (GRQ) & GRQ KEY
- ☐ DAILY LOG
- ☐ SUBJECT APPOINTMENT CALENDAR
- ☐ PILLS (Mon=01, Tues=04, Wed=07, Thur=10, Fri=13)
- ☐ WATER & CUPS
- ☐ ENTER S's BREAKFAST CHOICE FROM BASELINE DATA SHEET

AM DOSING SESSION:

☐ SUBJECT TO CONTROL ROOM E
- ☐ ARRIVAL TIME _____

☐ FOOD DIARY FROM PREVIOUS DAY (Check Food Diary. Retrieve missing information from S.)
- ☐ GIVE S NEW FOOD DIARY FOR CURRENT DAY. (Experimenter will instruct the S to record all food and drink consumed before S's arrival at MRI that day, as well as all food and drink consumed while at MRI.) (S will not receive a Food Diary on Day 5, Friday)

☐ ORAL TEMPERATURE _____ ( If Temp. ≥ 99.6°, refer to medical monitor)
- ☐ RECORD THERMOMETER # G-631

☐ BLOOD PRESSURE ____/_____ (If DBP is outside 50-90 mm/Hg, refer to medical monitor)
- ☐ CIRCLE BP CUFF SIZE IF OTHER THAN ADULT #G-6321
  Large# G-6322 Child# G-6323
- ☐ STETHOSCOPE # G-6327

☐ PULSE RATE _____ (If ≥ 20% below baseline pulse rate on Baseline Data Sheet, or < 50 bpm, refer to medical monitor)
- ☐ S REFERRED TO PHYSICIAN YES NO

☐ SERVE S BREAKFAST
- ☐ DAILY LOG (Check Daily Log and follow criteria for continuation of session as indicated in Daily Log procedures.)

SBJID#_____
DATE____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II
EXPERIMENTER_____

☐ DAILY LOG RESPONSES REFERRED TO PI YES NO

☐ GENERAL RESPONSE QUESTIONNAIRE (Check GRQ and follow criteria for continuation of session as indicated in GRQ procedures.)
☐ S REFERRED TO PHYSICIAN YES NO

☐ MORNING DOSE, TIME _____ (Experimenter will watch as S swallow pill.)

☐ REMIND S OF RETURN TIME _____ (Check the S's Appointment Calendar for return time.)

☐ DEPARTURE TIME _____

POST SESSION CLEAN UP:

☐ DISPOSE OF EMPTY BLISTER PACKS
☐ IF DOSE IS NOT TAKEN, RETURN UNUSED DOSE TO REFRIGERATOR
☐ NOTE DEVIATION ON CHECKLIST AND INFORM PI
☐ DISPOSE OF BREAKFAST WASTE
☐ RETURN S's CRF NOTEBOOK TO FILE AREA FOR DATA MANAGER

DEVIATIONS / OBSERVATIONS:

4863
Version: 1
Effective: 3/24/00

SBJID#_____
Date___/___/___
Day 1 2 3 4 5
Dose: 16:00 24:00
Phase I Phase II
Experimenter_____

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date _____ |
| PI Review _____ | Date _____ |

**DOSING – 16:00, 24:00**
**CHECKLIST**

**CIRCLE ONE:**

**REGULAR DOSE** **TELEPHONE DOSE**

**PRE SESSION PREPARATIONS:**

☐ CONTROL ROOM:
- ☐ S'S CRF NOTEBOOK
- ☐ PILLS (Mon=02, 03; Tues=05, 06; Wed=08, 09; Thurs=11, 12)
- ☐ WATER & CUPS
- ☐ IF TELEPHONE DOSE, PHONE NUMBER WHERE S CAN BE REACHED _____

☐ ARRIVAL TIME OR TIME OF PHONE CALL _____

**IF S COMPLAINS OF FEELING ILL:**
**FOR TELEPHONE DOSE:**
**REFER TO PHYSICIAN AND REMIND S TO NOT TAKE PILLS UNTIL INSTRUCTED BY PHYSICIAN**

☐ S REFERRED TO PHYSICIAN

**FOR REGULAR DOSE SESSIONS:**
**☐TAKE VITAL SIGNS AND GIVE GRQ**
☐ VITAL SIGNS
- ☐ ORAL TEMPERATURE _____ **(IF TEMP. ≥ 99.6°, REFER TO PHYSICIAN.)**
  **RECORD THERMOMETER #G-631**
- ☐ BLOOD PRESSURE _____ **(IF DBP IS OUTSIDE 50-90 mm/Hg, REFER TO PHYSICIAN.)**
  - ☐ **CIRCLE BP CUFF SIZE IF OTHER THAN ADULT# G-6321**
    Large# G-6322 Child# G-6323
  - ☐ STETHOSCOPE # G-6327

- ☐ PULSE RATE _____ **(IF < 50 BPM, REFER TO PHYSICIAN OR ≥20% BELOW BASELINE PULSE RATE-SEE BASELINE DATA SHEET)**

SBJID#_____
Date___/___/___
Day 1 2 3 4 5
Dose: 16:00 24:00
Phase I Phase II
Experimenter_____

☐ S REFERRED TO PHYSICIAN YES NO

☐ GRQ **(CHECK GRQ AND FOLLOW CRITERIA FOR CONTINUATION OF SESSION AS INDICATED IN GRQ PROCEDURES.)**

☐ S REFERRED TO PHYSICIAN YES NO

**IF S IS REFFERRED TO PHYSICIAN:**
- ☐INTERIM REFERRAL FORM COMPLETED
- ☐CALL PHYSICIAN AND MAKE APPT.
- ☐FAX REFERRAL FORM TO PHYSICIAN
- ☐INFORM PI

☐ **ACTUAL TIME OF DOSE** _____ (EXPERIMENTER WILL WATCH AS S SWALLOWS PILL OR CONFIRM DOSE OVER TELEPHONE.)

☐ REMIND S OF RETURN TIME _____ **(CHECK THE Ss APPOINTMENT CALENDAR FOR RETURN TIME.)**

☐ S DEPARTURE TIME _____

**POST SESSION ACTIVITIES:**
- ☐ RETURN S'S CRF NOTEBOOK TO FILE AREA FOR DATA MANAGER
- ☐ DISPOSE OF EMPTY BLISTER PACK AND CUP
- ☐ **IF INTERIM REFERRAL IS MADE, NOTE DEVIATION ON CHECKLIST AND INFORM PI**

**DEVIATIONS / OBSERVATIONS**

4863
Version 3
Effective 6/12/00

SBJID#_____
DATE ____/____/____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

| | |
|---|---|
| Data Entry 1st _____ | 2nd _____ |
| Reviewed by _____ | Date _____ |
| PI Review _____ | Date _____ |

## GENERAL RESPONSE QUESTIONNAIRE

FOR MORNING SESSIONS: Below, is a list of the kind of symptoms that people sometimes report to their doctor. Please read each symptom carefully. Put an X in the box that best describes each symptom: IF THE SYMPTOM HAS OCCURRED IN THE LAST 24 HOURS, PUT AN X IN THE BOX THAT BEST DESCRIBES HOW MUCH YOU WERE BOTHERED OR DISTRESSED BY EACH SYMPTOM. Check only one selection for each symptom and do not skip any items. If you change your mind, mark one line through your first answer, initial and date it, then put an X on your new choice.
FOR EXPERIMENTAL SESSIONS: Please answer according to how you felt in the chamber.
**In the last 24 hours, how much were you distressed or bothered by:**

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 1. Weakness | | | | | | | |
| 2. Trouble speaking | | | | | | | |
| 3. Chills | | | | | | | |
| 4. Blind spots in eyes | | | | | | | |
| 5. Temper outbursts | | | | | | | |
| 6. Chest pain | | | | | | | |
| 7. Excessive thirst | | | | | | | |
| 8. Nausea | | | | | | | |
| 9. Skin rash | | | | | | | |
| 10. Numbness | | | | | | | |
| 11. Headaches | | | | | | | |
| 12. Stiff neck | | | | | | | |
| 13. Night sweats | | | | | | | |
| 14. Depression | | | | | | | |
| 15. Nose bleeds | | | | | | | |
| 16. Unusual belching | | | | | | | |
| 17. Trouble swallowing | | | | | | | |
| 18. Blurred/double vision | | | | | | | |
| 19. Body aches | | | | | | | |

SBJID#_____
DATE ____/____/____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

| DESCRIPTION: | Did Not Occur | A Little | Some-what | Fairly | Quite a Bit | Very Much | Extremely |
|---|---|---|---|---|---|---|---|
| 20. Swollen lymph nodes | | | | | | | |
| 21. Urination problem | | | | | | | |
| 22. Shortness of breath | | | | | | | |
| 23. Bloating | | | | | | | |
| 24. Fainting | | | | | | | |
| 25. Dizziness | | | | | | | |
| 26. Memory impairment | | | | | | | |
| 27. Sore tongue | | | | | | | |
| 28. Vomiting | | | | | | | |
| 29. Heartburn | | | | | | | |
| 30. Bleeding gums | | | | | | | |
| 31. Fearfulness/anxiety | | | | | | | |
| 32. Diarrhea | | | | | | | |
| 33. Heart palpitations | | | | | | | |
| 34. Ringing in ears | | | | | | | |
| 35. Flatulence/passing gas | | | | | | | |
| 36. Hand tremors/shaking | | | | | | | |
| 37. Persistent cough | | | | | | | |
| 38. Skin itching | | | | | | | |
| 39. Fever | | | | | | | |
| 40. Nervousness | | | | | | | |
| 41. Abdominal pain | | | | | | | |
| 42. Sleep disturbance | | | | | | | |
| 43. Dark or bloody urine | | | | | | | |
| 44. Fatigue | | | | | | | |
| 45. Constipation | | | | | | | |

4863
Version 3
Effective 3/24/00

SBJID # _____
DATE ____ / ____ / ____
DAY 1 2 3 4 5
Phase I Phase II Training
Experimenter _____

Date Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# DAILY LOG

Please complete the following questionnaire. We are concerned only with the **last 24 hour period** so answer the questions for that time period only. If you want to change any of your answers, please clearly mark through your first answer, write your initial and the current date next to the mark, and then circle or write your new answer. If you have any questions, please ask for assistance.

1. Have you used or applied any insecticide, that is, chemicals used to kill insects, within the last twenty-four hours? YES NO

   If yes, please list the names of the chemicals you used: _____
   _____

2. Have you taken any of the following within the last twenty-four hours?

   a. **Prescription medications** YES NO
   If yes, please list medications: _____
   _____

   b. **Over-the-counter-medications** YES NO
   If yes, please list medications: _____
   _____

   c. **Vitamins or minerals** YES NO
   If yes, please list: _____
   _____

   d. **Health supplements** YES NO
   If yes, please list: _____
   _____

3. Have you consumed any herbal teas or drinks, or taken any herbal supplements within the last twenty-four hours? YES NO

   If yes, please list: _____
   _____

4863
Version 2
Effective 3/24/00

SBJID # _____
DATE _____ / _____ / _____
Phase I Phase II Training
Experimenter _____

Date Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# GLOBAL-RATING FORM

Please answer the following questions about the study phase you just completed.

1. IN YOUR JUDGMENT, WHICH PILLS DID YOU RECEIVE THIS PAST WEEK.
   1. _____ PYRIDOSTIGMINE
   2. _____ PLACEBO

2. HOW CONFIDENT ARE YOU OF THIS JUDGMENT? **(Circle one)**

   1 2 3 4 5
   **(Not at all confident)** **(Totally confident)**

3. WHAT ARE YOU BASING THIS JUDGMENT ON?

   _____
   _____
   _____
   _____

4. OVER THE PAST WEEK, HAVE YOU NOTICED ANY CHANGES IN YOUR:

   (1) PHYSICAL COORDINATION YES NO **(If Yes, Describe)** _____
   _____
   _____

   (2) VISUAL PERCEPTION YES NO **(If Yes, Describe)** _____
   _____
   _____

   (3) MEMORY YES NO **(If Yes, Describe)** _____
   _____
   _____

   (4) ATTENTION SPAN YES NO **(If Yes, Describe)** _____
   _____
   _____

   (5) SENSE OF TIME YES NO **(If Yes, Describe)** _____
   _____
   _____

4863(TT)

Reviewed by _____ Date _____
PI Review _____ Date _____

SBJID#_____
PHASE: 1 2 Training
DATE: ___ / ___ / ___

# FOOD DIARY

FOOD DIARY FOR: Sun. ___ Mon. ___ Tues. ___ Wed. ___ Thur. ___

| | FOOD EATEN | | BEVERAGES | |
|---|---|---|---|---|
| | DESCRIPTION (Any foods: Meat, beans, rice, vegetables, fruit, breads, potatoes, candy, etc.) ( Please describe fully.) | TIME | DESCRIPTION (Any drinks: Milk, water, soft drinks, juice, coffee, or tea, black or with cream or sugar, etc.) ( Please describe fully.) | TIME |
| **Breakfast** 1 | | | | |
| **Snacks** 2 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Lunch** 3 | | | | |
| **Snacks** 4 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Dinner** 5 | | | | |
| **Before Bed Snacks** 6 | (Any food eaten between meals) | | (Any beverages between meals) | |
| **Midnight Snacks** 7 | (Any food eaten between meals) | | (Any beverages between meals) | |

4863TT Study 2 SBJID#_____

# FOOD CHOICE MENU

## BREAKFAST:

_____Coffee _____Orange Juice
_____Hot Tea _____Apple Juice
_____Milk _____Coke
_____Pepsi _____Diet Pepsi _____Diet Coke

_____Cold Cereal
- _____Cheerios
- _____Frosted Flakes
- _____Apple Jacks

_____Hot Oat Meal
- _____Cinnamon Apple
- _____Strawberry
- _____Regular

_____Other Cereal _____

_____Instant Breakfast
- _____Chocolate
- _____Strawberry
- _____Vanilla

_____ Toaster Pastries/Pop Tarts/Toast
Flavor/Type _____

_____Apple
_____Orange

## LUNCH:

_____Turkey Sandwich
_____Ham Sandwich
- _____American Cheese
- _____Swiss or Provolone Cheese

_____Red Baron Pastry Pouches
- _____Chicken/Broccoli/Cheese
- _____Sausage/Pepperoni
- _____Beef/Cheddar

_____Regular Chips
_____BBQ Chips
_____Cookie
_____Dill Pickle
_____Apple
_____Orange

_____Coke _____Diet Coke
_____Pepsi _____Diet Pepsi
_____Sprite _____Diet Sprite
_____Bottled Water
_____Other_____

Vegetarian options (Kin Lin entree possible; see menu)
_____ Vegetarian Pizza
_____ Salad (please specify dressing type)
_____ Other _____

4863 STUDY 2
Version 2
Effective 06/13/00

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
EXPERIMENTER _____

Data Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# BATTERY CHECKLIST

## PRE SESSION PREPARATIONS:

➡ HOOK-UP ROOM:
- ☐ GRQ KEY
- ☐ CRF
- ☐ SCRUB TOP AND PILLOWCASE(S)
- ☐ STOPWATCH
- ☐ ECG HOOK-UP SUPPLIES
- ☐ PPI HOOK-UP SUPPLIES
- ☐ RECORD DOMINANT HAND ON PG. 2 OF CHECKLIST
- ☐ RECORD TIME OF NEXT DOSE ON PG. 4 OF CHECKLIST
- ☐ RECORD TIME OF EQUILIBRATION FROM BASELINE DATA SHEET_____
- ☐ RECORD LUNCH CHOICE FROM BASELINE DATA SHEET _____

➡ CHAMBER:
- ☐ TEMPERATURE LOG TO CHAMBER CONTROLLER **(Only on experimental days)**
- ☐ DISCONNECT LAN HOOK-UP
- ☐ POWER TO GRASS
- ☐ POWER TO STIM AND ACQ COMPUTERS, CANCEL PASSWORDS
- ☐ CHECK CHAMBER FURNITURE AND CABLE FOR PROPER SET UP

**Acq computer: PPI Collection**
- ☐ DOUBLE CLICK "GRASS LINK 15" ICON
- ☐ SELECT "MODEL 15"
- ☐ CLICK "CONNECT", select "TTPPI.set"
  **Wait for Channels to scroll through**
- ☐ CLICK "USE"
- ☐ MINIMIZE "LINK 15"
- ☐ DOUBLE CLICK "PPI" ICON
- ☐ CLICK "ACQUIRE"
- ☐ TYPE SESSION ID: tt##*PD*p.daq (##= sbjid, *P*=phase, *D*=day, p=PPI collection)

**STOP HERE** **(Do not press enter until subject is in chamber and ready.)**

## SUBJECT ARRIVES:

- ☐ SUBJECT ARRIVAL TIME _____

➡ SUBJECT TO BIO PREP ROOM
- ☐ BLOOD DRAW (for females, day 5 phase 1 pregnancy draw included)
- ☐ CALL CHAMBER CONTROLLER WHEN S ARRIVES. EXT. 1662

➡ SUBJECT TO CONTROL ROOM E
- ☐ SERVE SUBJECT LUNCH (ON DAY 5 ONLY: Collect Thursday's food diary and have Subject record Friday's food on back.)

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
EXPERIMENTER _____

➡ SUBJECT TO HOOK-UP ROOM

- ☐ ASK SUBJECT TO PUT ON SCRUB TOP
- ☐ EXPLAIN HOOK-UP
- ☐ ATTACH ECG ELECTRODES:
- ☐ ATTACH PPI SENSORS AND INSTRUCT S HOW TO PERFORM TASK

Impedance: PP1 / PP2_____

## SUBJECT TO CHAMBER:

- ☐ GIVE S PROTECTIVE HEADPHONES
- ☐ S IN CHAMBER **(For experimental heat sessions only, signal chamber controller to start equilibration)**
- ☐ **BATTERY START TIME** _____**(For experimental heat sessions, time is at end of equilibration)**

➡ **PRE-PULSE INHIBITION**

- ☐ PLUG IN TAIL
  - **(Black)--G1**
  - **(Green)--GROUND**
  - **(Red)--G2**
- ☐ ASK S TO INSERT EARPHONES AND EXPERIMENTER WILL SECURE.
- ☐ **FACE S AWAY FROM COMPUTER. REINSTRUCT S TO RELAX DURING TASK, KEEP EYES OPEN, BLINK NATURALLY**
- ☐ **INSTRUCT S TO COUNT DOUBLE TONES**
- ☐ PRESS ENTER ON GRASS TO BEGIN COLLECTION, THEN START STIM COMPUTER
- ☐ CLICK ON THE TITLE BAR OF THE ACQUISITION PROGRAM
- ☐ TO BEGIN, @ STIM COMPUTER ENTER **PPI #** (#=collection number: T, 1, 2, 3, 4)
  - Training = PPI T
  - Phase I = PPI 1, PPI 2
  - Phase II = PPI 3, PPI 4
- ☐ **E LEAVES CHAMBER DURING COLLECTION**, CHECK RECORDING
- ☐ AFTER TASK **370 SECONDS**, CLICK **STOP** @ ACQ COMPUTER
- ☐ CLICK **QUIT** @ ACQ COMPUTER
- ☐ ASK S HOW MANY DOUBLE TONES THEY COUNTED _____
- ☐ REMOVE PPI SENSORS, **LEAVE ON HEADPHONES**, AND STAY IN CHAMBER FOR HAND STEADINESS COLLECTION

➡ **HAND STEADINESS TEST** (USE DOMINANT HAND ONLY.)

- ☐ RECORD DOMINANT HAND: RIGHT _____, LEFT_____
- ☐ TYPE **"HANDST ## *PD*"** @ STIM COMPUTER TO BEGIN (##= sbjid, *P*=phase, *D*=day)
- ☐ INSTRUCT S **"INSERT STYLUS, STEADY, GO"**
- ☐ WHEN S IS READY, PRESS THE NUMBER THAT CORRESPONDS TO EACH HOLE

**(Repeat for hole 1 through 4 on bottom row. Make sure S keeps the stylus in the hole.)**

➡ **PERFORMANCE TASKS**

- ☐ REVIEW GENERAL PROCEDURES FOR PERFORMING TASK BATTERY

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
EXPERIMENTER _____

☐ ENTER START TIME _____
☐ RUN DEMO, TYPE <DEMO ##>
COMMANDS FOR TRAINING AND EXPERIMENTAL PERFORMANCE (##=sbjid):

| **TRAINING:** | **PHASE I:** | **PHASE II:** |
|---|---|---|
| <T2 ##> | THUR: <R1 ##> | THUR: <R2 ##> |
| | FRI: <F1 ##> | FRI: <F2 ##> |

➡ **ECG MEASUREMENT**

✶**(Subject will lie down for a total of 8.5 minutes. Subject will stand for a total of 8.5 minutes.)**

☐ATTACH LEADS AND PLUG IN TAIL
**(Black)–G1–LEFT RIB**
**(Green)–GROUND–LEFT CLAVICLE**
**(Red)–G2–RIGHT CLAVICLE**

☐ INSTRUCT SUBJECT TO LIE DOWN **(Instruct S to keep hands by side and don't cross feet. Remind S to lay very still, try not to talk, fidget, or sleep)**
**REMIND S THAT THE SIGNAL TO STAND WILL BE WHEN E TOUCHES S's ANKLE**

**Acq computer: ECG Collection**
☐ MAXIMIZE **"LINK 15"**
☐ SELECT **"FILE"**
☐ CLICK **"LOAD AMP SETTINGS"**, select **"TTECG.set"**
**Wait for Channels to scroll through**
☐ CLICK **"USE"**
☐ MINIMIZE **"LINK 15"**
☐ DOUBLE CLICK **"ECG"** ICON
☐ CLICK **"ACQUIRE"**
☐ TYPE SESSION ID: **tt##*PD*e.daq (##=sbjid, P=phase, D=day, e=ECG collection)**
☐ **CLICK "OK"** TO BEGIN COLLECTION
☐ CLICK ON THE TITLE BAR OF THE ACQUISITION PROGRAM
☐ CHECK RECORDING

☐ E WILL ENTER CHAMBER AND REMAIN FOR THE LENGTH OF THE ECG COLLECTION

☐ BEGIN **SUPINE** COLLECTION ***CLICK EVENT MARKER*** **(Use stopwatch to time 8.5 minutes)**
☐ WHEN **8.5 MINUTES** HAVE PASSED, TOUCH S ON ANKLE TO INSTRUCT S TO STAND **(as quickly and as comfortably as possible) *CLICK EVENT MARKER***
**(Use stopwatch to time additional 8.5 minutes)**
☐ WHEN **17 MINUTES** HAVE PASSED END COLLECTION ***CLICK EVENT MARKER***

☐ CLICK **STOP** @ ACQ COMPUTER
☐ CLICK **QUIT** @ ACQ COMPUTER
☐ REMOVE SENSORS AND PADS

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
EXPERIMENTER _____

☐ S COMPLETES MARI/WORKLOAD
Training = WMT2 ##
Phase I = WMR1 ##, WMF1 ##
Phase II = WMR2 ##, WMF2 ##

☐ EXIT CHAMBER
☐ GIVE S THE GRQ **(Instruct S to Answer according to how they felt while in the chamber)**
☐ DID YOU NOTICE THAT YOUR STRATEGY CHANGED ON HOW YOU PERFORMED THE TASKS, FROM THE FIRST TIME YOU DID THEM, UNTIL NOW?
YES NO
**(IF YES, DESCRIBE IN DEVIATIONS AND OBSERVATIONS SECTION)**

☐ ENTER ENDING TIME _____

➡ TO HOOK UP ROOM
☐ ALLOW S TO CHANGE
☐ DOES THE S HAVE ANY QUESTIONS?
☐ DID ANYTHING MAKE HIM/HER UNCOMFORTABLE?
☐ REMIND S TO COMPLETE FOOD DIARY **(if last training day or phase I, day 5, give S new food diary to begin on Sunday)**
☐ REMIND S TO RETURN FOR NEXT DAILY DOSE AT _____(TIME)

☐ BATTERY END TIME _____

POST SESSION CLEAN-UP
☐ CLEAN EARPHONES WITH ALCOHOL
☐ CHANGE PILLOW CASE(S) IN CHAMBER
☐ BACK UP, ECG, PPI, PERFORMANCE, AND WORKLOAD/MARI
☐ TURN OFF CHAMBER EQUIPMENT
☐ CLEAN PPI SENSORS
☐ CHECK ALL DATA FOR APPROPRIATE ID **(subject # and session date/time)**
☐ SUBJECT'S CRF RETURNED TO FILE AREA FOR DATA MANAGER

SBJID _____
DATE ____/____/____
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
EXPERIMENTER _____

## DEVIATIONS AND OBSERVATIONS

4863
Version 1
Effective 6/13/00

SBJID_____
DATE___/___/___
DAY 1 2 3 4 5
PHASE I PHASE II TRAINING
Experimenter_____
TEMP 75 95

Data Entry 1st _____, 2nd _____
Reviewed By _____ Date _____
PI Review _____ Date _____

## TEMPERATURE AND HUMIDITY

SUBJECTS ENTER INTO ENVIRONMENTAL CHAMBER AT 110°F TIME:_____

INITIATE TEMPERATURE CHANGE FROM 110° TO 95°F TIME:_____

TEMPERATURE REACHES 95°F OR S ENTERS AT 75°F
**(OBSERVATION #1 IS 15 MIN FROM THIS TIME)** TIME:_____

ENVIRONMENTAL CHAMBER TEMPERATURE LOG

| OBSERVATION NUMBER | TIME INTO TEST | ACTUAL TIME | CHAMBER TEMPERATURE | CHAMBER RELATIVE HUMIDITY | EXPERIMENTER INITIALS |
|---|---|---|---|---|---|
| 1 | 15 MIN | | | | |
| 2 | 30 MIN | | | | |
| 3 | 45 MIN | | | | |
| 4 | 1 HR | | | | |
| 5 | 1 HR 15 MIN | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| END READING | | | | | |

4863
Version: 2
Effective: 3/24/00

SBJID# _____
Date ___/___/____
Phase I Phase II
Experimenter_____

Data Entry 1st _____, 2nd _____
Reviewed by: _____ Date _____
PI Review _____ Date _____

# CHECKLIST
## BLOOD DRAW - MONDAY, DAY 8

**PRE SESSION PREPARATIONS:**

☐ **CONTROL ROOM E**

- ☐ GLOBAL RATING FORM
- ☐ RECEIPT FORM
- ☐ $225.00 COMPLETION PAYMENT
- ☐ PHYSICIAN REFERRAL FORM **(FOR EXIT EXAM, PHASE II ONLY)**
- ☐ APPOINTMENT CARD **(FOR EXIT EXAM, PHASE II ONLY)**

**MONDAY- DAY 8 SESSION:**

☐ ARRIVAL TIME _____

☐ BLOOD DRAW

- ☐ SHOW S TO BIO PREP ROOM

☐ GLOBAL RATING FORM

☐ **COMPLETION PAYMENT**

- ☐ $225.00 PHASE I, RECEIPT SIGNED YES NO
- ☐ $225.00 PHASE II, RECEIPT SIGNED YES NO

**PHASE II ONLY:**

☐ CONFIRM EXIT MEDICAL EXAMINATION APPOINTMENT ON S CALENDAR

- ☐ RECORD APPOINTMENT DATE ___/___/___ TIME _____
- ☐ COMPLETE PHYSICIAN REFERRAL FORM
- ☐ PHYSICIAN APPOINTMENT CARD TO S
- ☐ INFORM S: WHEN RESULTS OF EXIT EXAM ARE RECEIVED AT MRI, EXPERIMENTER WILL CALL S TO ARRANGE $100 BONUS PAYMENT
- ☐ REMIND S OF FOLLOW-UP CALL AT 3 MONTHS
- ☐ FOLLOW-UP TELEPHONE NUMBER **(GET TELEPHONE NUMBER WHERE S CAN BE REACHED IN 3 MONTHS FOR FOLLOW-UP INTERVIEW)**
  - ☐ RECORD TELEPHONE # _____ **(Enter into Scheduler)**

SBJID# _____
Date ___/___/___
Phase I Phase II
Experimenter_____

☐ DEPARTURE TIME _____

POST SESSION:

☐ FILE SIGNED PAYMENT RECEIPT IN LOCKED FILE CABINET

☐ S'S CRF RETURNED TO FILE AREA FOR DATA MANAGER

☐ **(For Phase II Only)** FAX REFERRAL FORM TO PHYSICIAN

☐ **(For Phase II Only)** PUT FOLLOW-UP APPOINTMENT ON SCHEDULER

DEVIATIONS AND OBSERVATIONS

SBJID # _____
DATE ____ / ____ / ____
DAY 1 2 3 4 ,5 8
Phase I Phase II Training
Experimenter _____

Data Entry 1st _____, 2nd _____
Reviewed by _____ Date _____
PI Review _____ Date _____

# EARLY EXIT CHECKLIST

☐ REASON FOR EARLY EXIT:

- ☐ INTERIM REFERRAL, PHYSICIAN'S RECOMMENDATIONS YES NO
- ☐ SUBJECT DROP YES NO
  REASON FOR DROP _____
- ☐ OTHER YES NO
  (IF YES) EXPLAIN _____

IF S EXITS DURING TRAINING:

- ☐ NUMBER OF TRAINING HOURS COMPLETED _____
- ☐ AMOUNT OF TRAINING PAYMENT (AT A RATE OF $5.00 PER HOUR OF TRAINING COMPLETED)_____
- ☐ RECEIPT SIGNED YES NO

IF S EXITS DURING PHASE I:

- ☐ NUMBER OF DAYS COMPLETED DURING PHASE I _____
- ☐ AMOUNT OF PHASE I PAYMENT (AT A RATE OF $25.00 PER DAY OF ACTUAL PARTICIPATION) _____
- ☐ RECEIPT SIGNED YES NO

IF S EXITS DURING PHASE II:

- ☐ NUMBER OF DAYS COMPLETED DURING PHASE II _____
- ☐ AMOUNT OF PHASE I PAYMENT (AT A RATE OF $25.00 PER DAY OF ACTUAL PARTICIPATION) _____
- ☐ RECEIPT SIGNED YES NO

SBJID # _____
DATE ____/____/____
DAY 1 2 3 4 5 8
Phase I Phase II Training
Experimenter _____

☐ SCHEDULE EXIT MEDICAL EXAMINATION

- ☐ RECORD APPOINTMENT DATE ___/___/___ APPOINTMENT TIME _____
- ☐ COMPLETE MEDICAL EXAMINATION REFERRAL FORM
- ☐ GIVE S A PHYSICIAN APPOINTMENT CARD
- ☐ INFORM S WHEN RESULTS OF EXIT EXAM ARE RECEIVED AT MRI, EXPERIMENTER WILL CALL S TO ARRANGE $100 BONUS PAYMENT.
- ☐ INFORM S THAT SOMEONE FROM MRI WILL CALL THEM IN 3 MONTHS TO FOLLOW UP.

POST SESSION:

- ☐ S's CRF RETURNED TO FILE AREA FOR DATA MANAGER
- ☐ FAX MEDICAL EXAMINATION REFERRAL FORM TO PROJECT PHYSICIAN.

## DEVIATIONS AND OBSERVATIONS

4863TT

**PAYMENT RECEIPT**
**EARLY EXIT**

SBJID_____

**PHASE I/PHASE II PARTIAL PARTICIPATION RECEIPT**

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF $_____ FOR MY PARTICIPATION IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE, AT $25.00 PER DAY.

SIGNATURE:_____

**TRAINING PARTIAL PARTICIPATION RECEIPT**

THIS IS TO CERTIFY THAT ON __ / __ / __ , I RECEIVED A TOTAL OF $_____ FOR _____ HOURS OF TRAINING TO PARTICIPATE IN A RESEARCH PROJECT PERFORMED AT MIDWEST RESEARCH INSTITUTE, AT $5.00 PER HOUR.

SIGNATURE:_____

4863
Version: 1
Effective: 3/24/00

MRI

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600

NAME:_____
SBJID:_____
Experimenter's Initials:_____

Data Entry 1st_____ 2nd_____
Reviewed by_____ Date_____
PI Review_____ Date_____

## Interim Referral

**Referral to:** **Mary Brothers, M.D.**
**Union Hill Commons**
**3037 Main, Suite 201**
**Kansas City, Mo. 64108-3323**
**Telephone: 561-3480**
**FAX: 561-4043**

**Appointment Date:**___/___/___ **Time:**_____

| *Interim referral* | *For doctor's use only* | *Doctor's signature* |
|---|---|---|
| Referral due to Vital Signs___<br><br>Referral due to General Response Questionnaire ____<br>Other | Medically approved to remain in study:<br>YES NO<br>Subject took pill:<br>YES NO | |

| **If subject will not return to study, schedule Exit Examination with Dr. Parmet** | Date | Time |
|---|---|---|

***Doctor's comments:***

**Instructions to Doctor:**
- Mark whether or not the subject is approved to remain in the study.
- If approved to remain in study, **watch the subject swallow pill. If not, return the pill to MRI.**
- If subject is approved to remain in study but wishes to quit, indicate this in Doctor's Comments.
- If subject will not return to study, schedule an Exit Examination. Enter Date and Time on form.
- Call MRI to state whether or not the subject remains in the study: **753-7600, ext. 1610**
- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

MRI

Midwest Research Institute
425 Volker Blvd.
Kansas City, MO 64110-2299
Telephone (816) 753-7600, ext 1610

NAME:_____
SBJID:_____
Experimenter's initials:_____

| |
|---|
| Data Entry 1st _____ 2nd _____ |
| Reviewed by_____ Date_____ |
| PI Review _____ Date_____ |

## Follow-up Referral

**Referral to:** **Mary Brothers, M.D.**
**Union Hill Commons**
**3037 Main, Suite 201**
**Kansas City, Mo. 64108-3323**
**Telephone: 561-3480**
**FAX: 561-4043**

**Appointment Date:**____/____/____ **Time:**_____

| *For doctor's use only* | *Doctor's signature* |
|---|---|
| Symptoms related to study<br>YES NO<br>Requires Doctor's Follow-up<br>YES NO | |

***Doctor's Comments:***

**Instructions to Doctor:**
- Mark whether or not the subject's symptoms are related to the study.
- Mark whether or not the subject requires doctor's follow-up for symptoms.
- Doctor's signature for all referrals completed.
- **FAX a copy of the signed referral to 753-7380.**

SBJID#_____
Date___/___/___
Date of Last Contact_____
Experimenter_____

## STUDY 2

Data Entry 1st _____, 2nd _____
Reviewed by_____ Date_____
PI Review_____ Date_____

## FOLLOW-UP TELEPHONE INTERVIEW

Hello, ___Subject___ this is __Experimenter__ with Midwest Research Institute. I'm calling because you participated in a study with us 3 months ago, and we'd like to see how you are doing. As a routine part of our study, we want to ask you some follow-up questions about your health and well being since the last time we spoke with you. Let me begin by asking you about your over-all health.

HOW HAVE YOU BEEN FEELING SINCE THE STUDY ENDED?

_____

_____

_____

DID SUBJECT REPORT COMPLAINT? YES NO
**(If S reports complaints, ask next question.)**

WOULD YOU ATTRIBUTE Complaint TO YOUR PARTICIPATION IN THE STUDY? YES NO

Now I want to read a list of symptoms to you that people who returned from the Gulf War said they sometimes experienced. We don't think that you will experience these symptoms because of this study, but the Army wants us to ask everyone who participates in the project about these symptoms.

SBJID#_____
Date___/___/___
Date of Last Contact_____
Experimenter_____

## STUDY 2

SINCE THE LAST TIME WE TALKED TO YOU, WOULD YOU SAY THAT YOU HAVE BEEN BOTHERED OR DISTRESSED BY ANY OF THE FOLLOWING THINGS?

**(Read each symptom to the S. For each yes answer, ask:)**
IS THIS AN UNUSUAL PROBLEM FOR YOU?
HAVE YOU SEEN A DOCTOR FOR **SYMPTOM** ? **(If yes)** WHEN?

| | SYMPTOM | | UNUSUAL SYMPTOM | | VISITED DOCTOR | | DOCTOR VISIT |
|---|---|---|---|---|---|---|---|
| | YES | NO | YES | NO | YES | NO | MO/DY/YR |
| 1. JOINT OR MUSCLE PAIN | | | | | | | |
| 2. VERTIGO OR DIZZINESS | | | | | | | |
| 3. PROBLEMS WITH YOUR ATTENTION SPAN | | | | | | | |
| 4. SKIN RASHES | | | | | | | |
| 5. UNINTENTIONAL WEIGHT LOSS | | | | | | | |
| 6. FEVERS | | | | | | | |
| 7. PERSISTENT COUGH | | | | | | | |
| 8. DAYTIME SLEEPINESS | | | | | | | |
| 9. SEVERE HEADACHES | | | | | | | |
| 10. IMPOTENCE **(Ask Males Only)** | | | | | | | |
| 11. INSOMNIA OR TROUBLE SLEEPING | | | | | | | |
| 12. DEPRESSION | | | | | | | |
| 13. MEMORY PROBLEMS | | | | | | | |
| 14. MUSCLE FATIGUE | | | | | | | |
| 15. LUMPS OR CYSTS IN BREASTS **(Females)** | | | | | | | |
| 16. DIFFICULTY REASONING | | | | | | | |
| 17. SLURRED SPEECH | | | | | | | |
| 18. SHORTNESS OF BREATH | | | | | | | |
| 19. CHEST PAIN | | | | | | | |
| 20. DIARRHEA | | | | | | | |
| 21. VISION OR EYE PROBLEMS | | | | | | | |
| 22. GYNECOLOGICAL PROBLEMS **(Females)** | | | | | | | |

SBJID#_____
Date___/___/___
Date of Last Contact_____
Experimenter_____

Thank you __SUBJECT__. That is all of the questions I have for you. We really appreciate the help you have given us with this important study.

**POST - PHONE CALL:**
Should Interim referral be made? YES NO

**(Interim Referral should be made if the subject reports an unusual symptom for which medical evaluation has not been sought. The Interim Referral form should be completed according to Interim Referral procedures.)**

## DEVIATIONS AND OBSERVATIONS

# Sample Record Form

Project 4863
Subject ID:_____
Male/Female:_____
Dosing Start Date:_____
Labeling Key: Subject #/Phase/Day

Regularly Drink Coffee? Yes or No

| | Training | Phase 1 | | | |
|---|---|---|---|---|---|
| **Blood Samples** | | Monday | Thursday | Friday | Monday |
| | Predose | Day 1 | Day 4 | Day 5 | Day 8 |
| Collection Date: | | | | | |
| Collection Time: | | | | | |
| Drawn by: (initials) | | | | | |
| ~ Amount Coffee in last 24 hrs (cups) | | | | | |
| Collection Tubes: | | | | | |
| SST Marble Top | | | | | } (females only) |
| ACD Yellow Top (prechilled) | | | | | |
| EDTA Purple Top (prechilled) | | | | | |
| Place yellow & purple top tubes into ice slurry | | | | | |
| Centrifuge Tubes for 20 min ~ 2800 g at 5°C | | | | | |
| **SST:** | | | | | |
| Transfer serum (#) | | | | | }(females only) |
| Assay for HCG | | | | | |
| Store 2 aliquots at ~ –20°C (time) | | | | | |
| **Yellow Top (ACD):** | | | | | |
| Pipette 1.0 mL aliquots plasma x3 (#) | | | | | |
| Store all aliquots at ~ –80°C (time) | | | | | |
| Transfer buffy coat layer x2 (#) | | | | | |
| Store buffy coat at ~ –80°C (time) | | | | | |
| Mix RBC with buffer | | | | | |
| ~ 500 µL aliquots RBC x4 (#) | | | | | |
| Store RBC aliquots at ~ –80°C (time) | | | | | |
| **Purple Top (EDTA):** | | | | | |
| ~ 500 µL aliquots plasma x4 (#) | | | | | |
| Store plasma aliquots at ~ –20°C (time) | | | | | |
| Samples processed by: (initials) | | | | | |

# Sample Record Form (Continued)

Project 4863
Subject ID:_____
Male/Female:_____
Dosing Start Date:_____
Labeling Key: Subject #/Phase/Day

Regularly Drink Coffee? Yes or No

| | Refresher | Phase 2 | | |
|---|---|---|---|---|
| **Blood Samples** | Females Only Pregnancy | Thursday Day 4 | Friday Day 5 | Monday Day 8 |
| Collection Date: | | | | |
| Collection Time: | | | | |
| Drawn by: (initials) | | | | |
| ~ Amount Coffee in last 24 hrs (cups) | | | | |
| Collection Tubes: | | | | |
| SST Marble Top | | | | |
| ACD Yellow Top (prechilled) | | | | |
| Place yellow tube into ice slurry | | | | |
| Centrifuge Tubes | | | | |
| for 20 min ~ 2800 g at ~ 5°C | | | | |
| **SST:** | | | | |
| Transfer serum x1 (#) | | | | |
| Assay for HCG | | | | |
| **Yellow Top (ACD):** | | | | |
| Pipette 1.0 mL aliquots plasma x3 (#) | | | | |
| Store all aliquots at ~ –80°C (time) | | | | |
| Mix RBC with buffer | | | | |
| ~ 500 µL aliquots RBC x4 (#) | | | | |
| Store RBC aliquots at ~ –80°C (time) | | | | |
| Samples processed by: (initials) | | | | |

# Sample Record Form (Continued)

Project 4863
Subject ID:_____
Male/Female:_____
Dosing Start Date:_____
Labeling Key: Subject #/Phase/Day

| **Interim Blood Samples** | **Phase ____/Day _____** |
|---|---|
| Collection Day: | |
| Collection Date: | |
| Collection Time: | |
| Drawn by: (initials) | |
| ~ Amount Coffee in last 24 hrs (cups) | |
| Collection Tubes: | |
| ACD Yellow Top (prechilled) | |
| Place yellow tube into ice slurry | |
| Centrifuge Tubes | |
| for 20 min ~2800g at 5°C | |
| **Yellow Top (ACD):** | |
| Pipette 1.0 mL aliquots plasma x3 (#) | |
| Store all aliquots at ~ –80°C (time) | |
| Mix RBC with buffer | |
| ~ 500 µL aliquots RBC x4 (#) | |
| Store RBC aliquots at ~ –80°C (time) | |
| Samples processed by: (initials) | |

16.1.3. List of IECs or IRBs (plus the name of the committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms

MRI's Multiple Projects Assurance (effective July 1, 1982, and approved through March 31, 2001) sets out Institutional Review Board (IRB) responsibilities and the procedures that will be used to protect human subjects. The current Multiple Projects Assurance (M-1051) complies with the Federal Policy for the Protection of Human Subjects (56 *FR* 28003), also known as the Common Rule, which became effective on August 19, 1991. The Common Rule established basic standards that are now honored by 16 different Federal departments and agencies.

MRI has established an IRB in accordance with DHHS's regulations on Protection of Human Subjects (45 *CFR* 46 as amended). Members of MRI's IRB are:

Dr. Eugene Podrebarac, IRB Chairman
Dr. R. Allen Chandler, Physician
Dr. Mary R. Cook, MRI Principal Advisor, Life Sciences Division
Mr. John Dinwiddie, MRI Senior Vice President and Corporate Treasurer (retired)
Mr. Robert Donaldson, Special Assistant to MRI Senior Vice President/Treasurer
Dr. Charles Graham, MRI Principal Advisor, Life Sciences Division
Mr. Al Guyot, MRI Director, Corporate Human Resources
Dr. Don Justesen, Veterans Administration Hospital (retired)
Dr. John McCalla, Physician (retired)
Ms. Rosemary Moran, MRI Quality Assurance Officer
Dr. Eugene Smith, Physician

16.1.3.1. Study 1 Consent Form

Study Copy

Sbjid:_____
Call#_____

MIDWEST RESEARCH INSTITUTE
VOLUNTEERS' INFORMED CONSENT

Study #1
Project # 4863
Revision date: 05/21/98
Revision 3.0

Individual Differences in Neurobehavioral Effects of Pyridostigmine: Study 1

I,_____residing at

_____

_____

hereby acknowledge and certify to the following:

1. I hereby volunteer and consent to be a subject in a research study sponsored by the U. S. Army Medical Research and Materiel Command (USAMRMC) and conducted at Midwest Research Institute by Drs. Mary R. Cook and Antonio Sastre. I understand this study will evaluate the short-term effects of pyridostigmine bromide on physiology and performance in normal, healthy young men and women. Pyridostigmine has a long history of use in the medical treatment of a condition called myasthenia gravis. It has been alleged that pyridostigmine bromide is associated with Persian Gulf War veterans' illnesses. Pyridostigmine is important to the Army because it has properties that enable it to protect people in the event of a chemical warfare attack. The Food and Drug Administration, however, has not approved pyridostigmine for use in healthy people and I understand its use is investigational in this research study. The most frequent side effects of pyridostigmine are upset stomach, cramps, gas, diarrhea, and excessive salivation. Pyridostigmine should be avoided when a woman is pregnant. I am also aware that in a previous study at MRI, only a few of the 25 healthy, young men who took pyridostigmine reported any symptoms, and these consisted of mild stomach upset, gas and feelings of tiredness. I also understand that this is a double-blind study. This means that during any given phase of the experiment, pyridostigmine may actually be in the pills I take, or it may not. The investigators will not know, and I will not know, which pill is which. In this way, any effects due to pyridostigmine can be separated from those that might be due to a person's expectations about taking pyridostigmine.

I understand I will receive free a complete medical examination at the start of the study. This evaluation will include medical history, drug screen, urinalysis, electrocardiogram, blood chemistry, complete blood count, lung function test, and medical examination. For women, the examination will include a pregnancy test. The physician will tell me about any problems he/she finds during the evaluation, and advise me about follow-up. I will then come to MRI to be trained to perform tests that measure my memory, attention, perception, and sensory abilities. During training, sensors will be attached to my head and wrist to measure my brain waves, pulse and blood pressure. I understand that sensor attachment is painless and presents no risk to my health. Training will require about 10 hours of my time spaced over a week.

I will then be randomly assigned to one of two groups. One group takes 60 mg pyridostigmine, every 8 hours (180 mg/day) and one takes 30 mg every 8 hours (90 mg/day); both groups take placebo. These doses of pyridostigmine are less than the doses typically used by medical patients (120 mg 6 times/day; 720 mg/day). The study will be performed in two phases, separated by six days off. Each Phase will last eight days, and each will involve the same sequence of activities. I understand I will be asked to come to MRI to take pills every eight hours for the first four days of each phase, followed by one additional pill on the fifth day. I will have my blood pressure, pulse, and temperature recorded. I will complete a food diary and a questionnaire about any symptoms I may be experiencing. Blood samples (about 1 ounce) will be collected via venipuncture from a vein in my arm on days 1, 4, 5 and 8. White blood cells from some of these samples will be sent to another laboratory for special analysis, and I understand that, for this reason, I will be asked to sign a donation form. On days 4 and 5, I will provide urine samples and perform the tests I learned earlier. I will keep a diary of what I eat and drink for the first 4 days of each Phase. MRI will provide breakfast and lunch for me on certain days. At the end of Phase 2, I will visit the project physician again for a brief follow-up medical examination. Three, six and 12 months after I finish the study, I will be contacted by MRI staff to determine whether I have experienced any effects that I think might be due to my participation in this study. If so, they will arrange for further medical evaluation.

See Deviation 1/25/00

I agree to not use drugs or alcohol during the study and to inform the investigators of any medications I may need to take. I understand that standard medical procedures will be followed when drawing blood, but that bruising or soreness can sometimes occur. I further understand that this is a basic research study, and that I will not benefit from being in it, except that I will receive a full medical examination at no charge, and I will be reimbursed for the time and effort required for participation. If I complete all study requirements, I will receive a total of $600 ($50 for training, $225 for each phase, and $100 completion bonus); if not, I will be paid $25.00 per day of actual participation.

2. I have been given, in my opinion, an adequate explanation of the nature, duration, and purpose of the study, the means by which the study will be conducted, and any possible inconvenience, hazards, discomfort, risks, and adverse effects on my health which could result from my participation.

3. I understand my questions concerning procedures which affect me will be answered fully and promptly by either Dr. Mary R. Cook, Principal Investigator, Dr. Antonio Sastre, Co-Principal Investigator, or by Dr. Eugene Podrebarac, Chairman of the MRI Institutional Review Board for Human Studies, which reviewed and approved this study (816/753-7600). The address of the Institute is 425 Volker Boulevard, Kansas City, MO.

4. I understand that I have the right to withdraw my consent and to discontinue participation in this experiment at any time without prejudice regardless of the status of the experiment and regardless of the effect of such withdrawal on the objectives and results of the experiment; and I also understand that my participation in the experiment may be terminated at any time by the investigator in charge of the project.

5. I agree that any information obtained from me, by MRI, or its authorized representatives, in connection with this study may be utilized by MRI in publications and reports without identifying me. Because the use of pyridostigmine is investigational for this study, I am also aware that representatives of the Food and Drug Administration and/or the U.S. Army Medical Research and Materiel Command may

wish to review the records of my participation and perhaps contact me to ask specific questions about my experiences. I understand that MRI agrees with this policy of openness in this type of study, and that it will provide personally identifying information about me to allow these agencies to contact me if they so wish. I understand this information will be limited to the following: my name, address, social security number, the name of this study, and the dates of my participation in it. This information will be maintained by the USAMRMC in its confidential Volunteer Registry Data Base. The intent of this procedure is two fold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

6. If I experience any symptoms I feel should be reviewed with a physician, I can call the medical monitor, who will schedule an appointment with me as soon as possible. The United States Department of Defense is funding this research project. Should I be injured as a direct result of participating in this research project, I will be provided medical care, at no cost to me, for that injury. I will not receive any injury compensation, only medical care. I understand that this is not a waiver or release of my legal rights. I further understand that I should discuss this issue thoroughly with the Principal Investigator before enrolling in this study. Other than the medical care that may be provided (and the other benefits stated above in section # 1 of this consent form), there is no other compensation available for my participation in this research study.

7. I will be given a copy of this consent form to keep.

My age is ____; The date of my birth is_____

I am executing this Volunteer's Consent as my free act and deed.

Today's date is _____, 19_____

Executed in the presence of each other

_____ _____ Date:_____
Signature of Volunteer Initials

_____Date:_____
Signature of Investigator

To: Dr. Gene Podrebarac
From: Dr. Mary Cook
Subject: 4863-02 - Protocol Deviation
January 25, 2000

In the consent form for Study 1, we stated that the volunteer would complete 4 food diary forms during each testing week. Near the end of the study, one volunteer mentioned to Dr. Gerkovich that actually 5 food diaries were completed during each phase. She changed the number on the printed form and initialed it, and made the same correction on two other consent forms (SS 88, 95 and 97). No formal change in the consent form was made, and other investigators who obtained informed consent did not notice the original error. Consequently, almost all of the signed consent forms mention completing 4 diaries/phase, when in fact 5 diaries were completed.

cc: Dr. Sastre

Please let me know if you have any questions.

MIDWEST RESEARCH INSTITUTE
SAMPLE DONATION FORM

**Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 1**

I, _____residing at

_____

voluntarily and freely donate blood samples to the study sponsor, the U. S. Army Medical Research and Materiel Command, and hereby relinquish all right, title, and interest to said items. The samples donated will not contain any information that identifies me personally.

_____ Date:_____
Signature of Volunteer

_____ Date:_____
Signature of Experimenter

16.1.3.2. Study 2 Consent Form

Study 2 Copy

Call # _____

**MIDWEST RESEARCH INSTITUTE**
**VOLUNTEER'S INFORMED CONSENT**

Individual Differences in Neurobehavioral Effects of Pyridostigmine: Study 2

I,_____residing at

_____

_____

hereby acknowledge and certify to the following:

1. I hereby volunteer and consent to be a subject in a research study sponsored by the U. S. Army Medical Research and Materiel Command (USAMRMC) and conducted at Midwest Research Institute by Drs. Mary R. Cook and Antonio Sastre. I understand this study will evaluate the short-term effects of the combination of environmental heat and pyridostigmine bromide (PB) on physiology and performance in approximately 24 normal, healthy young men and women. PB has a long history of use in the medical treatment of a condition called myasthenia gravis. It has been alleged that PB is associated with Gulf War Veteran's Illnesses. PB is important to the Army because it has properties that enable it to protect people in the event of a chemical warfare attack. The Food and Drug Administration, however, has not approved PB for use in healthy people and I understand its use is investigational in this research study. The most frequent side effects of PB are upset stomach, cramps, gas, diarrhea, and excessive salivation. I am also aware that in two previous studies at MRI, only a few of the over 90 volunteers who took PB reported any symptoms, and these consisted of mild stomach upset, gas and feelings of tiredness. I understand that administration of PB, as with any other drug, may involve risks to me (or an embryo or fetus) that are currently unforeseeable. I understand that women who participate in this study should avoid becoming pregnant for two weeks after participation in the study. To avoid becoming pregnant, I should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. I also understand that this is a double-blind study. This means that during any given phase of the experiment, PB may actually be in the pills I take, or it may not. The investigators will not know, and I will not know, which pill is which. In this way, any effects due to PB can be separated from those that might be due to a person's expectations about taking PB.

I understand I will receive free a complete medical examination at the start of the study. This evaluation will include medical history, drug screen, urinalysis, electrocardiogram, blood chemistry, complete blood count, lung function test, and medical examination. For women, the examination will include a pregnancy test. The physician will tell me about any problems he/she finds during the evaluation, and advise me about follow-up. I will then come to MRI to be trained to perform tests that measure my memory, attention, and sensory abilities. During training, sensors will be attached to my chest to measure my heartbeat, and below my eyes to measure my eye blink response. I understand that sensor attachment is painless; however, it is remotely possible that the attachment of sensors can cause irritation or scratches in particularly sensitive people. Training will require no more than 6 hours of my time spaced over a week.

Call # _____

I will then be randomly assigned to one of two groups. Both groups take 30 mg PB every 8 hours (90 mg/day), and both groups take placebo. These doses of PB are less than the doses typically used by medical patients (120 mg 6 times/day; 720 mg/day). The study will be performed in two phases, separated by two days off. Each Phase will last five days and each will involve the same sequence of activities. I will keep a diary of what I eat and drink for each of the 12 days of the study. I understand I will be asked to come to MRI to take pills every eight hours for the first four days of each phase, followed by one additional pill on the fifth day. I will have my blood pressure, pulse, and temperature recorded each morning, and I will complete a questionnaire about any symptoms I may be experiencing. I will be asked to provide blood samples (about 1 ounce) via venipuncture from a vein in my arm, once during training, on days 1, 4, and 5 of each phase, and on the Monday following the final dose. I understand that standard medical procedures will be followed when drawing blood, but that bruising or soreness can sometimes occur. To minimize this risk, MRI employs highly trained phlebotomists to conduct blood draws. These samples will be used to find out how much PB is in my blood, and how it has affected my cholinesterase levels. Some of the samples that I am donating under this study may be used by another laboratory for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. Should my donated samples lead to the development of a commercial product, the other laboratory will own it and may take action to patent and license the product. I will not be provided with additional compensation for donating these blood samples and will not receive any notice of future uses of my samples. The samples donated will not contain any information that identifies me personally. I understand that, for this reason, I will be asked to sign a separate donation form. On days 4 and 5, sensors will be attached, and I will perform the tests I learned earlier. On one day, I will perform the tests at room temperature, and on the other day at a temperature of approximately 95°F. This temperature may cause mild discomfort, similar to a hot summer day in Kansas City. Testing will take about one hour. MRI will provide breakfast for me every day that I take pills, and will provide lunch for me on test days. At the end of the study, I will return to MRI for a final blood sample, and will visit the project physician again for a brief follow-up medical examination. Three months after I finish the study, I will be contacted by MRI staff to determine whether I have experienced any effects that I think might be due to my participation in this study. If so, they will arrange for further medical evaluation.

I agree to not use drugs or alcohol during the study and to inform the investigators of any medications I may need to take. I understand that this is a basic research study, and that I will not benefit from being in it, except that I will receive a full medical examination at no charge, and I will be reimbursed for the time and effort required for participation. If I complete all study requirements, I will receive a total of $600 ($50 for training, $225 for each phase and $100 completion bonus). If I should choose to withdraw from the study during a dosing week, I will be paid $25.00 per day of actual participation and I will also be expected to see the project physician for a final medical examination. I will still be contacted three months after my last day of participation to determine whether I've experienced any effects that I think might be due to my participation. If I choose to withdraw during the training week I will be compensated at a rate of $5.00 per hour of training and I will not be contacted for follow up.

2. I have been given, in my opinion, an adequate explanation of the nature, duration, and purpose of the study, the means by which the study will be conducted, and any possible inconvenience, hazards, discomfort, risks, and adverse effects on my health which could result from my participation.

Call # _____

3. I understand my questions concerning procedures which affect me will be answered fully and promptly by either Dr. Mary R. Cook, Principal Investigator, Dr. Antonio Sastre, Co-Principal Investigator, or by Dr. Eugene Podrebarac, Chairman of the MRI Institutional Review Board for Human Studies, which reviewed and approved this study (816/753-7600). The address of the Institute is 425 Volker Boulevard, Kansas City, MO.

4. I understand that I have the right to withdraw my consent and to discontinue participation in this experiment at any time without prejudice regardless of the status of the experiment and regardless of the effect of such withdrawal on the objectives and results of the experiment. I also understand that my participation in the experiment may be terminated at any time by the investigator in charge of the project.

5. I agree that any information obtained from me, by MRI, or its authorized representatives in connection with this study, may be utilized by MRI in publications and reports without identifying me. Because the use of pyridostigmine is investigational for this study, I am also aware that representatives of the Food and Drug Administration and/or the U.S. Army Medical Research and Materiel Command may wish to review the records of my participation and perhaps contact me to ask specific questions about my experiences. I understand that MRI agrees with this policy of openness, and that it will provide personally identifying information about me to these agencies to allow them to contact me if they so wish. I understand this information will be limited to the following: my name, address, social security number, the name of this study, and the dates of my participation in it. This information will be maintained by the USAMRMC in its confidential Volunteer Registry DataBase. The intent of this procedure is two fold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

6. If I experience any symptoms I feel should be reviewed with a physician, I can call the medical monitor, Dr. Mary Brothers (816)561-3480 Home (913)727-6168 , who will schedule an appointment with me as soon as possible. The United States Department of Defense is funding this research project. Should I be injured as a direct result of participating in this research project, I will be provided medical care, at no cost to me, for that injury. I will not receive any injury compensation, only medical care. I understand that this is not a waiver or release of my legal rights. I further understand that I should discuss this issue thoroughly with the Principal Investigator before enrolling in this study. Other than the medical care that may be provided (and the other benefits stated above in section # 1 of this consent form), there is no other compensation available for my participation in this research study.

7. I will be given a copy of this consent form to keep.

Call # _____

My age is ____; The date of my birth is_____

I am executing this Volunteer's Consent as my free act and deed.

Today's date is _____, 19_____

Executed in the presence of each other

| _____ | _____ | Date:_____ | _____ |
|---|---|---|---|
| Name of Volunteer | Signature of Volunteer | | Initials |
| _____ | _____ | Date:_____ | _____ |
| Name of Investigator | Signature of Investigator | | Initials |
| _____ | _____ | Date:_____ | _____ |
| Name of Witness | Signature of Witness | | Initials |

4863
5/4/00

CALL# _____

# MIDWEST RESEARCH INSTITUTE
# SAMPLE DONATION FORM

## Individual Differences in Neurobehavioral Effects of Pyridostigmine, Study 2

I, _____ residing

at _____

Voluntarily donate any and all blood samples to Midwest Research Institute (MRI). These samples will be used to find out how much Pyridostigmine Bromide is in my blood, and how it has affected my cholinesterase levels. Some of the samples that I am donating under this study may be used by another laboratory for special analysis and may also be used by them for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. Should my donated samples lead to the development of a commercial product, the other laboratory will own it and it is possible that it will be patented and licensed by them. I will not be provided with additional compensation for donating these blood samples and will not receive any notice of future uses of my samples. The samples donated will not contain any information that identifies me personally.

_____ Date: _____
Signature of Volunteer

_____ Date: _____
Signature of Experimenter

_____ Date: _____
Signature of Witness

16.1.4 List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study.

## Mary R. Cook

Principal Advisor for Life Sciences
Midwest Research Institute

Dr. Cook serves as principal or co-principal investigator for research programs in the areas of health behavior, psychophysiology, and human neurobehavioral toxicology (including drug effects). She is skilled in experimental design, statistical analysis, and the conduct of comprehensive critical literature reviews, and has played a key role in numerous interdisciplinary research programs. Trained in biological psychology, Dr. Cook's specific research focus is to apply the principles of psychophysiology and experimental psychology to problems of human health, behavior, and productivity.

Until 1999, Dr. Cook was head of biobehavioral sciences research at MRI, and had technical and administrative responsibility for a team of scientists specializing in psychophysiology, cognitive and experimental psychology, neurobehavioral toxicology, and health and medical psychology. Prior to joining MRI in 1974, Dr. Cook was a Research Associate at the Institute of the Pennsylvania Hospital. During this period she was involved in research studies of the cardiovascular system, lie detection, sleep loss and recovery, and the mechanisms underlying physiological self-regulation. She held academic appointments in both the Department of Psychiatry and the Department of Psychology at the University of Pennsylvania.

Dr. Cook has over 100 publications and presentations in her areas of expertise. She is a member of Phi Beta Kappa; is listed in *Who's Who in America, Who's Who of American Women, American Men and Women in Science,* and *Who's Who in the Biobehavioral Sciences*; and is a past chapter president of Sigma Xi. Dr. Cook is a member of the Society for Psychophysiological Research, International Organization of Psychophysiology, and the American Psychological Society. She served as coeditor of *Biofeedback and Self-Regulation* and as consulting editor for four other scientific journals. Dr. Cook was presented the 1982 Professional Award from MRI's Council of Principal Scientists.

Dr. Cook received her B.A. (with distinction) in Psychology (1961) and her Ph.D. in Biological Psychology (1970) from the University of Oklahoma Medical Center.

## Mary M. Gerkovich

Section Manager, Biobehavioral Sciences Section
Midwest Research Institute

Dr. Gerkovich has over 25 years of experience in experimental psychology, psychophysiology, and the collection of psychological, physiological, and biochemical measures. As head of biobehavioral sciences research at MRI, she has the technical and administrative responsibility for a team of scientists specializing in psychophysiology, cognitive and experimental psychology, neurobehavioral toxicology, and health and medical psychology. Trained in experimental psychology, Dr. Gerkovich specializes in the analysis and interpretation of research data and has experience with SAS, BMDP, Systat, and SPSS statistical packages. Her specific research focus is on human health behavior issues and the application of multivariate and psychometric statistical techniques.

Dr. Gerkovich has responsibility for the data management and handling tasks and the statistical analyses that are performed for projects conducted in the Biobehavioral Sciences Section. She coordinates and supervises data management and analysis, using both PC and mainframe computers. She has developed software for the laboratory's statistical packages, and built special-purpose data management programs for project applications.

Dr. Gerkovich is involved in MRI research activities concerning a variety of human health-related topics. Her most recent research emphasis has been on studies of the effects of low doses of pyridostigmine bromide on physiology, performance, and biochemistry; effects of exposure to 60-Hz electric and magnetic fields on human health and behavior; and the application of reversal theory to health behavior. In these efforts, she contributes to the design, execution, analysis, and interpretation of the research studies.

Dr. Gerkovich received the B.A. in Psychology (1972) from the University of Kansas, the M.A. in Psychology (1981) from the University of Missouri-Kansas City, and the Ph.D. in Experimental Psychology with emphasis on quantitative methods from the University of Kansas (1998). She has taken special courses in statistics, statistical software packages, computer programming, and computer operating systems. She is a member of the Society for Psychophysiological Research, American Psychological Society, American Psychological Association, Psychometrics Society, Reversal Theory Society, Sigma Xi, and the local SAS Users Group.

Dr. Gerkovich joined MRI in 1975. She has received MRI Staff Development Awards in 1981, 1993, and 1997, and was presented the Achievement Award from MRI's Council of Principal Scientists in 1988.

## Charles Graham

Principal Advisor for Life Sciences
Midwest Research Institute

Dr. Graham's research focus is the interdisciplinary study of human performance and complex cognitive function under stress. He has specialized in two areas: experimental psychology (human performance assessment, attention, and decision-making) and neurobehavioral research (environmental, drug, medication effects on humans).

For the last 10 years, Dr. Graham has been Principal Investigator on federal, state, and industry sponsored studies to evaluate the effects of exposure to power frequency electromagnetic fields on human behavior, physiology, and biochemistry. These studies have involved the design, construction, and expansion of a unique human exposure test facility and the development of multitask neurobehavioral test batteries. Dr. Graham has served as EMF expert on technical review panels for DOE, NIOSH, EPA, and NIEHS.

In addition, Dr. Graham has directed research programs for the U.S. Army, U.S. Air Force, and five National Institutes of Health. He was Co-Principal Investigator for the initial U.S. study of pyridostigmine as a chemical defense protection drug. He supervised neurobehavioral test development and administration in studies of the intake of exposure to methanol vapor. He was Principal Investigator for basic research in physiological learning and self-regulation, for an evaluation of adjunct treatments for cancer pain, and for an examination of possible beneficial effects of fragmented sleep on cognitive efficiency under stress. Dr. Graham developed specialized embedded performance assessment techniques for the evaluation of command and control functions during sustained operations. He also directed an evaluation of the use of physiological self-regulation techniques during opiate withdrawal.

Prior to joining MRI in 1974, Dr. Graham was a research associate at the Institute of the Pennsylvania Hospital and a faculty member for the Physician Education Project. He was involved in research on the quantification of pain, the physiological effects of hypnosis, and human performance during sleep deprivation. Dr. Graham also held academic appointments in the Departments of Psychology and Psychiatry at the University of Pennsylvania.

Dr. Graham is a member of the American Psychological Association, Society for Psychophysiological Research, Bioelectromagnetics Society, and Sigma Xi (Scientific Research Society of North America). He is listed in *Who's Who in America*, *Who's Who in Science and Engineering*, and in *Who's Who in Medicine and Health Care*. Dr. Graham has a B.S. in Psychology from the University of Maryland (1966) and an M.S. (1968) and Ph.D. (1970) in Experimental Psychology from Pennsylvania State University.

# Antonio Sastre

Senior Advisor for Life Sciences
Midwest Research Institute

Dr. Sastre specializes in systemic, cellular, and molecular physiology and pharmacology; mathematical and biophysical modeling; and digital signal processing and bioelectromagnetics. As Senior Advisor in MRI's Life Sciences Department, he applies these specialties to projects in the Institute's Health Assessment and Research Center. He has researched human cardiovascular responses to various exposures such as pharmaceuticals and controlled magnetic field exposure. He also conducted biophysical and mathematical studies on electromagnetic field exposure to single cells inside models of humans.

In previous positions as Principal Scientist of Bailey Research Associates, Inc., and Senior Scientist for Environmental Research Information, Inc., Dr. Sastre conducted biophysical and exposure assessment research on combined DC and AC magnetic field exposure and quantitative determination of biophysical models of biological effects of electromagnetic fields. A number of these endeavors have required the application of Fourier methods and the development of new wavelet digital signal processing techniques.

Dr. Sastre was a member of the full-time faculty at the Johns Hopkins University of Medicine from 1977 to 1988. From 1977 to 1984 he held the position of Assistant Professor in the Department of Physiology, and from 1980 to 1984 he was also Assistant Professor in the Department of Neuroscience. He later served as Associate Professor in the departments of Physiology (1984-1988) and Neuroscience (1984-1987). While at the medical school, he conducted research in the following areas: (1) physiology and pharmacology of cardiac and vascular adrenergic and cholinergic receptors; (2) allosteric site in muscarinic cholinergic receptors with functional implication for atropinic drugs as antidotes to organophosphate poisoning; (3) neurotoxin action in nerve-muscle and cardiac tissue preparations in vitro; (4) glutamate-induced neurotoxicity in neuroblastoma-glioma cells. Dr. Sastre also supervised research on muscarinic cholinergic and alpha-adrenergic receptor-linked second-messenger (phophatidylinositol) systems.

As an Instructor at Cornell University Medical College, Department of Pharmacology, and as a Lecturer in Neurobiology at Cornell University, Dr. Sastre examined the electrophysiologic basis of action of the neurotoxins saxitoxin, tetrodotoxin, batrachotoxin, veratrum alkaloids, and alpha-bungarotoxin using in vitro innervated and denervated skeletal muscle. He also studied steroid modulation of cholinergic neurotransmitter uptake and release in mammalian synaptosomes.

Dr. Sastre's professional advisory and peer-review activities have included work with the National Research Council, the National Institutes of Health, the American Heart Association, and the National Science Foundation. He is coauthor of more than 35 peer-reviewed publications and has participated in several workshops and symposia. Dr. Sastre received a B.S. in Mathematics (1970) and a M.S. (1973) and Ph.D. (1974) in Applied Mathematics, with concentration in Neurobiology, from Cornell University.

**Allen J. Parmet**

PII Redacted

Curriculum vitae as of May 31, 1997

Office:Midwest Occupational Medicine
3037 Main, Suite 201
Kansas City, MO 64108
(816) 561-3480
FAX 561-4043

[redacted]

[redacted]

[redacted]

Education

Undergraduate : United States Air Force Academy - B.S. 1972
Medical School: University of Kansas - M.D. 1976
Internship : David Grant Medical Center,
Travis AFB, California - 1977
Residency : Phase I - University of Texas
School of Public Health at
Houston - M.P.H. 1981

Phase II - USAF School of Aerospace
Medicine Brooks AFB, Texas - 1982

Fellowship : Space Medicine - NASA/Johnson
Space Center, Houston, Texas - 1982

Post-Graduate Work: University of Kansas School of Medicine, Department of Toxicology 1995-

License

Kansas #17322 December 9, 1977
Texas #F1185 June 12, 1978
Missouri #R2G63 August 22, 1986
Colorado #31655 April 9, 1992

Educational Short Courses

Aerospace Medicine Primary, USAF School of Aerospace Medicine, Brooks AFB, TX, 1977

Combat Casualty Care Course, Brooke Army Medical Center, Ft. Sam Houston, TX, 1982.
Forensic Accident Investigation, Armed Forces Institute of Pathology, Walter Reed Army Instiute of Research, Washington, DC, 1983

Crash Investigators Course, Arizona State University, 1983

Aircraft Accident Investigation Course, University of Southern California Safety Systems Institue, Los Angeles, 1988.

Certificates & Examinations

National Board of Medical Examiners Certificate #176115
American Board of Preventive Medicine Certification:
Aerospace Medicine-Diplomate January 27, 1983
Occupational Medicine-Diplomate January 31, 1989
Medical Review Officer Certification Council-June 13, 1993
American Board of Forensic Examiners-Sept, 1996

Medical Job History

1994 - Medical Director, Trans World Airlines

1993-95 Medical Director, St. Lukes's Occupational Medicine Group, Kansas City, Missouri

1995- Adjunct Faculty for Aviation Safety, Institute of Safety and Systems Management, University of Southern California, Los Angeles, California

1992 - Great Plains College of Occupational and Environmental Medicine:

President, 1996-97
1st Vice-President, 1995-6
2nd Vice-President, 1994-5
Secretary-Treasurer, 1993-4

1992-94 Consultant, Mid-America Coalition on Health Care/Workers'·Compensation Task Group, Kansas City, Missouri

1992- Adjunct Professor, Department of Aerospace

Medicine, USAF School of Aerospace Medicine, Brooks AFB, TX

1990- 94 Adjunct Assistant Professor of Preventive Medicine and Biometrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD

1988- Associate Clinical Professor, Dept. of Community Medicine Wright State University School of Medicine, Dayton, OH

1987 - Associate Editor, **Aviation, Space and Environmental Medicine**

1987 - 92 Professor, Department of Aerospace Medicine, United States Air Force School of Aerospace Medicine, Brooks AFB, TX:

Course Director, Aerospace Medicine Primary, 1987, 88, 89 & 91.

Course Director, Operational Aeromedical Problems 1988, 89, 92.

Course Director, Health Professions Scholarship Program, 1990, 91 & 92.

Course Director, Aeromedical Readiness and Management Course, 1990, 91 & 92.

Course Director, Global Medicine Course, 1991 & 92.

Deputy Director, Residency in Aerospace Medicine, 1989 - 92.

1985 - 87 Associate Professor of Health Sciences, Chapman College Extension, Los Angeles, CA. Courses taught: Epidemiology, Genetics, Infectious Disease.

1984 - 96 Series Editor, "Cases From the Aerospace

Medicine Residents' Teaching File" in
Aviation Space and Environmental Medicine

1984 - 87 Space Transportation System Medical Director/
Chief of Aerospace Medicine, Vandenberg AFB, CA

1982 - 84 Chief of Flight Evaluations, School of
Aerospace Medicine, Brooks AFB, Tx

1979 - 80 Flight Surgeon, Randolph AFB Clinic, Tx

1977 - 79 Flight Surgeon, Officer Training School Clinic,
Lackland AFB, Tx

Other Activities

1982-1986 Member, Education and Training Committee;
1988-1992 Aerospace Medical Association

1984-87 Member, NASA/USAF Space Transportation System
Personnel Assurance Program Review Committee

1986-89 Member, History and Archives Committee;
Aerospace Medical Association

1987-89 Chairman, Reinartz Education and Training
1990-92 Committee; Society of USAF Flight Surgeons

1982-1986 Member, USAF Manned Spaceflight Engineer
Selection Panel

1987-1991 Member, USAF Astronaut Nomination Panel

1987- Member, USAF School of Aerospace Medicine
Residency Advisory Committee

1991- Member, Awards Committee (1992- Vice-Chair);
Aerospace Medical Association

1993- Senior Aviation Medical Examiner, Federal
Aviation Administration

1993-96 Chairman, Occupational Medicine Section, St.

Lukes Hospital Department of Medicine.

1993-1995 Member, Infection Control Committee, St. Lukes Hospital Department of Medicine.

1995- Chairman, Quality Assurance Committe, St. Lukes Hospital Department of Medicine.

Honors

Fellow, American College of Preventive Medicine
Fellow, Aerospace Medical Association
Fellow, International Association of Aviation and Space Medicine
Fellow, American College of Forensic Examiners

Awards

Society of USAF Flight Surgeons Howard Unger Annual Award for Best Publication - 1984
USAF Meritorious Service Medal - 1984
USAF Meritorious Service Medal, 1st OLC - 1987
USAF Meritorious Service Medal, 2nd OLC - 1992
Strategic Air Command Flight Surgeon of the Year - 1985
Peter T. Bohan Lecturer, University of Kansas - 1986
Outstanding Clinical Instructor for the Residency in Aerospace Medicine - 1989

Associations

American Medical Association
Aerospace Medical Association
American College of Occupational & Environmental Medicine
American College of Preventive Medicine
American College of Forensic Examiners

**Curriculum Vitae - Dr. Mary E. Brothers**

**MARY ELIZABETH (CENTNER) BROTHERS, M.D., FACOEM, FAADEP**

PII Redacted

[redacted]

**Office Address:** dba, **Midwest Occupational Medicine®,** Owner
3037 Main Street, Suite 201
Kansas City, Missouri 64108-3323

**Office Phone/FAX:** (816) 561-3480 (answering machine after hours)
(816) 561-4043 - Fax

[redacted]

**Education:** Bishop Miege High School, Mission, Kansas; College Prep Program, 1963-1967
Saint Mary College, Leavenworth, Kansas; BA in Biology, with Honors, 1971

**Medical Education:**

**1971-1974** University of Kansas School of Medicine, Kansas City, Kansas M.D. in September, 1974; 3 year curriculum ('74 B)

**Post-Graduate Medical Education:**

Sept - Dec, 1974 KU: electives in emergency medicine, radiology and anesthesiology

Jan - June, 1975 Externship in General Surgery and Orthopedics, Eisenhower VA Medical Center, Leavenworth, Kansas

June '95 - July 28, 1979 Four year Residency in General Surgery, Eisenhower VA Medical Center; Chief Resident 1978-1979. (Former Program Chief - Mary P. McAnaw, MD, FACS

1982-1984 "Mini" Residency in Occupational Medicine, University of Cincinnati, Cincinnati, Ohio; (144 hours); Sidney Lerner, MD, FACOM, Director (deceased)

September 1994 Began graduate program for MPH, University of Kansas

Medical Center. 1st year, 1994-1995 (epidemiology, biostatistics, public health policy/admin., Environmental health). Anticipate completion of course work in Spring of 1998 and degree by Fall, 1999.

**Medical Licensure:**

| | |
|---|---|
| **04/18/77** | National Board of Medical Examiners |
| **12/07/77** | **Kansas** # 017191 (currently "exempt" status) |
| **04/13/79** | **Missouri** # MD R9252 |

**Medical Boards/Fellowship:**

| | |
|---|---|
| 05/05/87 | **Fellow,** ACOEM (formerly American Occupational Medical Association.) - **FACOEM** |
| Nov 1989 | **Fellow,** American Academy of Disability Evaluating Physicians - **FAADEP** |
| Feb 1997 | **Board Certified, Preventive Medicine/Occupational Medicine** 01/20/97 - examinee # 23833 |

**Summary of Medical Practice:**

| | |
|---|---|
| 07/31/79 - Present | Entered into practice of industrial injury with Paul J. Centner, MD, FACS, (father) at 2727 Main Street, Kansas City, Missouri. [Part-time until 1983, then full-time] |

**In addition:**

| | |
|---|---|
| 1980-07/15/81 | Medical Director for Midwest Grain, Inc., (formerly Midwest Solvents), Atchison, Kansas. Helped to establish company wellness and Occ Med programs. On courtesy staff, Atchison Community Hospital from 12/19/79-01/21/82. |
| 05/80-06/81 | Part-time staff and instructor in general surgery, Eisenhower VAMC, Leavenworth, Kansas. |
| 07/82-03/83 | Assisted as locum tenens in Occupational Medicine for Dr. James Hall, Landmark Medical Clinic, Kansas City, Missouri. On staff at Liberty Hospital, Liberty, Missouri during this period. |

| | |
|---|---|
| 1988-1992 | Purchased practice from Dr. Centner; practice incorporates Occupational Medicine and Disability Evaluation; practice name changed to **Midwest Occupational Medicine®** 1991-1992, at time of relocation to Union Hill Commons. |

**Hospital Staff Appointments:**

| | |
|---|---|
| 1979-1989 | St. Mary Hospital, Kansas City, Missouri (ceased to exist 1989 at purchase by Trinity Lutheran); active staff in general surgery. |
| 05/80-06/81 | Eisenhower VA, Leavenworth, Kansas, part-time staff surgeon. |
| 12/79-01/82 | Atchison Community Hospital, courtesy staff in general surgery. |
| 07/82-03/83 | Liberty Hospital, Liberty, Missouri, courtesy staff. |
| 1989-present | Trinity Lutheran Hospital, Kansas City, Missouri; active staff, department of Family Practice, sub-section of Occupational Medicine. |
| 1989-06/25/97 | Baptist Medical Center, Kansas City, Missouri. Adjunct staff in General Surgery. Resigned, 06/25/97. |
| 1992-1996 | Menorah Medical Center, Kansas City, Missouri; active staff, department of Family Practice/Section of Occupational Medicine. (Resigned when Hospital moved to Kansas, 1996.) |
| 1997 | North Kansas City Hospital - application pending. |

**Professional Memberships/Offices Held:**

**American College of Occupational/Environmental Medicine:**
**(Great Plains COEM - local chapter)**

| | |
|---|---|
| 1979-present | Membership |
| 1981-1982 | Secretary-treasurer |
| 1982-1983 | Second Vice-president |
| 1983-1984 | First Vice-president |
| 1984-1985 | President-elect |
| 1985-1986 | President |

| | |
|---|---|
| 1986-1987 | Past-president |
| 1989-1992 | Delegate to ACOEM |
| 1992-1995 | Second term as delegate to ACOEM |
| 1996-1999 | Alternate delegate to ACOEM |
| 1987-1991 | Member, Committee on Ethical Practice |
| 1990-1992 | Editor, Newsletter of the Section on Work Fitness/Disability Evaluation |
| 1992 | Alternate for election to three year term on the ACOEM Board of Directors |

**American Academy of Occupational Medicine - elected a member 11/87**

**American Medical Women's Association**

| | |
|---|---|
| Present | Life member |
| 1984-1986 | Secretary-treasurer, Kansas City |
| 1986-1988 | Vice-president and President-elect |
| 1988-1990 | President |
| 1985 | Faculty, Regional conference on Women in Medicine, Kansas City, Missouri |
| 1989 | First Legislative Conference on Politics of Women's Medicine, Washington, D.C. |

**American Medical Association**

| | |
|---|---|
| 1979-present | Member except for Jan-August 1992, due to practice relocation expenses. Rejoined August, 1992. |

**Metropolitan Medical Society of Kansas City (formerly Jackson County Medical Society)**

| | |
|---|---|
| 1980-present | Member |
| 1984 | Election Committee Chairperson |
| 1985-1988 | Public Relations Committee; Chairperson 1986-1988 (concerned with public complaints about physicians) |

| | |
|---|---|
| 1988-1990 | Medico-legal Liaison Committee Chairperson (dealt with liaison between physicians and bar association) |
| 11/17/88 | Attended local leadership conference, Kansas City, Missouri |

**Missouri State Medical Society**

| | |
|---|---|
| 1980-1991 | Member |

**Kansas State Medical Society**

| | |
|---|---|
| 1980-1982 | Member during practice in Kansas |

**Kansas City Surgical Society**

| | |
|---|---|
| 09/15/83-1991 | Member; resigned end of 1991 to devote full-time practice to Occupational Medicine CME activity |

**Teaching Appointments:**

| | |
|---|---|
| Spring, 1975 | Faculty, Saint Mary College, Leavenworth, Kansas; Histology and Micro technique. |
| 1980-06/10/81 | Part-time instructor in General Surgery, Eisenhower VA Medical Center. |
| 1987-present | Preceptor in Occupational Medicine; Trinity Lutheran Hospital Family Medicine Residency (formerly St. Mary's Hospital Family Medicine.) Scott Thompson, MD, Director. |

**Directorships:**

| | |
|---|---|
| Late 1980's | Co-Director, (with Dr. Centner), SHARE Program for Occupational Health Nursing, St. Mary's Hospital, Kansas City, Missouri. |
| 10/1992-12/31/93 | Co-Director, MedWorks Managed Occupational Health Network, Menorah Medical Center, Kansas City, Missouri. |
| 1994-1995 | MedWorks Director/Advisor; Mariner Rehabilitation (formerly Pinnacle Rehabilitation). |

**Curriculum Vitae - Dr. Mary E. Brothers**

**Consultant:**

| | |
|---|---|
| 10/01/92-10/1995 | Contract Occupational Physician Consultant, Federal Occupational Health-US Public Health Service, Region VII. |
| Fall, 1997 | Pending application to resume consulting position for Region VII, Public Health Service. |

**Hospital Committee Work:**

| | |
|---|---|
| St. Mary's Hospital | By-laws<br>Medical Records & Audit Chairperson, 1983-1986<br>Tissue Sub-committee, 1984-1988<br>ER/Outpatient Committee<br>Developed the Ambulatory Surgery Unit with Sr. Susan Scholl, SSM |
| Trinity Lutheran Hospital | By-laws, 1989-present<br>ER/Outpatient Committee, 1989-1996<br>Physician's Health Committee, 1997-present |

**Lectures:**

| | |
|---|---|
| 09/27-29/75 | Chairperson, panel on ER Medical Care, AMWA Regional Conference, Kansas City, Missouri |
| 07/09/80 | High Pressure Injection Injury; Leavenworth CME circuit Eisenhower VAMC |
| 07/27/89 & 10/26/89 | Two-part lecture on "Permanent Partial Disability Determination Within the Workers' Compensation System", for staff of OHS, Dr. Ed Kinports, Director |
| 11/02/89 | Rating Workers' Compensation Injuries - the Physician's Role; Fourth Annual Missouri Work Comp Seminar (Mo. Bar/UMKC Law School), Allis Plaza, Kansas City |
| 04/30/90 | Confidentiality of Company Medical Records-The Private Practice Experience; ACOEM Post-grad seminar in Ethics; American Occupational Health Conference, Houston, Texas |
| 04/28/91 | Committing Truth - The Occupational Physician on the Firing Line; ACOEM Post-grad seminar in Ethics; |

| | |
|---|---|
| | American Occupational Health Conference, San Francisco, California |
| 07/28/92 | Lecture on Disability Evaluation and Workers' Compensation; Physical therapy-orthopedic study group, Trinity Lutheran Hospital |
| 03/10/94 | Organophosphate Pesticide Poisoning, Kansas City, E.P.A. |
| 02/01/95 | Cumulative Trauma Disorders, Praxair Surface Technologies, Inc., Kansas City, Missouri |

**Publications:**

| | |
|---|---|
| 1971 | (Unpublished) Honors research paper on Chemoattractants in Fasciola hepatica and snail hosts; Saint Mary College, Leavenworth, Kansas |
| 1971 | An Analysis of Particulate Matter in the Lungs and Air Sacs of Columba livia; section of NSF-SOS Report on "Air and Water Pollution in Atchison, Kansas". Benedictine College Research Grant |
| 1990 | "You're Just the Company Doctor"; issue of the Kansas City Health Journal, in conjunction with Baptist Medical Center |

**Awards:**

| | |
|---|---|
| 1977; 1978 | Outstanding Young Women of America |

**Political Experience:**

See addendum "A"

**Continuing Medical Education:**

| | |
|---|---|
| 07/16/79-present | Physician's Recognition Award of the AMA |

See Addendum "B"

**Other:**

| | |
|---|---|
| 07/13/80-present | Aviation Medical Examiner for the FAA; completed the |

Senior Examiner's Seminar, Oklahoma City, in October, 1985.

August, 1990 - update seminar, Kansas City, Missouri

February, 1995 - update seminar, Savannah, Georgia

Fall, 1993 - Present

Appointed to serve as Committee member, Mid-America Coalition on Health Care Committee on Workers' Compensation, Kansas City, Missouri; background work on Robert Wood Johnson Grant applications project. Various presentations to KCMO business community, 1995-1996.

**Personal Information:**

[redacted]

PII Redacted

[redacted]

[redacted]

**Personal Memberships**

American Horticulture Society
The Audubon Society
The Nature Conservancy
Nash Car Club of America/Historic Trails Region
Smithsonian Institution

16.1.5 Signatures

Mary R. Cook, Ph.D. (Company Signatory)
Principal Investigator
Principal Advisor
Midwest Research Institute

2-27-01
Date

Richard Brown
Director, Life Sciences Division
Midwest Research Institute

2-27-01
Date

James E. Dworak, Ph.D.
Quality Assurance Officer
Midwest Research Institute

2/27/01
Date

16.1.6 N/A

16.1.7 Randomization Schemes

Table 16.1.7.1

Subject Number Assignment (Study 1)

| Group | Number of Subjects | Subject Identification | |
|---|---|---|---|
| | | Subjects used in analysis | Subject numbers that were unassigned or dropped |
| M A 60 mg Pyr/Pl | 4 | 13 01 04 46 | 15 37 |
| F A 60 mg Pyr/Pl | 4 | 63 66 60 99 | 86 |
| M B 60 mg Pyr/Pl | 5 | 22 05 36 48 | 02 27 42 |
| F B 60 mg Pyr/Pl | 5 | 71 75 85 92 97 | 81 77 |
| Extra 60 mg Pyr/Pl | 3 | 44 | 101 106 122 |
| | | | |
| M A 60 mg Pl/Pyr | 5 | 03 31 33 35 38 | 19 |
| F A 60 mg Pl/Pyr | 5 | 51 69 88 | 62 82 58 87 |
| M B 60 mg Pl/Pyr | 4 | 20 10 39 | 29 14 |
| F B 60 mg Pl/Pyr | 4 | 54 83 68 | 79 |
| Extra 60 mg Pl/Pyr | 3 | 45 95 | 102 103 120 |
| | | | |
| M A 30 mg Pyr/Pl | 5 | 09 08 30 32 17 | |
| F A 30 mg Pyr/Pl | 5 | 53 65 80 76 70 | |
| M B 30 mg Pyr/Pl | 4 | 24 26 43 47 | 21 34 |
| F B 30 mg Pyr/Pl | 4 | 64 74 89 | 78 57 |
| Extra 30 mg Pyr/Pl | 3 | | 107 109 119 94 |
| | | | |
| M A 30 mg Pl/Pyr | 4 | 07 25 28 06 | |
| F A 30 mg Pl/Pyr | 4 | 52 55 56 | 84 98 |
| M B 30 mg Pl/Pyr | 5 | 11 23 12 40 41 | 16 18 |
| F B 30 mg Pl/Pyr | 5 | 61 67 90 91 | 72 73 59 |
| Extra 30 mg Pl/Pyr | 3 | | 104 111 115 93 96 |

Table 16.1.7.2

Subject Number Assignment (Study 2)

| Group | Number of Subjects | Subject Identification | |
|---|---|---|---|
| | | Subjects used in analysis | Subject numbers that were unassigned or dropped |
| M R/H Pyr/Pl | 3 | 08 09 10 | |
| M H/R Pyr/Pl | 3 | 01 12 | 02 |
| | | | |
| F R/H Pyr/Pl | 3 | 56 57 | 55 |
| F H/R Pyr/Pl | 3 | 53 54 | 52 |
| | | | |
| Extra Pyr/Pl | 4 | 80 82 | 84 87 |
| | | | |
| M R/H Pl/Pyr | 3 | 06 07 11 | |
| M H/R Pl/Pyr | 3 | 03 04 05 | |
| | | | |
| F R/H Pl/Pyr | 3 | 58 60 61 | |
| F H/R Pl/Pyr | 3 | 51 59 62 | |
| | | | |
| Extra Pl/Pyr | 4 | | 81 83 85 86 |

16.1.8 N/A
16.1.9 N/A
16.1.10 N/A
16.1.11 N/A

Appendix 16.2

16.2.1 N/A
16.2.2 N/A
16.2.3 N/A

16.2.4

Demographic Data Summary Tables

**Study 1**

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 1 | 31 | M | white |
| 3 | 22 | M | black |
| 4 | 30 | M | white |
| 5 | 29 | M | white |
| 6 | 26 | M | white |
| 7 | 28 | M | white |
| 8 | 27 | M | white |
| 9 | 34 | M | white |
| 10 | 29 | M | white |
| 11 | 32 | M | white |
| 12 | 21 | M | white |
| 13 | 18 | M | black |
| 17 | 35 | M | white |
| 20 | 28 | M | white |
| 22 | 19 | M | white |
| 23 | 18 | M | white |
| 24 | 22 | M | white |
| 25 | 19 | M | white |
| 26 | 21 | M | white |
| 28 | 30 | M | white |
| 30 | 24 | M | black |
| 31 | 18 | M | hispanic |
| 32 | 19 | M | asian |
| 33 | 19 | M | white |
| 35 | 24 | M | black |
| 36 | 24 | M | white |
| 38 | 23 | M | hispanic |
| 39 | 27 | M | white |
| 40 | 21 | M | white |
| 41 | 19 | M | asian |
| 43 | 25 | M | white |
| 44 | 21 | M | white |
| 45 | 19 | M | white |
| 46 | 23 | M | white |
| 47 | 25 | M | white |
| 48 | 19 | M | asian |
| 51 | 28 | F | white |
| 52 | 32 | F | white |
| 53 | 28 | F | white |
| 54 | 24 | F | white |
| 55 | 19 | F | white |
| 56 | 19 | F | white |
| 60 | 21 | F | white |
| 61 | 35 | F | white |
| 63 | 23 | F | white |
| 64 | 19 | F | black |

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 65 | 21 | F | black |
| 66 | 24 | F | white |
| 67 | 18 | F | white |
| 68 | 26 | F | white |
| 69 | 27 | F | black |
| 70 | 23 | F | asian |
| 71 | 18 | F | white |
| 74 | 22 | F | white |
| 75 | 24 | F | white |
| 76 | 28 | F | black |
| 80 | 28 | F | white |
| 83 | 20 | F | white |
| 85 | 18 | F | white |
| 88 | 24 | F | white |
| 89 | 20 | F | white |
| 90 | 18 | F | white |
| 91 | 24 | F | white |
| 92 | 21 | F | white |
| 95 | 22 | F | white |
| 97 | 24 | F | white |
| 99 | 23 | F | white |

16.2.4

Demographic Data Summary Tables

**Study 2**

| SBJID | Age | Gender | Ethnic |
|---|---|---|---|
| 1 | 32 | M | white |
| 3 | 24 | M | asian |
| 4 | 19 | M | white |
| 5 | 25 | M | white |
| 6 | 19 | M | asian |
| 7 | 19 | M | asian |
| 8 | 31 | M | white |
| 9 | 29 | M | white |
| 10 | 21 | M | asian |
| 11 | 19 | M | white |
| 12 | 22 | M | white |
| 82 | 23 | M | white |
| 84 | 21 | M | white |
| 51 | 19 | F | white |
| 53 | 26 | F | white |
| 54 | 19 | F | white |
| 56 | 32 | F | white |
| 57 | 32 | F | white |
| 58 | 25 | F | white |
| 59 | 21 | F | white |
| 60 | 19 | F | white |
| 61 | 18 | F | black |
| 62 | 19 | F | white |
| 80 | 19 | F | white |

16.2.5 Drug Concentration Data

Table 16.2.5.1
Plasma Levels of Pyridostigmine Bromide, Study 1

**PLASMA PB LEVELS**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL1 | PL4 | PL5 | PL8 | PB 1 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 8.6 | 10.5 | 11.8 | 0 |
| 30 | 7 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 9.6 | 23.5 | 9.9 | 0 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7.2 | 16.9 | 12.4 | 0 |
| 30 | 9 | M | PB/PL | U / AK | 0 | 0 | 0 | 0 | 0 | 11.9 | 27.2 | 25.9 | 0 |
| 30 | 11 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 17.8 | 41 | 23.2 | 0 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 8.9 | 18.1 | 12 | 0 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 15.4 | 18.2 | 19.7 | 0 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 7.1 | 14.7 | 12.8 | 0 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 7.5 | 22.6 | 17.1 | 0 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 0 | 0 | 0 | 10.9 | 6.8 | 0 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 23 | 22.2 | 20 | 0 |
| 30 | 28 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 8.1 | 17.1 | 19.1 | 0 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 9.4 | 15.9 | 23.6 | 0 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 0 | 12.2 | 9.2 | 0 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 0 | 0 | 23.2 | 13.2 | 24.6 | 0 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 18.9 | 17.7 | 16 | 0 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 7.9 | 7.4 | 8.1 | 0 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 12.1 | 20.8 | 17.9 | 0 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 0 | 0 | 0 | 15.3 | 17.2 | 0 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7.6 | 27.4 | 17.8 | 0 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 21.3 | 25.5 | 38.8 | 0 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 13.2 | 23.9 | 18 | 0 |
| 30 | 61 | F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 16.9 | 22 | 30.6 | 0 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 8.5 | 14.9 | 15.5 | 0 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 10.7 | 25.4 | 14.3 | 0 |
| 30 | 67 | F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 7 | 20.6 | 28.8 | 0 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 11.7 | 16 | 26.8 | 0 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 5 | 19.7 | 16.8 | 0 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 10.2 | 13.5 | 17.1 | 0 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 7.4 | 12.2 | 13.4 | 0 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 15.3 | 17.7 | 21.4 | 0 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 13.7 | 11.2 | 20 | 0 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 0 | 9.4 | 13.1 | 0 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 12 | 26.6 | 26.1 | 0 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 16.4 | 28.2 | 29.2 | 0 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 21.8 | 35.9 | 28 | 0 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7 | 17.8 | 18.8 | 0 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 22.1 | 21.9 | 29.4 | 0 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 12.1 | 47.5 | 43.2 | 0 |
| 60 | 20 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 10.1 | 29.1 | 30.1 | 0 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 17.8 | 31.4 | 22.7 | 0 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 16.3 | 26 | 29.7 | 0 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 16.3 | 28.9 | 25.4 | 0 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 0 | 0 | 12.4 | 24 | 21.8 | 0 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 31 | 32.3 | 32.9 | 0 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 17 | 29.1 | 20.1 | 0 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 32.7 | 36.5 | 39.7 | 0 |

Table 16.2.5.1
Plasma Levels of Pyridostigmine Bromide, Study 1

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 27.9 | 30.6 | 17.4 | 0 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 19 | 35.2 | 20.8 | 0 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 31.2 | 42.8 | 56.7 | 0 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 16.4 | 24.1 | 21.6 | 0 |
| 60 | 51 F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 28.5 | 26.8 | 56.2 | 0 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 17.1 | 17.1 | 18.7 | 0 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 22.8 | 45.3 | 37.8 | 0 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 14.7 | 29.6 | 36 | 0 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 25.5 | 31.4 | 42.2 | 0 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 13.5 | 42.7 | 24.9 | 0 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 21.5 | 32.1 | 13.8 | 0 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 13.3 | 20.3 | 29.6 | 0 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7.5 | 20 | 23.4 | 0 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 10.5 | 34.1 | 36.2 | 0 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 27.2 | 55.2 | 59 | 0 |
| 60 | 88 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 22.3 | 36.3 | 44.1 | 0 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 17.3 | 46.4 | 51.7 | 0 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 13.9 | 23.4 | 18.5 | 0 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 9.5 | 17 | 22.1 | 0 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 22.1 | 27.5 | 16.9 | 0 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.2
Plasma Levels of THMP, Study 1

**PLASMA THMP**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL1 | PL4 | PL5 | PL8 | PB 1 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 11.3 | 13.3 | 16.5 | 0 |
| 30 | 7 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 9 | 19.8 | 15.5 | 0 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 6.8 | 8.9 | 7.3 | 0 |
| 30 | 9 | M | PB/PL | U / AK | 0 | 18.8 | 7.4 | 0 | 8.8 | 21.7 | 31.1 | 28.4 | 0 |
| 30 | 11 | M | PL/PB | U / K | 0 | 6.4 | 0 | 0 | 0 | 10.4 | 22.8 | 14 | 0 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 5.7 | 8.5 | 9 | 0 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 9.5 | 11.7 | 9.8 | 0 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 20.3 | 0 | 5.9 | 14.7 | 85 | 0 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 10.6 | 19.9 | 14.9 | 0 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9.2 | 0 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 19.2 | 22 | 17.4 | 0 |
| 30 | 28 | M | PL/PB | U / K | 0 | 7.8 | 0 | 0 | 13.4 | 9.5 | 14.1 | 35.4 | 12.5 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7 | 11.8 | 15.7 | 0 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 6.8 | 0 | 6.7 | 0 | 13.7 | 12.1 | 5.8 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 0 | 0 | 17.4 | 13.3 | 21 | 0 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 9.5 | 8.9 | 7.7 | 0 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 4.9 | 6.1 | 7.3 | 0 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 12.7 | 13.6 | 13.9 | 0 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 0 | 0 | 0 | 9.6 | 9.8 | 0 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 5.3 | 11.7 | 10.9 | 0 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 23.3 | 27.3 | 35.8 | 0 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 13.1 | 19.6 | 18.7 | 0 |
| 30 | 61 | F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 10.5 | 12.1 | 18.1 | 0 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 6.7 | 10.2 | 8.9 | 0 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 11 | 16.7 | 8.2 | 0 |
| 30 | 67 | F | PL/PB | U / K | 0 | 0 | 11.4 | 0 | 0 | 8.7 | 13.8 | 15.1 | 0 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 5.1 | 9.2 | 12.6 | 0 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 9.5 | 25.1 | 17.3 | 0 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 5.3 | 0 | 0 | 6.9 | 9.7 | 10.4 | 0 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 8.3 | 12.7 | 13.7 | 0 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 15.7 | 21.7 | 22.3 | 0 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 10.6 | 10.7 | 15.6 | 0 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 0 | 6.8 | 8.8 | 0 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 10.6 | 21.9 | 21.7 | 0 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 14.7 | 21.4 | 23.6 | 0 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 16.6 | 20.1 | 19.1 | 0 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 6.8 | 23.4 | 15.8 | 0 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 13.1 | 12.9 | 16.7 | 0 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 11 | 24.2 | 24.7 | 14.1 |
| 60 | 20 | M | PL/PB | U / U | 0 | 17.6 | 10 | 13.2 | 8.7 | 25.9 | 29.5 | 42.8 | 0 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 21.6 | 22.8 | 20.2 | 0 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 11.8 | 16.1 | 24.5 | 0 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 13 | 24.6 | 23.8 | 0 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 0 | 0 | 11.7 | 19.8 | 18.8 | 0 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 17.6 | 16.2 | 17.2 | 0 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 14.1 | 18.8 | 13.1 | 0 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 21.8 | 27.4 | 28.6 | 0 |

Table 16.2.5.2
Plasma Levels of THMP, Study 1

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 21.2 | 18.1 | 13.1 | 0 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 14.8 | 24.2 | 14.6 | 0 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 0 | 9.5 | 5.2 | 28.2 | 33.8 | 34.7 | 0 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 10.9 | 14.6 | 10.9 | 0 |
| 60 | 51 F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 17.8 | 15.7 | 22.7 | 0 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 18.7 | 13 | 15.9 | 0 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 23.6 | 32.8 | 31.5 | 0 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 21.5 | 11.5 | 21.2 | 22 | 0 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 19.1 | 20.9 | 26.4 | 0 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 0 | 0 | 24.7 | 28.7 | 22.9 | 0 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 13.6 | 18.1 | 10.3 | 0 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 8.9 | 17.9 | 18.8 | 0 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 7.1 | 15.2 | 19 | 0 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 0 | 12.6 | 32.3 | 35 | 0 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 0 | 0 | 15.4 | 28.6 | 29.9 | 0 |
| 60 | 88 F | PL/PB | U / U | 0 | 28.2 | 0 | 0 | 0 | 19.5 | 20.3 | 30.7 | 0 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 15.3 | 35.1 | 37.3 | 0 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 7.3 | 0 | 18 | 33.2 | 25.7 | 0 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 12.3 | 18.1 | 20.3 | 0 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 0 | 0 | 11.6 | 13.6 | 11.2 | 0 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.3
Corrected Urinary THMP, Study 1

**CORRECTED URINARY THMP**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL4 | PL5 | PB 4 | PB 5 |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 1.6 | 2.3 | 0 | 3.6 | 5 |
| 30 | 7 | M | PL/PB | U / U | 2.2 | 0 | 1.3 | 4.3 | 6.4 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 2.5 | 2 |
| 30 | 9 | M | PB/PL | U / AK | 1.2 | 0 | 0 | 8.8 | 9.5 |
| 30 | 11 | M | PL/PB | U / K | 0 | 0 | 0 | 4.4 | 2.7 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 2.4 | 2.3 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 2.6 | 2.1 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 2.7 | 3.5 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 8.5 | 6.9 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 1.4 | 3 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 6.3 | 4.8 |
| 30 | 28 | M | PL/PB | U / K | 0 | 0 | 0 | 3.5 | 4.1 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 9.8 | 8.5 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 2.6 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 5.2 | 5.1 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 1.6 | 2 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 1.9 | 2 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 4.2 | 5 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 4.7 | 4.1 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 5.3 | 5.9 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 6.9 | 12.8 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 6.4 | 5.7 |
| 30 | 61 | F | PL/PB | U / K | 0 | 1.6 | 0 | 6.4 | 9.1 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 2.9 | 2.6 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 5.3 | 2.7 |
| 30 | 67 | F | PL/PB | U / K | 0 | 3.1 | 0 | 5.7 | 4.6 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 4.3 | 5.8 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 9.5 | 7.1 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 0 | 4 | 3.8 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 13.6 | 4.8 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 9 | 7.9 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 2.2 | 5.8 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 3 | 3.8 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 6.7 | 5.1 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 6.4 | 6.4 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 6.8 | 5.7 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 7.4 | 5.5 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 3.8 | 4.8 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 6.1 | 6.3 |
| 60 | 20 | M | PL/PB | U / U | 13.8 | 6.5 | 1.5 | 9.5 | 12.8 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 5 | 4.4 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 4.9 | 4.6 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 6.1 | 5.6 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 4.1 | 4 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 3.9 | 4.4 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 5.8 | 3.4 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 8.2 | 11 |

Table 16.2.5.3
Corrected Urinary THMP, Study 1

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 6.4 | 4 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 5.6 | 9.3 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 2.4 | 9.5 | 8.3 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 4.2 | 2.6 |
| 60 | 51 F | PL/PB | U / K | 1.3 | 0 | 0 | 11 | 5.8 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 7.6 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 4.7 | 7.3 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 7.5 | 6.2 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 9.1 | 12.2 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 11.6 | 9.9 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 9.2 | 5.6 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 6.8 | 8.2 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 11.5 | 7.2 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 10.1 | 14.5 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 11.6 | 12 |
| 60 | 88 F | PL/PB | U / U | 0 | 2.1 | 0 | 10.4 | 12.3 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 12.8 | 11.1 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 24.3 | 12 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 9.9 | 12.3 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 4.4 | 4.9 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.4
Urinary Levels of THMP, Study 1

**UNCORRECTED URINARY THMP**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL4 | PL5 | PB 4 | PB 5 |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 1.6 | 2.3 | 0 | 5.2 | 2.1 |
| 30 | 7 | M | PL/PB | U / U | 2.2 | 0 | 1.3 | 7.9 | 11.3 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 2.1 | 2.1 |
| 30 | 9 | M | PB/PL | U / AK | 1.2 | 0 | 0 | 7 | 5.9 |
| 30 | 11 | M | PL/PB | U / K | 0 | 0 | 0 | 2 | 2.5 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 4.2 | 2.5 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 2 | 3.3 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 2 | 3.1 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 4.1 | 4.5 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 1.9 | 2.1 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 15.4 | 8.1 |
| 30 | 28 | M | PL/PB | U / K | 0 | 0 | 0 | 4.7 | 3.8 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 26 | 13.9 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 0 | 0 | 2.8 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 3.3 | 2.6 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 3.8 | 5 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 2 | 1.7 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 11.7 | 5.1 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 2.4 | 1.2 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 2.7 | 11.3 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 10.4 | 22.2 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 13.4 | 6.7 |
| 30 | 61 | F | PL/PB | U / K | 0 | 1.6 | 0 | 3.6 | 16.4 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 3.6 | 2 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 12.2 | 6.5 |
| 30 | 67 | F | PL/PB | U / K | 0 | 3.1 | 0 | 10.9 | 10.2 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 2.9 | 5 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 7.2 | 8.8 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 0 | 2.6 | 3.7 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 2.2 | 1.8 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 13.2 | 14 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 4.2 | 6.3 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 2.9 | 10 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 5.1 | 4.4 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 4.7 | 6.9 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 2.4 | 7.9 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 6.2 | 2.3 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 2.8 | 1.9 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 13.5 | 18.1 |
| 60 | 20 | M | PL/PB | U / U | 13.8 | 6.5 | 1.5 | 5.7 | 1.4 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 4.6 | 7.1 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 2.3 | 8.3 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 8.9 | 6.2 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 5.3 | 1.1 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 10.4 | 10.6 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 17.4 | 8.3 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 5.1 | 7.5 |

Table 16.2.5.4
Urinary Levels of THMP, Study 1

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 24.8 | 6.9 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 8.2 | 11.9 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 2.4 | 19.6 | 19.4 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 9.3 | 5 |
| 60 | 51 F | PL/PB | U / K | 1.3 | 0 | 0 | 2.2 | 6.6 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 0 | 2.7 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 9.8 | 9 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 1.9 | 3 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 13.8 | 10.1 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 4.4 | 3.3 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 7.8 | 3 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 7.2 | 8.3 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 6.4 | 4.2 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 5.5 | 17.3 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 16.4 | 14.2 |
| 60 | 88 F | PL/PB | U / U | 0 | 2.1 | 0 | 5.1 | 9 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 5 | 9.9 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 3 | 2.2 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 4.2 | 3.1 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 3.9 | 2.8 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.5
Corrected Urinary Levels of Pyridostigmine Bromide, Study 1

**CREATINE, CORRECTED URINARY PB**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL4 | PL5 | PB 4 | PB 5 |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 0 | 0 | 0 | 6.9 | 9.6 |
| 30 | 7 | M | PL/PB | U / U | 0 | 0 | 0 | 9.9 | 7.3 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 7 | 6 |
| 30 | 9 | M | PB/PL | U / AK | 0 | 0 | 0 | 9.7 | 13.9 |
| 30 | 11 | M | PL/PB | U / K | 0 | 0 | 0 | 15.9 | 7.6 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 5.6 | 6.2 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 6.9 | 6.2 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 6.4 | 8.5 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 8.7 | 9.8 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 4.4 | 8 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 13 | 9.9 |
| 30 | 28 | M | PL/PB | U / K | 0 | 0 | 0 | 8.5 | 7.6 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 27.1 | 23.5 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 0 | 5.1 | 4.7 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 8.6 | 15 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 6.9 | 8.4 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 5.8 | 6.7 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 11.4 | 8.6 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 10.9 | 10.3 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 16.7 | 18 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 16 | 21.9 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 12.2 | 10.7 |
| 30 | 61 | F | PL/PB | U / K | 0 | 0 | 0 | 15.2 | 25.2 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 5.7 | 7.3 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 13 | 7.1 |
| 30 | 67 | F | PL/PB | U / K | 0 | 0 | 0 | 12.9 | 10.9 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 17 | 24.3 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 15.4 | 10.3 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 0 | 10.7 | 10.2 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 8 | 9.8 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 16.3 | 14.6 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 4.3 | 12.7 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 4.8 | 7.7 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 12.3 | 11.2 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 18.4 | 17.9 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 22.9 | 22 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 14.7 | 13.6 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 12.9 | 15.1 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 25.6 | 26.2 |
| 60 | 20 | M | PL/PB | U / U | 0 | 0 | 0 | 15.3 | 21 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 14.6 | 12.4 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 14.3 | 14.1 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 9.7 | 8.8 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 9.4 | 8.7 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 12.7 | 17.5 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 18.3 | 9.4 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 22.2 | 19.7 |

Table 16.2.5.5
Corrected Urinary Levels of Pyridostigmine Bromide, Study 1

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 21.6 | 11.2 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 16 | 20 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 0 | 22.4 | 20.3 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 16.7 | 10 |
| 60 | 51 F | PL/PB | U / K | 0 | 0 | 0 | 37 | 24.2 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 20.6 | 16.9 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 9.7 | 17.5 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 21.2 | 18.3 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 23.6 | 35.1 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 31.5 | 17.8 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 22.1 | 8 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 21.2 | 24.2 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 17.1 | 19.2 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 25.8 | 41 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 33.5 | 39.3 |
| 60 | 88 F | PL/PB | U / U | 0 | 0 | 0 | 24.1 | 29.9 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 17.9 | 24.1 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 15.4 | 15.9 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 20.9 | 28.2 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 17.1 | 19.1 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

TAble 16.2.5.6

Urinary Levels of Pyridostigmine Bromide, Study 1

**UNCORRECTED URINARY PB**

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL4 | PL5 | PB 4 | PB 5 |
|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 0 | 0 | 0 | 9.9 | 4 |
| 30 | 7 | M | PL/PB | U / U | 0 | 0 | 0 | 18.1 | 12.8 |
| 30 | 8 | M | PB/PL | U / K | 0 | 0 | 0 | 5.9 | 6.2 |
| 30 | 9 | M | PB/PL | U / AK | 0 | 0 | 0 | 7.7 | 8.6 |
| 30 | 11 | M | PL/PB | U / K | 0 | 0 | 0 | 7.2 | 7.1 |
| 30 | 12 | M | PL/PB | U / U | 0 | 0 | 0 | 9.9 | 6.8 |
| 30 | 17 | M | PB/PL | U / U | 0 | 0 | 0 | 5.4 | 9.6 |
| 30 | 23 | M | PL/PB | U / U | 0 | 0 | 0 | 4.8 | 7.4 |
| 30 | 24 | M | PB/PL | U / U | 0 | 0 | 0 | 4.2 | 6.4 |
| 30 | 25 | M | PL/PB | U / AK | 0 | 0 | 0 | 6 | 5.5 |
| 30 | 26 | M | PB/PL | U / U | 0 | 0 | 0 | 31.5 | 16.8 |
| 30 | 28 | M | PL/PB | U / K | 0 | 0 | 0 | 11.4 | 7.1 |
| 30 | 30 | M | PB/PL | U / K | 0 | 0 | 0 | 71.7 | 38.2 |
| 30 | 32 | M | PB/PL | U / K | 0 | 0 | 0 | 1.7 | 5.1 |
| 30 | 40 | M | PL/PB | K / AK | 0 | 0 | 0 | 5.5 | 7.7 |
| 30 | 41 | M | PL/PB | U / U | 0 | 0 | 0 | 16.3 | 20.6 |
| 30 | 43 | M | PB/PL | U / U | 0 | 0 | 0 | 6.2 | 5.8 |
| 30 | 47 | M | PB/PL | U / U | 0 | 0 | 0 | 31.7 | 8.8 |
| 30 | 52 | F | PL/PB | U / AK | 0 | 0 | 0 | 5.5 | 3 |
| 30 | 53 | F | PB/PL | U / K | 0 | 0 | 0 | 8.6 | 34.7 |
| 30 | 55 | F | PL/PB | U / U | 0 | 0 | 0 | 24 | 38 |
| 30 | 56 | F | PL/PB | U / U | 0 | 0 | 0 | 25.4 | 12.6 |
| 30 | 61 | F | PL/PB | U / K | 0 | 0 | 0 | 8.5 | 45.5 |
| 30 | 64 | F | PB/PL | U / U | 0 | 0 | 0 | 7.2 | 5.6 |
| 30 | 65 | F | PB/PL | U / K | 0 | 0 | 0 | 29.8 | 16.9 |
| 30 | 67 | F | PL/PB | U / K | 0 | 0 | 0 | 24.4 | 24.3 |
| 30 | 70 | F | PB/PL | U / U | 0 | 0 | 0 | 11.5 | 21.1 |
| 30 | 74 | F | PB/PL | U / K | 0 | 0 | 0 | 11.7 | 12.8 |
| 30 | 76 | F | PB/PL | U / U | 0 | 0 | 0 | 7 | 10 |
| 30 | 80 | F | PB/PL | U / U | 0 | 0 | 0 | 1.3 | 3.7 |
| 30 | 89 | F | PB/PL | U / U | 0 | 0 | 0 | 23.9 | 25.9 |
| 30 | 90 | F | PL/PB | U / K | 0 | 0 | 0 | 8.3 | 13.8 |
| 30 | 91 | F | PL/PB | U / U | 0 | 0 | 0 | 4.7 | 20 |
| 60 | 1 | M | PB/PL | U / U | 0 | 0 | 0 | 9.4 | 9.7 |
| 60 | 3 | M | PL/PB | U / U | 0 | 0 | 0 | 13.5 | 19.4 |
| 60 | 4 | M | PB/PL | U / U | 0 | 0 | 0 | 8.1 | 30.2 |
| 60 | 5 | M | PB/PL | U / K | 0 | 0 | 0 | 12.3 | 5.7 |
| 60 | 10 | M | PL/PB | U / U | 0 | 0 | 0 | 9.6 | 6 |
| 60 | 13 | M | PB/PL | U / U | 0 | 0 | 0 | 56.3 | 75 |
| 60 | 20 | M | PL/PB | U / U | 0 | 0 | 0 | 9.2 | 2.3 |
| 60 | 22 | M | PB/PL | U / K | 0 | 0 | 0 | 13.6 | 20.1 |
| 60 | 31 | M | PL/PB | U / U | 0 | 0 | 0 | 6.7 | 25.5 |
| 60 | 33 | M | PL/PB | U / K | 0 | 0 | 0 | 14.3 | 9.7 |
| 60 | 35 | M | PL/PB | K / K | 0 | 0 | 0 | 12 | 2.4 |
| 60 | 36 | M | PB/PL | U / U | 0 | 0 | 0 | 34.2 | 41.8 |
| 60 | 38 | M | PL/PB | U / U | 0 | 0 | 0 | 54.7 | 23.1 |
| 60 | 39 | M | PL/PB | U / K | 0 | 0 | 0 | 13.8 | 13.5 |

TAble 16.2.5.6
Urinary Levels of Pyridostigmine Bromide, Study 1

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 60 | 44 M | PB/PL | U / U | 0 | 0 | 0 | 83.6 | 19.2 |
| 60 | 45 M | PL/PB | U / U | 0 | 0 | 0 | 23.6 | 25.5 |
| 60 | 46 M | PB/PL | U / U | 0 | 0 | 0 | 46.2 | 47.3 |
| 60 | 48 M | PB/PL | U / U | 0 | 0 | 0 | 37 | 19.3 |
| 60 | 51 F | PL/PB | U / K | 0 | 0 | 0 | 7.4 | 27.5 |
| 60 | 54 F | PL/PB | U / U | 0 | 0 | 0 | 1.5 | 6 |
| 60 | 60 F | PB/PL | U / K | 0 | 0 | 0 | 20.3 | 21.7 |
| 60 | 63 F | PB/PL | U / U | 0 | 0 | 0 | 5.4 | 8.8 |
| 60 | 66 F | PB/PL | U / U | 0 | 0 | 0 | 36 | 29.1 |
| 60 | 68 F | PL/PB | U / K | 0 | 0 | 0 | 11.9 | 5.9 |
| 60 | 69 F | PL/PB | U / U | 0 | 0 | 0 | 18.7 | 4.3 |
| 60 | 71 F | PB/PL | U / K | 0 | 0 | 0 | 22.5 | 24.6 |
| 60 | 75 F | PB/PL | U / K | 0 | 0 | 0 | 9.5 | 11.2 |
| 60 | 83 F | PL/PB | U / U | 0 | 0 | 0 | 14 | 49 |
| 60 | 85 F | PB/PL | U / K | 0 | 0 | 0 | 47.4 | 46.7 |
| 60 | 88 F | PL/PB | U / U | 0 | 0 | 0 | 11.8 | 21.9 |
| 60 | 92 F | PB/PL | U / U | 0 | 0 | 0 | 7 | 21.4 |
| 60 | 95 F | PL/PB | U / U | 0 | 0 | 0 | 1.9 | 2.9 |
| 60 | 97 F | PB/PL | U / U | 0 | 0 | 0 | 8.9 | 7.1 |
| 60 | 99 F | PB/PL | U / U | 0 | 0 | 0 | 15.1 | 10.8 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.7
Plasma Pyridostigmine Levels, Study 2

**PLASMA PB**

| SBJID | GENDER | DRGORD | BL1 | BL2 | PL4 | PL5 | PL8 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 51 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 15.9 | 13.3 | 0 |
| 3 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 15.8 | 17.5 | 0 |
| 62 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 35.2 | 26.6 | 0 |
| 61 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 24.4 | 12.9 | 0 |
| 60 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 5.1 | 15.5 | 0 |
| 59 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 18.7 | 12.6 | 0 |
| 58 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 24.4 | 22.1 | 0 |
| 4 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 16.5 | 18 | 0 |
| 5 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 11.7 | 17.9 | 0 |
| 6 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 11.3 | 12.2 | 0 |
| 7 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 0 |
| 11 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 21.8 | 22.2 | 0 |
| 8 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 10 | 8.9 | 0 |
| 9 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 14.6 | 10.7 | 0 |
| 10 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 14.7 | 15.2 | 0 |
| 1 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 16.6 | 17.4 | 0 |
| 84 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 11.9 | 22.6 | 0 |
| 82 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 18.7 | 24.2 | 0 |
| 53 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 6.4 | 4.7 | 0 |
| 54 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 24.7 | 27.3 | 0 |
| 56 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 25.3 | 19.1 | 0 |
| 57 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 15.8 | 18.2 | 0 |
| 80 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 16.9 | 25.1 | 0 |
| 12 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 3.2 | 25.5 | 0 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.5.8
Plasma Levels of THMP, Study 2

**PLASMA THMP**

| SBJID | GENDER | DRGORD | BL1 | BL2 | PL4 | PL5 | PL8 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 51 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 13.6 | 11.6 | 0 |
| 3 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 17.6 | 17.4 | 0 |
| 62 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 26.9 | 22.9 | 0 |
| 61 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 17.2 | 11.1 | 0 |
| 60 | F | PL/PB | 0 | 0 | 0 | 0 | 0 | 6.7 | 13.5 | 0 |
| 59 | F | PL/PB | 0 | 0 | 0 | 10.4 | 0 | 21.4 | 14.7 | 0 |
| 58 | F | PL/PB | 4.3 | 0 | 0 | 0 | 0 | 17.3 | 15.7 | 4.6 |
| 4 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 12.8 | 13.1 | 0 |
| 5 | M | PL/PB | 18.8 | 0 | 7.7 | 8.1 | 0 | 25.1 | 21.2 | 0 |
| 6 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 14.6 | 9.6 | 0 |
| 7 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 16.6 | 8.3 | 0 |
| 11 | M | PL/PB | 0 | 0 | 0 | 0 | 0 | 18.5 | 18.7 | 0 |
| 8 | M | PB/PL | 12.5 | 4.3 | 7 | 7.3 | 0 | 23 | 36.2 | 0 |
| 9 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 12.2 | 8.8 | 0 |
| 10 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 11 | 11.1 | 0 |
| 1 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 16.1 | 17.1 | 0 |
| 84 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 17.1 | 23.2 | 0 |
| 82 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 14.4 | 20.7 | 0 |
| 53 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 17.7 | 18.6 | 0 |
| 54 | F | PB/PL | 18.1 | 0 | 0 | 30.4 | 0 | 22.8 | 25.1 | 0 |
| 56 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 25.4 | 21.6 | 0 |
| 57 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 18.1 | 18.6 | 0 |
| 80 | F | PB/PL | 0 | 0 | 0 | 0 | 0 | 16.2 | 18.4 | 0 |
| 12 | M | PB/PL | 0 | 0 | 0 | 0 | 0 | 27.8 | 34.1 | 0 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

16.2.6 N/A

16.2.8 Individualized Laboratory Measurements

Table 16.2.8.1
Acetylcholinesterase Activities for Each Volunteer
on Each Test Day, Study 1

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL1 | PL4 | PL5 | PL8 | PB 1 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 4.4 | 4.5 | 4.9 | 4.4 | 4.5 | 4.3 | 3.1 | 1.8 | 4.8 |
| 30 | 7 | M | PL/PB | U / U | 3.9 | 4.1 | 4.2 | 4.1 | 3.9 | 2.9 | 2.2 | 2.8 | 4.1 |
| 30 | 8 | M | PB/PL | U / K | 4.5 | 4.1 | 4.1 | 4.2 | 4.1 | 3.6 | 3 | 3 | 4.1 |
| 30 | 9 | M | PB/PL | U / AK | 4.5 | 4.4 | 4.3 | 4.1 | 4 | 3.3 | 2.8 | 2.9 | 4.5 |
| 30 | 11 | M | PL/PB | U / K | 5.1 | 4.9 | 4.3 | 4.8 | 4.3 | 3.3 | 2.6 | 3.2 | 4.6 |
| 30 | 12 | M | PL/PB | U / U | 4.1 | 4.1 | 5 | 4.2 | 4.2 | 3.3 | 2.7 | 3.1 | 4.1 |
| 30 | 17 | M | PB/PL | U / U | 5.7 | 5.1 | 4.7 | 4.8 | 4.7 | 3.6 | 3.6 | 3.1 | 4.7 |
| 30 | 23 | M | PL/PB | U / U | 2.6 | 3.3 | 3.1 | 3.3 | 3.2 | 2.4 | 2.2 | 2 | 3.2 |
| 30 | 24 | M | PB/PL | U / U | 3.2 | 3.1 | 3.4 | 3.2 | 3.5 | 2.5 | 2.3 | 2.2 | 3.2 |
| 30 | 25 | M | PL/PB | U / AK | 3.9 | 3.8 | 3.7 | 3.9 | 3.7 | 3 | 2.9 | 2.8 | 3.9 |
| 30 | 26 | M | PB/PL | U / U | 3 | 3.2 | 3.3 | 3.3 | 3.2 | 2 | 2 | 2.3 | 3.4 |
| 30 | 28 | M | PL/PB | U / K | 4.9 | 4.8 | 3.9 | 5.3 | 4.6 | 4.2 | 3.3 | 3.4 | 5.3 |
| 30 | 30 | M | PB/PL | U / K | 3.1 | 4.3 | 4.6 | 4.3 | 4.3 | 3.4 | 3.1 | 2.6 | 4.6 |
| 30 | 32 | M | PB/PL | U / K | 3.4 | 2.3 | 3.3 | 2.8 | 3.2 | 3 | 1.6 | 1.1 | 1.7 |
| 30 | 40 | M | PL/PB | K / AK | 4.7 | 4.8 | 4.6 | 5.3 | 6 | 3.1 | 3.7 | 3.4 | 4.2 |
| 30 | 41 | M | PL/PB | U / U | 4 | 4.2 | 3.6 | 4.5 | 4.1 | 3 | 2.6 | 2.8 | 4.3 |
| 30 | 43 | M | PB/PL | U / U | 5.8 | 5.9 | 5.3 | 4.7 | 5.2 | 4.9 | 4.5 | 4.1 | 5.6 |
| 30 | 47 | M | PB/PL | U / U | 4.8 | 5.3 | 4.8 | 5 | 4.8 | 4.1 | 3.1 | 3.7 | 5 |
| 30 | 52 | F | PL/PB | U / AK | 4.3 | 4.7 | 4.7 | 4.6 | 3.8 | 3.8 | 3.4 | 2.8 | 4.4 |
| 30 | 53 | F | PB/PL | U / K | 4.8 | 5.4 | 5.3 | 5.2 | 5.2 | 4.5 | 3.2 | 3.7 | 5.3 |
| 30 | 55 | F | PL/PB | U / U | 4.7 | 4.4 | 4.5 | 4.9 | 4.5 | 2.7 | 2.5 | 2.2 | 4.3 |
| 30 | 56 | F | PL/PB | U / U | 4.5 | 4.7 | 4.4 | 4.7 | 4.5 | 3.5 | 2.8 | 3 | 4.5 |
| 30 | 61 | F | PL/PB | U / K | 4.6 | 4.3 | 4.8 | 4.7 | 4.5 | 3.5 | 2.9 | 2.4 | 4.4 |
| 30 | 64 | F | PB/PL | U / U | 5.5 | 4.8 | 3.8 | 4.7 | 4.7 | 3.7 | 3.8 | 3.6 | 5.1 |
| 30 | 65 | F | PB/PL | U / K | 4.1 | 3.6 | 3.9 | 3.7 | 3.8 | 3.6 | 2.9 | 2.9 | 4.3 |
| 30 | 67 | F | PL/PB | U / K | 3.9 | 4.7 | 4.3 | 4.9 | 4.7 | 3.9 | 3.2 | 2.6 | 4.9 |
| 30 | 70 | F | PB/PL | U / U | 3.6 | 3.7 | 3.6 | 3.7 | 3.8 | 2.5 | 2.3 | 2 | 3.6 |
| 30 | 74 | F | PB/PL | U / K | 5.7 | 5 | 5.4 | 5.3 | 5.3 | 4.8 | 3.2 | 3.7 | 5.3 |
| 30 | 76 | F | PB/PL | U / U | 4.6 | 4.9 | 5 | 4.9 | 4.7 | 3.8 | 3.2 | 3.3 | 5 |
| 30 | 80 | F | PB/PL | U / U | 4.1 | 4.1 | 4.3 | 4 | 3.9 | 3.3 | 2.8 | 2.7 | 3.8 |
| 30 | 89 | F | PB/PL | U / U | 3.9 | 3.9 | 3.2 | 2.7 | 4.4 | 2.9 | 2.5 | 4.2 | 2.5 |
| 30 | 90 | F | PL/PB | U / K | 5.2 | 5.2 | 4.3 | 4.5 | 4.9 | 4.2 | 3.5 | 3 | 5.1 |
| 30 | 91 | F | PL/PB | U / U | 3.6 | 3.9 | 3.7 | 3.5 | 3.6 | 3.3 | 3.2 | 2.7 | 3.7 |
| 60 | 1 | M | PB/PL | U / U |  | 3.7 | 4 | 4.1 | 3.6 |  |  |  | 3.6 |
| 60 | 3 | M | PL/PB | U / U | 4.5 | 4.6 | 4.5 | 4.2 | 4.5 | 3.1 | 2.8 | 2.6 | 4.4 |
| 60 | 4 | M | PB/PL | U / U | 3.9 | 4.3 | 4.4 | 3.9 | 4 | 2.8 | 1.9 | 2.5 | 4.4 |
| 60 | 5 | M | PB/PL | U / K | 4.4 | 4.7 | 3.2 | 3.3 | 3.9 | 3.2 | 2.8 | 2.5 | 4.4 |
| 60 | 10 | M | PL/PB | U / U | 4.1 | 3.5 | 4.3 | 3.9 | 4.2 | 2.9 | 2.4 | 2.2 | 4 |
| 60 | 13 | M | PB/PL | U / U | 5.4 | 4.1 | 3.6 | 4.5 | 5.1 | 3.6 | 2.3 | 2.2 | 4.2 |
| 60 | 20 | M | PL/PB | U / U | 4.3 | 4.7 | 4.2 | 4.3 | 4.7 | 3 | 2.2 | 2.7 | 4.7 |
| 60 | 22 | M | PB/PL | U / K | 2.6 | 3.1 | 3.3 | 3.1 | 3 | 1.8 | 1.4 | 1.6 | 3.2 |
| 60 | 31 | M | PL/PB | U / U | 3.5 | 3.3 | 3.1 | 3 | 3 | 1.9 | 1.6 | 1.5 | 3.3 |
| 60 | 33 | M | PL/PB | U / K | 3.7 | 3.8 | 3.7 | 3.6 | 3.8 | 2.4 | 1.9 | 2.2 | 3.5 |
| 60 | 35 | M | PL/PB | K / K | 3.7 | 3.6 | 3.9 | 3.6 | 3.7 | 2.6 | 1.9 | 1.9 | 3.5 |
| 60 | 36 | M | PB/PL | U / U | 4.2 | 4 | 4 | 4.1 | 3.8 | 2.2 | 2.3 | 2.2 | 4.4 |
| 60 | 38 | M | PL/PB | U / U | 5.8 | 4.9 | 4.3 | 4.9 | 5.1 | 3.3 | 2.4 | 2.9 | 5 |

Table 16.2.8.1
Acetylcholinesterase Activities for Each Volunteer
on Each Test Day, Study 1

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 39 M | PL/PB | U / K | 3.6 | 4 | 4.1 | 4.1 | 4 | 2.1 | 1.9 | 1.9 | 4 |
| 60 | 44 M | PB/PL | U / U | 4.7 | 5.4 | 4.2 | 4 | 4.3 | 2.9 | 2.7 | 2.9 | 4.6 |
| 60 | 45 M | PL/PB | U / U | 3.8 | 4.1 | 4.2 | 4.1 | 3.9 | 2.4 | 2 | 1.8 | 3.9 |
| 60 | 46 M | PB/PL | U / U | 3.8 | 4.3 | 4.4 | 4.2 | 4.4 | 2.4 | 1.8 | 1.8 | 4.2 |
| 60 | 48 M | PB/PL | U / U | 5 | 5.5 | 5.1 | 5.6 | 5.6 | 3.5 | 2.9 | 3.1 | 5.1 |
| 60 | 51 F | PL/PB | U / K | 4.7 | 5 | 7.1 | 4.9 | 5.1 | 2.6 | 2.5 | 2.2 | 4.7 |
| 60 | 54 F | PL/PB | U / U | 4.1 | 4.5 | 5.5 | 7.5 | 5.8 | 2.6 | 3.5 | 3.6 | 5.1 |
| 60 | 60 F | PB/PL | U / K | 4.3 | 4.8 | 4.6 | 4.5 | 4.5 | 2.6 | 2.3 | 2.1 | 4.2 |
| 60 | 63 F | PB/PL | U / U | 3.3 | 3.1 | 3.1 | 3.2 | 3.2 | 1.9 | 1.5 | 1.4 | 2.9 |
| 60 | 66 F | PB/PL | U / U | 2.9 | 2.9 | 3.1 | 2.8 | 2.8 | 1.6 | 1.4 | 1.3 | 2.9 |
| 60 | 68 F | PL/PB | U / K | 4.2 | 4.1 | 3.9 | 4.1 | 3.7 | 2.8 | 2.3 | 2.4 | 4.2 |
| 60 | 69 F | PL/PB | U / U | 3.7 | 3.5 | 3.5 | 3.4 | 3.3 | 2.1 | 1.7 | 2.4 | 3.6 |
| 60 | 71 F | PB/PL | U / K | 4.7 | 4.6 | 4.7 | 4.4 | 4.8 | 3.4 | 2.3 | 2.5 | 4.6 |
| 60 | 75 F | PB/PL | U / K | 3.3 | 3.5 | 3.3 | 3.2 | 3.2 | 2.9 | 2.1 | 1.9 | 3.2 |
| 60 | 83 F | PL/PB | U / U | 4.7 | 4.7 | 4.8 | 4.6 | 4.4 | 3.4 | 2.2 | 2.1 | 4.5 |
| 60 | 85 F | PB/PL | U / K | 6.3 | 5 | 4.5 | 4.2 | 4.7 | 3.2 | 2.4 | 2.4 | 4.5 |
| 60 | 88 F | PL/PB | U / U | 4.8 | 5.3 | 4.9 | 5.1 | 5 | 2.9 | 2.3 | 2 | 5.1 |
| 60 | 92 F | PB/PL | U / U | 4.4 | 4.8 | 4.6 | 4.4 | 4.9 | 3.6 | 2.5 | 2.5 | 4.4 |
| 60 | 95 F | PL/PB | U / U | 4.2 | 4.5 | 3.8 | 4.1 | 4 | 2.7 | 2.4 | 2.6 | 4.1 |
| 60 | 97 F | PB/PL | U / U | 3.6 | 3.7 | 3.9 | 3.6 | 3.6 | 2.5 | 2 | 2.1 | 3.5 |
| 60 | 99 F | PB/PL | U / U | 4 | 4.2 | 4 | 4.1 | 3.6 | 2.6 | 2.3 | 2.2 | 4.1 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.8.2
Butyrylcholinesterase Values for Each Volunteer
on Each Test Day, Study 1

| DOSE | SBJID | GENDER | DRGORD | GENETIC | BL1 | PL1 | PL4 | PL5 | PL8 | PB 1 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 6 | M | PL/PB | U / K | 1.3 | 1.5 | 1.4 | 1.3 | 1.4 | 1.4 | 1.4 | 1.3 | 1.6 |
| 30 | 7 | M | PL/PB | U / U | 2.3 | 2.6 | 2.8 | 2.8 | 2.6 | 2.6 | 2.3 | 2.3 | 2.8 |
| 30 | 8 | M | PB/PL | U / K | 2.7 | 2.6 | 2.6 | 2.6 | 2.4 | 2.5 | 2.3 | 2.2 | 2.2 |
| 30 | 9 | M | PB/PL | U / AK | 1.6 | 1.7 | 1.9 | 1.7 | 1.7 | 1.6 | 1.5 | 1.3 | 1.6 |
| 30 | 11 | M | PL/PB | U / K | 1.9 | 1.8 | 2.4 | 2.3 | 2.3 | 2.3 | 2.1 | 2.2 | 2.7 |
| 30 | 12 | M | PL/PB | U / U | 2 | 1.9 | 2 | 2.1 | 2.2 | 2.2 | 2.1 | 2.1 | 2.4 |
| 30 | 17 | M | PB/PL | U / U | 2.4 | 2.2 | 2.8 | 2.5 | 2.9 | 2 | 2 | 2 | 2.1 |
| 30 | 23 | M | PL/PB | U / U | 1.7 | 2 | 1.8 | 1.7 | 1.9 | 1.7 | 1.6 | 1.8 | 2.1 |
| 30 | 24 | M | PB/PL | U / U | 1.9 | 1.9 | 2.1 | 1.9 | 1.8 | 1.8 | 1.7 | 1.7 | 1.9 |
| 30 | 25 | M | PL/PB | U / AK | 1.6 | 1.6 | 1.7 | 1.7 | 1.7 | 1.8 | 1.6 | 1.7 | 1.7 |
| 30 | 26 | M | PB/PL | U / U | 2.2 | 2.8 | 2.5 | 2.7 | 2.4 | 2.1 | 2.2 | 2.2 | 2.3 |
| 30 | 28 | M | PL/PB | U / K | 3.9 | 3.4 | 3.4 | 3.2 | 3.5 | 3.7 | 2.9 | 3.3 | 3.7 |
| 30 | 30 | M | PB/PL | U / K | 2.4 | 2.3 | 2.4 | 2.2 | 2.5 | 2.1 | 2.3 | 2.3 | 2.1 |
| 30 | 32 | M | PB/PL | U / K | 1.4 | 1.6 | 1.9 | 1.8 | 1.9 | 1.4 | 1.4 | 1.2 | 1.2 |
| 30 | 40 | M | PL/PB | K / AK | 1.3 | 1.4 | 1.2 | 1.1 | 1.2 | 1.1 | 1.1 | 1.1 | 1.1 |
| 30 | 41 | M | PL/PB | U / U | 2.4 | 2.7 | 2.5 | 2.6 | 2.3 | 2.4 | 2.1 | 2 | 2 |
| 30 | 43 | M | PB/PL | U / U | 2.4 | 3 | 2.9 | 2.8 | 2.6 | 2.3 | 2.1 | 1.9 | 2.4 |
| 30 | 47 | M | PB/PL | U / U | 2.3 | 2.4 | 2.4 | 2.3 | 2.7 | 2 | 2 | 2 | 2.3 |
| 30 | 52 | F | PL/PB | U / AK | 1.4 | 1.4 | 1.6 | 1.5 | 1.8 | 1.4 | 1.6 | 1.5 | 1.6 |
| 30 | 53 | F | PB/PL | U / K | 2.1 | 2.3 | 2.1 | 2.1 | 2.1 | 2.1 | 2 | 2.3 | 2.4 |
| 30 | 55 | F | PL/PB | U / U | 3.7 | 3.7 | 3.3 | 3.2 | 3.7 | 2.7 | 2.7 | 2.8 | 3.3 |
| 30 | 56 | F | PL/PB | U / U | 2.2 | 2 | 2 | 2 | 2.2 | 2.2 | 2.1 | 2 | 2.2 |
| 30 | 61 | F | PL/PB | U / K | 2.2 | 2 | 1.9 | 1.9 | 2 | 2 | 1.8 | 1.6 | 2.4 |
| 30 | 64 | F | PB/PL | U / U | 3.1 | 3 | 3.3 | 3 | 3 | 2.6 | 2.6 | 2.5 | 2.9 |
| 30 | 65 | F | PB/PL | U / K | 1.4 | 1.4 | 1.5 | 1.4 | 1.3 | 1.7 | 1.4 | 1.7 | 1.6 |
| 30 | 67 | F | PL/PB | U / K | 1.5 | 1.5 | 1.4 | 1.5 | 1.6 | 1.6 | 1.3 | 1.3 | 1.7 |
| 30 | 70 | F | PB/PL | U / U | 2.8 | 2.8 | 2.7 | 2.8 | 2.7 | 2 | 2.4 | 2.5 | 2.7 |
| 30 | 74 | F | PB/PL | U / K | 2.1 | 2 | 2 | 2 | 2.5 | 2.1 | 1.7 | 1.8 | 1.9 |
| 30 | 76 | F | PB/PL | U / U | 3.4 | 2.9 | 3.1 | 3.2 | 3.5 | 3.1 | 3 | 3.1 | 3.1 |
| 30 | 80 | F | PB/PL | U / U | 1.7 | 1.7 | 1.6 | 1.7 | 1.6 | 1.5 | 1.3 | 1.8 | 1.7 |
| 30 | 89 | F | PB/PL | U / U | 2.1 | 3 | 2.6 | 2.7 | 3 | 2 | 1.7 | 1.9 | 2.6 |
| 30 | 90 | F | PL/PB | U / K | 1.8 | 1.8 | 1.8 | 1.5 | 1.8 | 1.9 | 1.5 | 1.3 | 1.6 |
| 30 | 91 | F | PL/PB | U / U | 1.5 | 1.6 | 1.6 | 1.7 | 1.9 | 1.2 | 1.4 | 1.3 | 1.4 |
| 60 | 1 | M | PB/PL | U / U | 2.1 | 2.4 | 2.1 | 2.2 | 2.1 | 2 | 2.1 | 1.9 | 2.3 |
| 60 | 3 | M | PL/PB | U / U | 2.3 | 2.3 | 2.4 | 2.1 | 2.3 | 2 | 2.1 | 1.8 | 2.5 |
| 60 | 4 | M | PB/PL | U / U | 2.6 | 3.3 | 3.2 | 3.4 | 3 | 2.6 | 2.7 | 2.6 | 3 |
| 60 | 5 | M | PB/PL | U / K | 2.6 | 2.3 | 2.6 | 2.6 | 2.5 | 2.4 | 2.5 | 2.4 | 2.3 |
| 60 | 10 | M | PL/PB | U / U | 2.5 | 3.1 | 3.2 | 2.8 | 3.2 | 2.6 | 2.9 | 2.2 | 2.8 |
| 60 | 13 | M | PB/PL | U / U | 2.7 | 2.8 | 2.8 | 2.7 | 2.9 | 2.5 | 2.4 | 2.2 | 2.8 |
| 60 | 20 | M | PL/PB | U / U | 2.4 | 2.1 | 1.9 | 2.3 | 2.2 | 2.1 | 2.1 | 2.1 | 2.3 |
| 60 | 22 | M | PB/PL | U / K | 1.7 | 1.5 | 1.4 | 1.4 | 1.6 | 1.4 | 1.3 | 1.3 | 1.6 |
| 60 | 31 | M | PL/PB | U / U | 1.4 | 1.2 | 1.1 | 1.2 | 1.2 | 1.2 | 1.1 | 1.1 | 1.4 |
| 60 | 33 | M | PL/PB | U / K | 1.4 | 1.5 | 1.6 | 1.4 | 1.5 | 1.2 | 1.3 | 1.2 | 1.4 |
| 60 | 35 | M | PL/PB | K / K | 1.7 | 1.6 | 1.8 | 1.8 | 1.7 | 1.5 | 1.8 | 1.5 | 1.8 |
| 60 | 36 | M | PB/PL | U / U | 2 | 2 | 2 | 2 | 1.9 | 1.9 | 1.8 | 1.5 | 2.3 |
| 60 | 38 | M | PL/PB | U / U | 2.4 | 2.3 | 2.6 | 2.6 | 2.2 | 2.1 | 2 | 2.2 | 2.5 |

Table 16.2.8.2
Butyrylcholinesterase Values for Each Volunteer
on Each Test Day, Study 1

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 39 | M | PL/PB | U / K | 2.3 | 2 | 2.1 | 2.1 | 1.9 | 1.9 | 1.9 | 2 | 2.3 |
| 60 | 44 | M | PB/PL | U / U | 2.3 | 3 | 3.4 | 2.9 | 2.8 | 2.5 | 2.5 | 2.6 | 3 |
| 60 | 45 | M | PL/PB | U / U | 1.9 | 2 | 1.8 | 1.8 | 1.8 | 1.6 | 1.5 | 1.5 | 2 |
| 60 | 46 | M | PB/PL | U / U | 1.6 | 1.6 | 1.8 | 1.8 | 1.8 | 1.2 | 1.2 | 1.2 | 1.5 |
| 60 | 48 | M | PB/PL | U / U | 1.9 | 2.3 | 2.1 | 2.1 | 2.3 | 2.1 | 1.9 | 1.9 | 2.2 |
| 60 | 51 | F | PL/PB | U / K | 2.1 | 2.4 | 2.1 | 2.3 | 2.7 | 2.1 | 2.3 | 1.8 | 2.6 |
| 60 | 54 | F | PL/PB | U / U | 2.2 | 2.2 | 2.3 | 2.3 | 2.4 | 2.1 | 2.2 | 2.1 | 2.4 |
| 60 | 60 | F | PB/PL | U / K | 1.9 | 1.7 | 1.6 | 1.5 | 1.6 | 1.7 | 1.4 | 1.3 | 1.9 |
| 60 | 63 | F | PB/PL | U / U | 2.4 | 2.3 | 2.1 | 2.2 | 2 | 2.7 | 1.7 | 1.9 | 2.1 |
| 60 | 66 | F | PB/PL | U / U | 1.5 | 1.4 | 1.6 | 1.5 | 1.4 | 1.3 | 1 | 1.2 | 1.2 |
| 60 | 68 | F | PL/PB | U / K | 1.6 | 1.5 | 1.7 | 1.4 | 1.6 | 1.5 | 1.3 | 1.4 | 1.7 |
| 60 | 69 | F | PL/PB | U / U | 1.9 | 1.8 | 1.8 | 1.8 | 1.8 | 1.9 | 1.7 | 1.8 | 2 |
| 60 | 71 | F | PB/PL | U / K | 1.7 | 1.9 | 1.8 | 1.8 | 1.8 | 1.5 | 1.6 | 1.6 | 1.9 |
| 60 | 75 | F | PB/PL | U / K | 1.7 | 1.6 | 1.7 | 1.6 | 1.6 | 1.7 | 1.5 | 1.5 | 1.5 |
| 60 | 83 | F | PL/PB | U / U | 1.8 | 2 | 2.1 | 2.2 | 2.2 | 1.8 | 1.7 | 1.5 | 1.8 |
| 60 | 85 | F | PB/PL | U / K | 2.1 | 2.4 | 2.6 | 2.5 | 2.6 | 1.9 | 2 | 1.9 | 2 |
| 60 | 88 | F | PL/PB | U / U | 1.5 | 1.3 | 1.4 | 1.3 | 1.5 | 1.1 | 1.1 | 0.9 | 1.4 |
| 60 | 92 | F | PB/PL | U / U | 2.1 | 1.8 | 2.1 | 1.8 | 2.2 | 1.9 | 1.5 | 1.6 | 1.7 |
| 60 | 95 | F | PL/PB | U / U | 1.4 | 1.4 | 1.6 | 1.5 | 1.6 | 1.5 | 1.2 | 1.2 | 1.5 |
| 60 | 97 | F | PB/PL | U / U | 1.2 | 1 | 0.9 | 1 | 1.3 | 1.1 | 0.9 | 0.9 | 1.2 |
| 60 | 99 | F | PB/PL | U / U | 2.2 | 1.9 | 2.2 | 2.2 | 1.9 | 1.9 | 1.7 | 1.6 | 2 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.8.3
Acetylcholinesterase Activity for Each Volunteer
on Each Test Day, Study 2

| SBJID | GENDER | DRGORD | BL1 | BL2 | PL4 | PL5 | PL8 | PB 4 | PB 5 | PB 8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 51 | F | PL/PB | 3.3 | 2.9 | 3.5 | 3.3 | 3.2 | 1.9 | 2 | 3.2 |
| 3 | M | PL/PB | 2.9 | 2.7 | 2.8 | 2.9 | 2.9 | 1.5 | 1.4 | 2.5 |
| 62 | F | PL/PB | 3.8 | 3.6 | 3.3 | 3.6 | 3.4 | 1.6 | 1.9 | 3.8 |
| 61 | F | PL/PB | 2.8 | 2.4 | 2.6 | 2.7 | 2.4 | 1.5 | 1.6 | 2.5 |
| 60 | F | PL/PB | 2.8 | 3.1 | 3.1 | 2.9 | 3.4 | 2.9 | 1.6 | 3.3 |
| 59 | F | PL/PB | 3.5 | 3.5 | 3.2 | 3.4 | 3.3 | 1.9 | 2 | 3.2 |
| 58 | F | PL/PB | 3.2 | 3.4 | 3.3 | 3.2 | 3.2 | 2 | 1.5 | 3.1 |
| 4 | M | PL/PB | 3.8 | 3.7 | 3.2 | 3 | 3.3 | 1.7 | 1.9 | 3.1 |
| 5 | M | PL/PB | 3.3 | 3.3 | 4.1 | 3.3 | 3.5 | 2.1 | 2 | 3.7 |
| 6 | M | PL/PB | 3.3 | 3.4 | 3 | 3.3 | 3 | 2.5 | 1.9 | 2.9 |
| 7 | M | PL/PB | 3.3 | 3.4 | 3.3 | 3.4 | 3 | 2.4 | 2.1 | 3.3 |
| 11 | M | PL/PB | 2.8 | 2.6 | 2.9 | 2.7 | 2.7 | 1.4 | 1.4 | 2.7 |
| 8 | M | PB/PL | 3.1 | 3.2 | 3.6 | 3.6 | 3.5 | 2.4 | 2.1 | 3.8 |
| 9 | M | PB/PL | 3 | 2.6 | 2.5 | 2.3 | 2.8 | 1.7 | 2 | 2.7 |
| 10 | M | PB/PL | 3.1 | 3.6 | 3.3 | 3.4 | 3.3 | 2 | 2.1 | 3.7 |
| 1 | M | PB/PL | 3.8 | 4.2 | 3.5 | 3.7 | 3.9 | 2.2 | 2.7 | 3.8 |
| 84 | M | PB/PL | 3.7 | 3.7 | 3.7 | 3.7 | 3.9 | 2.4 | 2.2 | 3.7 |
| 82 | M | PB/PL | 4.8 | 4.2 | 4.2 | 4.2 | 4.1 | 2.6 | 2.3 | 4.2 |
| 53 | F | PB/PL | 4 | 3.9 | 3.3 | 3.5 | 3.6 | 2.7 | 2.9 | 3.6 |
| 54 | F | PB/PL | 3.2 | 1.8 | 3.2 | 3.2 | 3.2 | 1.7 | 1.4 | 3.5 |
| 56 | F | PB/PL | 2.8 | 2.8 | 3.2 | 2.7 | 3.3 | 1 | 1.4 | 3 |
| 57 | F | PB/PL | 3.2 | 3 | 3.1 | 3.5 | 3.4 | 2.1 | 2 | 3.2 |
| 80 | F | PB/PL | 3.6 | 3 | 3.2 | 3.5 | 3.6 | 2.1 | 2 | 3.4 |
| 12 | M | PB/PL | 3.1 | 3 | 2.9 | 3.2 | 3.2 | 2 | 1.7 | 3.2 |

BL = Baseline
PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.8.4
Side Effects Scores, Study 1

**STUDY 1, SIDE EFFECTS SUMMARY**

| SBJID | GENDER | DRGORD | DOSE | PL | PB |
|---|---|---|---|---|---|
| 1 | M | PB/PL | 60 | 0 | 0 |
| 3 | M | PL/PB | 60 | 5 | 18 |
| 4 | M | PB/PL | 60 | 0 | 0 |
| 5 | M | PB/PL | 60 | 0 | 4 |
| 6 | M | PL/PB | 30 | 3 | 2 |
| 7 | M | PL/PB | 30 | 0 | 0 |
| 8 | M | PB/PL | 30 | 7 | 7 |
| 9 | M | PB/PL | 30 | 0 | 0 |
| 10 | M | PL/PB | 60 | 0 | 0 |
| 11 | M | PL/PB | 30 | 1 | 0 |
| 12 | M | PL/PB | 30 | 3 | 4 |
| 13 | M | PB/PL | 60 | 0 | 3 |
| 17 | M | PB/PL | 30 | 2 | 0 |
| 20 | M | PL/PB | 60 | 0 | 0 |
| 22 | M | PB/PL | 60 | 0 | 6 |
| 23 | M | PL/PB | 30 | 0 | 3 |
| 24 | M | PB/PL | 30 | 2 | 2 |
| 25 | M | PL/PB | 30 | 1 | 0 |
| 26 | M | PB/PL | 30 | 0 | 1 |
| 28 | M | PL/PB | 30 | 9 | 1 |
| 30 | M | PB/PL | 30 | 4 | 4 |
| 31 | M | PL/PB | 60 | 4 | 5 |
| 32 | M | PB/PL | 30 | 0 | 15 |
| 33 | M | PL/PB | 60 | 0 | 0 |
| 35 | M | PL/PB | 60 | 0 | 6 |
| 36 | M | PB/PL | 60 | 0 | 8 |
| 38 | M | PL/PB | 60 | 0 | 1 |
| 39 | M | PL/PB | 60 | 5 | 0 |
| 40 | M | PL/PB | 30 | 17 | 27 |
| 41 | M | PL/PB | 30 | 14 | 6 |
| 43 | M | PB/PL | 30 | 4 | 0 |
| 44 | M | PB/PL | 60 | 2 | 3 |
| 45 | M | PL/PB | 60 | 4 | 1 |
| 46 | M | PB/PL | 60 | 4 | 10 |
| 47 | M | PB/PL | 30 | 0 | 4 |
| 48 | M | PB/PL | 60 | 0 | 10 |
| 51 | F | PL/PB | 60 | 20 | 52 |
| 52 | F | PL/PB | 30 | 4 | 5 |
| 53 | F | PB/PL | 30 | 2 | 14 |
| 54 | F | PL/PB | 60 | 17 | 24 |
| 55 | F | PL/PB | 30 | 1 | 7 |
| 56 | F | PL/PB | 30 | 14 | 13 |
| 60 | F | PB/PL | 60 | 0 | 3 |
| 61 | F | PL/PB | 30 | 5 | 9 |
| 63 | F | PB/PL | 60 | 10 | 8 |
| 64 | F | PB/PL | 30 | 0 | 0 |
| 65 | F | PB/PL | 30 | 1 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| 66 | F | PB/PL | 60 | 0 | 3 |
| 67 | F | PL/PB | 30 | 3 | 4 |
| 68 | F | PL/PB | 60 | 1 | 2 |
| 69 | F | PL/PB | 60 | 9 | 4 |
| 70 | F | PB/PL | 30 | 10 | 32 |
| 71 | F | PB/PL | 60 | 2 | 0 |
| 74 | F | PB/PL | 30 | 0 | 0 |
| 75 | F | PB/PL | 60 | 0 | 1 |
| 76 | F | PB/PL | 30 | 0 | 0 |
| 80 | F | PB/PL | 30 | 0 | 28 |
| 83 | F | PL/PB | 60 | 0 | 16 |
| 85 | F | PB/PL | 60 | 0 | 0 |
| 88 | F | PL/PB | 60 | 13 | 11 |
| 89 | F | PB/PL | 30 | 1 | 0 |
| 90 | F | PL/PB | 30 | 13 | 8 |
| 91 | F | PL/PB | 30 | 2 | 0 |
| 92 | F | PB/PL | 60 | 0 | 18 |
| 95 | F | PL/PB | 60 | 2 | 20 |
| 97 | F | PB/PL | 60 | 3 | 6 |
| 99 | F | PB/PL | 60 | 4 | 4 |

PL = Placebo Phase
PB = Pyridostigmine Phase

Table 16.2.8.5
Side Effects Scores, Study 2

**STUDY 2, SIDE EFFECTS SUMMARY**

| SBJID | GENDER | DRGORD | PL | PB |
|---|---|---|---|---|
| 1 | M | PB/PL | 1 | 5 |
| 3 | M | PL/PB | 4 | 7 |
| 4 | M | PL/PB | 2 | 2 |
| 5 | M | PL/PB | 2 | 0 |
| 6 | M | PL/PB | 4 | 2 |
| 7 | M | PL/PB | 22 | 10 |
| 8 | M | PB/PL | 0 | 0 |
| 9 | M | PB/PL | 7 | 9 |
| 10 | M | PB/PL | 12 | 6 |
| 11 | M | PL/PB | 0 | 3 |
| 12 | M | PB/PL | 10 | 2 |
| 51 | F | PL/PB | 7 | 2 |
| 53 | F | PB/PL | 0 | 19 |
| 54 | F | PB/PL | 0 | 4 |
| 56 | F | PB/PL | 4 | 4 |
| 57 | F | PB/PL | 0 | 2 |
| 58 | F | PL/PB | 5 | 2 |
| 59 | F | PL/PB | 0 | 0 |
| 60 | F | PL/PB | 1 | 0 |
| 61 | F | PL/PB | 3 | 2 |
| 62 | F | PL/PB | 0 | 2 |
| 80 | F | PB/PL | 2 | 1 |
| 82 | M | PB/PL | 7 | 2 |
| 84 | M | PB/PL | 8 | 6 |

PL = Placebo Phase
PB = Pyridostigmine Phase