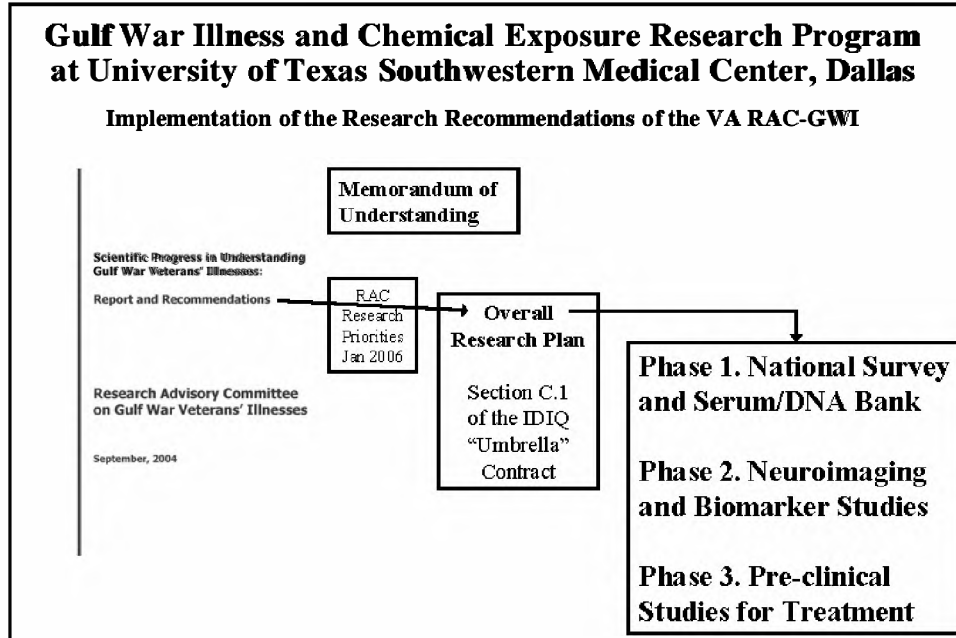


Presentation 2 – Robert Haley



**Gulf War Illness and Chemical Exposure Research Program
at University of Texas Southwestern Medical Center, Dallas**

- Congressional mandate
 - FY 2006 budget—announced November 2005
 - Establish a Gulf War illness research center at UT Southwestern Medical Center in Dallas
 - In collaboration with a VA medical center
 - Funded at \$15 million per year for 5 years
 - Through the Department of Veterans Affairs

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 - In collaboration with a VA medical center
 - Funded at \$15 million per year for 5 years
 - Through the Department of Veterans Affairs
- **Funding mechanism set up by VA**
 - Indefinite Delivery, Indefinite Quantity (IDIQ) contract
 - Individual projects funded through task orders under the IDIQ “umbrella” contract

**Gulf War Illness and Chemical Exposure Research Program
at University of Texas Southwestern Medical Center, Dallas**

- **The IDIQ “Umbrella” Contract**
 - \$15 M received in the middle of each fiscal year FY’06 through FY’10
 - 2 fiscal years to obligate the funds in a task order which can run for 5 years.
 - Contract administered by Dallas VA contracting office
 - Contract officer
 - Contracting officer’s technical representative (COTR)
 - Federal Acquisition Regulations (FAR) and VA regulations and policies for Research Funds
 - Subject to audit by the VA OIG

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas

- **The IDIQ “Umbrella” Contract**
 - Section C: Merit Review Process
 - Projects reviewed by UT Southwestern Merit Review Group, chaired by Dean Al Gilman
 - MRG approves an *Overall Research Plan*
 - Projects must implement the *Overall Research Plan*
 - Human subjects protection and animal use governed by:
 - UT Southwestern IRB and IACUC if performed at UT Southwestern
 - UT Southwestern and VA IRBs/IACUC if a VAMC involved
 - All data and samples owned by VA but possession ceded to UT Southwestern indefinitely
 - Data storage subject to VA IT Security Requirements
 - Serum/DNA storage subject to VA Tissue Banking Requirements

Members of the Merit Review Group

Al Gilman, M.D., MRG chair, UT Southwestern Dean/Provost

Eric Nestler, M.D., Ph.D., chair, Dept. of Psychiatry

Stephen Cannon, M.D., Ph.D., chair, Dept. of Neurology

James Stull, Ph.D., chair, Dept. of Physiology

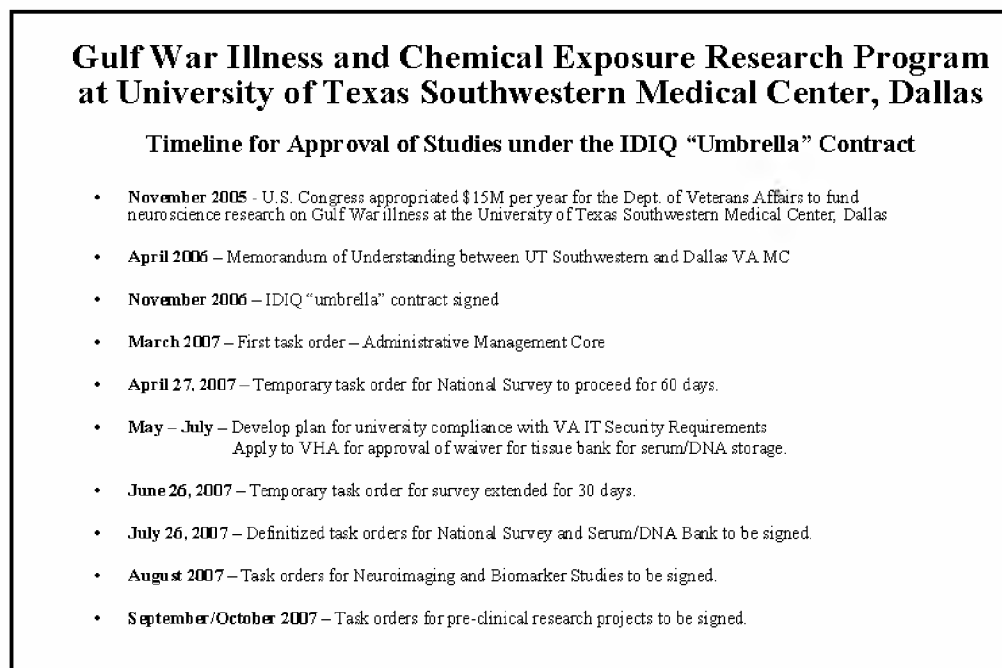
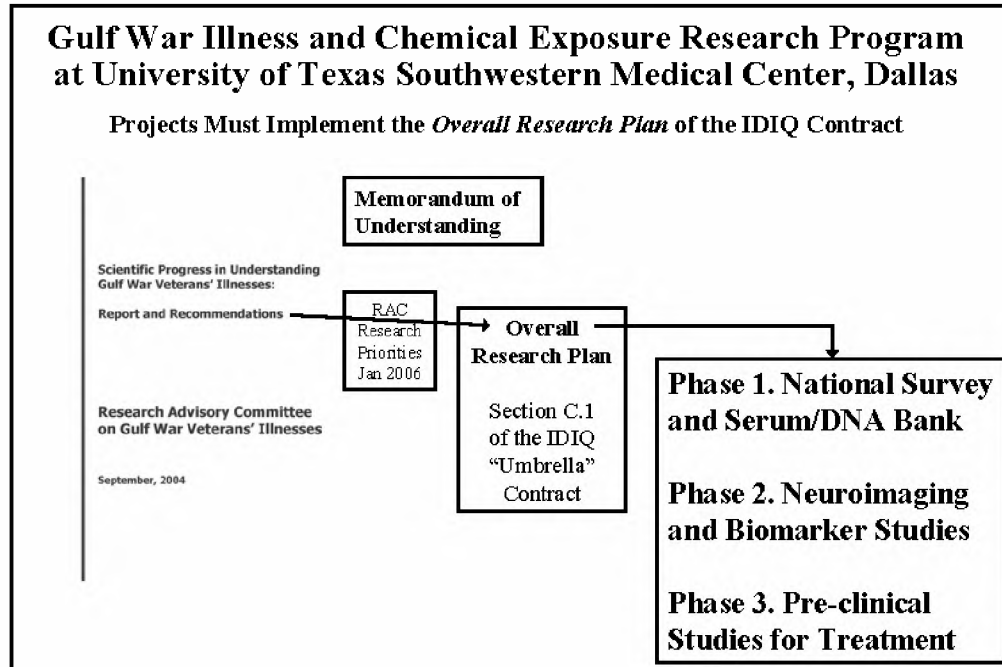
Milton Packer, M.D., chair, Dept. of Clinical Sciences

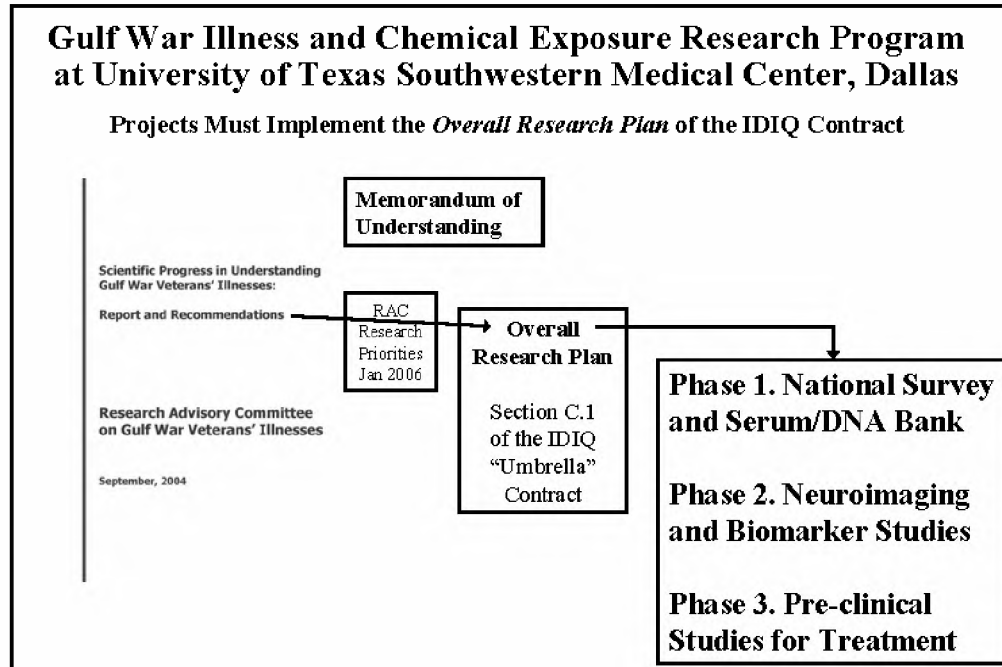
Craig Malloy, M.D., medical director, Advanced Imaging Research Center

James O’Callaghan, Ph.D., head, Molecular Toxicology Laboratory, CDC

Ex officio member

Perrie Adams, Ph.D., Vice President for Research Administration

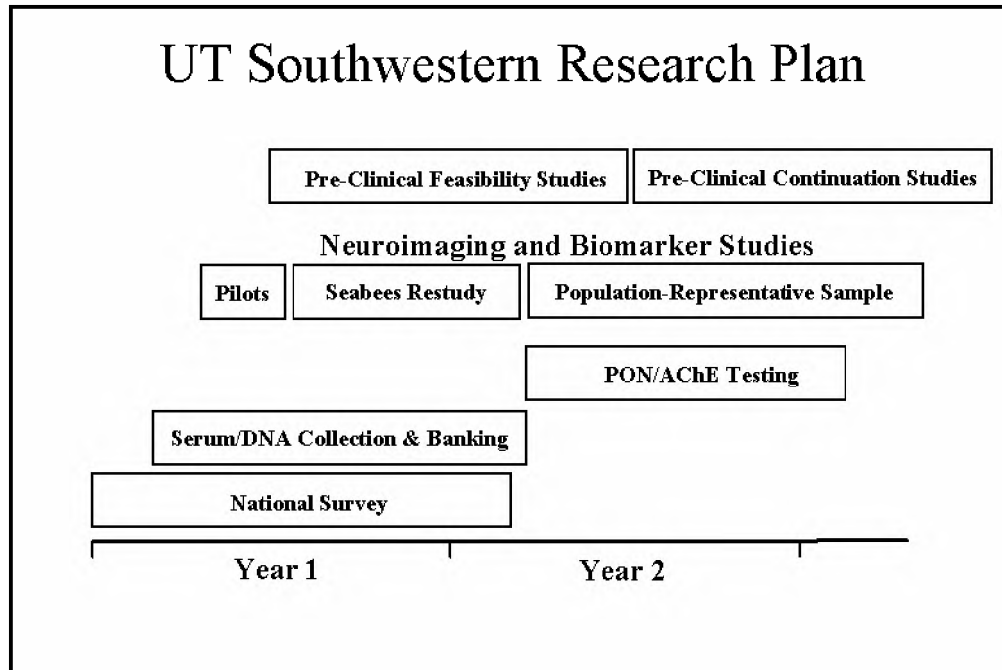




- Overall Research Plan
Approved by the MRG on 9 Nov 2006**
- **Specific Research Objective #1:
National Survey and Serum/DNA Bank**

 - **Specific Research Objective #2:
Sensitive Brain Imaging Procedures and
Biomarker Studies**

 - **Specific Research Objective #3:
Pre-clinical Studies of Effects of Gulf War
Exposures on Cells**



VA Research Advisory Committee *Research Priorities –January 2006*

Gulf War Research: General Principles (6)

Highest Priority Areas of Interest for Gulf War Illness Research (9)

Other Topics of Importance (8)

Gulf War Research: General Principles

1. Evaluate epidemiologic, clinical, and laboratory parameters in Gulf War veterans stratified into subgroups defined according to exposures, locations, units, or other characteristics potentially associated with the outcome of interest, as opposed to evaluation of all deployed veterans as a single group
2. Identify measurable differences between symptomatic and healthy Gulf War veterans, particularly specific markers that distinguish individual GWI cases from controls

Overall Research Plan (ORP) Objective #1: National Survey and Serum/DNA Bank

- Telephone interview survey in a random sample of Gulf War-era veterans (N = 14,754)
 - Stratification
 - Age, sex, race/ethnicity, active/reserve status, deployment, sarin exposure risk zones
 - Stratified random sample of deployed and nondeployed era veterans (N = 10,077)
 - Deployed to high risk zone (N = 4,609) “High risk zone” = Near Kuwaiti border on 20 Jan 91
 - Deployed elsewhere in KTO (N = 3,502) Also in Kharrisiyah plume
 - Deployable nondeployed (N = 1,757)
 - Medically nondeployable (N = 209) Separated out to control of “healthy warrior effect”
 - Special strata (N = 4,677)
 - 10 year followup of the 24th Reserve Naval Mobile Construction Battalion (Seabees, N = 235)
 - Twins discordant on deployment to theater and high risk areas (N = 1,238)
 - Air Force pilots and ground crews (N = 1,817)
 - Units exposed to ammunition dump explosions at Camp Doha (N = 736)
 - All Gulf War-era veterans with postwar Goldenhar birth defect child (N = 53)
 - Content
 - Case definitions: Haley, Steele, Fukuda, Kang (?), CFS, FM, MCS, Diagnosable Conditions, SF-12, etc.
 - Stratification measures, exposure measures, confounding variables, birth denominator data
- Tissue bank for serum, plasma and DNA from sample (N = 2,064)
 - Sample characteristics:
 - All seabees and twins, all Haley or Steele syndrome, sample of the subsyndromic, sample of the non-syndromic
 - High priority tests
 - Paraoxonase & butyryl-cholinesterase isoenzyme activity and genotyping
 - Genomic screening of SNP array (being planned)

Overall Research Plan (ORP) Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The following groups will be admitted to UT Southwestern GCRC for 5-day neuroimaging and biomarker study:
 - Pilot study samples
 - 20 ill and 20 well members of 24th Seabees studied by similar tests in 1998
 - 80 randomly selected from U.S. Military Health Survey (20 ea from syndromes 1, 2 and 3 and 20 healthy controls)

- The testing protocol includes:
 - MR spectroscopy, MRI for volumetrics, DTI, Connectivity, high res. EEG, ESL, SPECT with cholinergic challenge, and fMRI paradigms probing regions/functions thought to be impaired.
 - Neuropsychological testing, brain dopamine turnover, dexamethasone suppression test, autonomic evaluation, quantitative sensory, and audiovestibular testing

- Past and ongoing statistical research has identified a new approach to the analysis of brain imaging and EEG data that greatly increases the power to detect subtle group differences in brain structure and function.

Clinical Case-Control Study Testing Schedule

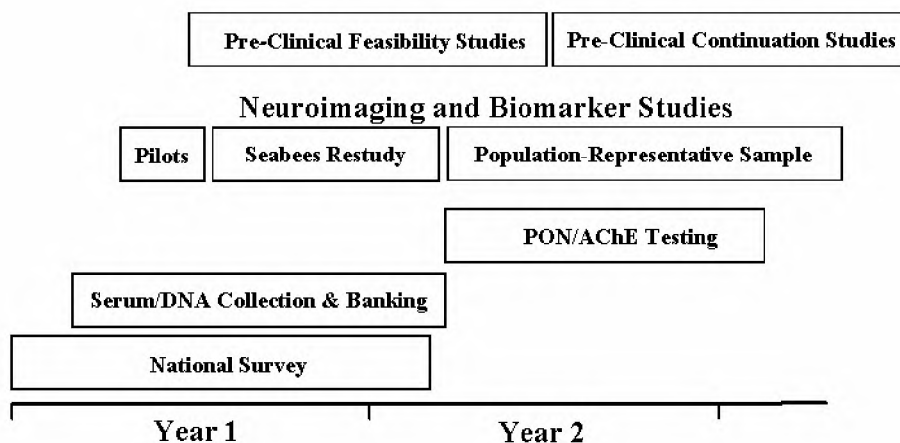
[Dates]	Sun	Mon	Tues	Wed	Thur	Fri	Sat
7:00		BFAST	BFAST	BFAST	BFAST	BLOOD	
7:15							
7:30			MRI Instruct		MRI Instruct	BFAST	BFAST
7:45							
8:00		Autonomic	MRI Ventrat	NP Testing	MRI Conjoint	NP Testing	
8:15							
8:30							
8:45							
9:00			BREAK				
9:15			MRI Emotval			BREAK	
9:30							
9:45							
10:00						MRI CmpVtVt	
10:15		MRI Instruct					
10:30			QuantSens				
10:45		MRI - MTL					
11:00				LUNCH		SCID	
11:15					BREAK		
11:30					DTI, FXL CON		
11:45				EEG			
12:00						LIQ LUNCH	
12:15		LUNCH	LUNCH				LUNCH
12:30							
12:45							
1:00		NeuroAtaxia Exam	INFUSION saline only		INFUSION saline + physio	AudioVestib	DC GCRC
1:15							
1:30							
1:45			HMPAO Inj		HMPAO Inj		
2:00			ASL		ASL		
2:15			AbnTest		AbnTest		
2:30							
2:45		MRI Instruct					
3:00				MRI Instruct			
3:15		MRI - FSSD		MRI Cerebellum			
3:30			SPECT PMH		SPECT PMH		
3:45							
4:00			SPECT EG		SPECT EG		
4:15	Admit GCRC						
4:30	CONSENT	BREAK		BREAK			
4:45		MRS 1		MRS 2			
5:00	MID EXAM						
5:15			DINNER		DINNER		
5:30			Language NP Tests		Language NP Tests		
5:45							
6:00	DINNER					DINNER	
6:15	Ca	DINNER		DINNER		Ca	
6:30		Ca		Ca		DEX @ 5	

Version 6 13-9-2006

Measurement Technologies Capable of Demonstrating Subtle Brain Differences

- **Clinical measurements**
 - Neuropsychological testing
 - Autonomic—High frequency heart rate variability, clinical autonomic battery
 - Quantitative sensory testing (cooling, heat pain and vibratory thresholds)
 - Brainstem evaluation tests—ENG, brainstem evoked potentials
 - HPA axis—Dexamethasone suppression test
 - Brain neurotransmitter production—Brain dopamine (plasma HVA/MHPG ratio)
- **Biomarkers for organophosphate exposure**
 - Paraoxonase (PON1) isoenzyme activity and genotype
 - Butyryl-cholinesterase (BChE) activity and variant genotypes
- **Magnetic resonance scanning (new 3T magnets at UT Southwestern and Dallas VA)**
 - MR Spectroscopy (MRS scanning)
 - Volumetric analysis of MRI images (brain volume changes)
 - Functional MRI (fMRI), Functional Connectivity and simultaneous fMRI/EEG
 - Diffusion Tensor Imaging (DTI, tractography)
- **Nuclear tracer scanning**
 - Single photon-emission computed tomography (SPECT with cholinergic challenge)
 - Positron-emission tomography (PET, ¹¹C-R-PK11195 radioligand, PBR receptors)
- **Analysis with new *Spatial Modeling* statistical approach**
 - To increase power to detect subtle group differences

UT Southwestern Research Plan



Gulf War Research: General Principles

3. Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments

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ORP Objective #1: National Survey

- Survey includes battery of questions on what medications veterans have tried and whether each has been beneficial, ineffective or harmful for reducing symptoms.

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- Will test previously framed hypotheses about pathophysiology potentially amenable to treatment.

3. Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Immune system
 - Neuro-inflammation
 - Cholinergic signaling
 - Mitochondrial health
 - Intracellular calcium signaling
 - The ubiquitin-proteasome intracellular complex
 - Autonomic nervous system function
 - Hippocampal function
 - Fear conditioning
 - A mouse model of motor neuron disease
 - A mouse model of glioblastoma brain cancer
 - Effects of in-utero exposure on post-natal brain development

Gulf War Research: General Principles

4. Integrate findings from experimental studies that characterize effects of Gulf War-related exposures with human studies of Gulf War veterans

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ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- A whole-animal mouse model of delayed effects of repetitive low-dose exposure of pesticide, sarin and pyridostigmine will assess the following at 12 weeks and one year post exposure:
 - Behavioral tests
 - Sleep patterns
 - 24 hour patterns of heart rate variability
 - Auditory evoked potentials (audiovestibular tests)
 - High field (12.5 T) MR spectroscopy for NAA concentrations
 - SPECT before and after cholinergic challenge
 - Other neuroimaging parameters found to be abnormal in GW veterans

Gulf War Research: General Principles

5. Studies of Gulf War illnesses should use well-constructed and clearly-described case definitions for Gulf War-associated multisymptom conditions and illness subsets.

Gulf War Research: General Principles

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ORP Objective #1: National Survey

- **Case definitions of Haley, Steele, Fukuda, Kang, SF-12, CFS, FM(s), MCS, etc.**
- **If Seabees longitudinal study shows substantial change in the illness profile, a new case definition may be developed with validation in split halves of the national sample and twins sample.**

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- **The final sample will be population representative.**
- **The neuroimaging protocols will be tested in pilot studies and in the Seabees sample before study of the population-representative sample.**

Gulf War Research: General Principles

6. Proposals whose principal focus is on psychological stress or psychiatric conditions as the primary cause of Gulf War illnesses should not be considered under this RFP.

Gulf War Research: General Principles

6. Proposals whose principal focus is on psychological stress or psychiatric conditions as the primary cause of Gulf War illnesses should not be considered under this RFP.

ORP Objective #3: Pre-clinical Studies of Effects of Gulf War Exposures on Cells

- **One planned study will assess possible alterations of fear conditioning *caused by* exposure to pesticides, sarin and/or pyridostigmine and combinations.**

Highest Priority Areas of Interest for Gulf War Illness Research (9)

1. Epidemiologic studies of neurological diseases
2. Neuroimaging
3. Biological and genetic predisposition to GW exposures
4. Molecular differences between ill and healthy groups
5. Autonomic function
6. Animal models of effects of GW exposures
7. Inflammatory effects on GW veterans
8. Animal models of effects of GW exposures on inflammatory processes
9. Identification of retained markers of GW exposures

Interest Area 1: Epidemiologic studies of neurological diseases

Epidemiologic studies of rates of diagnosed neurological diseases (e.g., multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, brain cancer)—as well as CNS abnormalities that are difficult to precisely diagnose—in Gulf War veterans and appropriate comparison groups

ORP Objective #1: National Survey

- The survey is powered to study the rates of GW case definitions (difficult to diagnose conditions) and the effects of risk factors within the defined strata.
- The sample will be inadequate to estimate population rates of the diagnosable neurological conditions, but significant relative risks might be obtainable if rates of any of these conditions occur at high rates in certain exposure comparison groups or GW illness subgroups.
- If rates of self-report neurological conditions show epidemiologically important group differences, the diagnoses will be confirmed by medical record review upon recontacting veterans who have given permission to be recontacted.

Interest Area 2: Neuroimaging

Use of state-of-the art neuroimaging and electroencephalography technologies to characterize aspects of brain structure and function that may distinguish ill Gulf War veterans (including illness/exposure subgroups) from healthy veterans

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The testing protocol includes:
 - MR spectroscopy, MRI for volumetrics, DTI, Connectivity, high res. EEG, ESL, SPECT with cholinergic challenge, and fMRI paradigms probing regions/functions thought to be impaired.
 - Neuropsychological testing, brain dopamine turnover, dexamethasone suppression test, autonomic evaluation, quantitative sensory, audiovestibular testing
- Past and ongoing statistical research has identified a new approach to the analysis of brain imaging and EEG data that greatly increases the power to detect subtle group differences in brain structure and function.

Interest Area 3: Biological and genetic predisposition to GW exposures
Studies that investigate biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, for example, associations between Gulf War illnesses and genotype/activity levels of enzymes (e.g. paraoxonase, butyrylcholinesterase, acetylcholinesterase) responsible for uptake and metabolism of Gulf War-related neurotoxic exposures

Interest Area 4: Molecular differences between ill and healthy groups
Studies that utilize new technologies (e.g., proteomic, genomic, and metabolomic methods) capable of characterizing molecular differences between ill Gulf War veterans and healthy comparison groups

ORP Objective #1: National Survey and Serum/DNA Bank

- Blood for banking serum, plasma and DNA collected from all meeting Haley or Steele, random sample of healthy, and seabees and twins (N = 2,064).
 - Paraoxonase and butyryl-cholinesterase serum activity and genotyping
 - (Genomic screening of SNP array being planned)

Interest Area 5: Autonomic function

Comprehensive evaluation of autonomic nervous system function in Gulf War veterans with multisymptom conditions and in illness and/or exposure subgroups

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The testing protocol for the seabees study and the population-representative cases and controls includes:
 - Autonomic evaluation including 24-hour measurement of heart rate variability and the Mayo Clinical battery of clinical neurology tests of autonomic function.

Interest Area 6: Animal models of effects of GW exposures

Studies that characterize molecular, cellular, systemic, and behavioral effects of individual and combined exposures to neurotoxic substances to which Gulf war veterans were exposed during deployment (e.g., pyridostigmine bromide, low-dose chemical agents, pesticides, insect repellants)

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Immune system
 - Neuro-inflammation
 - Cholinergic signaling
 - Mitochondrial health
 - Intracellular calcium signaling
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 - A mouse model of motor neuron disease
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 - Effects of in-utero exposure on post-natal brain development

- A whole-animal mouse model of delayed effects of repetitive low-dose exposure of pesticide, sarin and pyridostigmine will assess the following at 12 weeks and one year post exposure:
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 - High field (12.5 T) MR spectroscopy for NAA concentrations
 - SPECT before and after cholinergic challenge
 - Other neuroimaging parameters found to be abnormal in GW veterans

Interest Area 7: Inflammatory effects on GW veterans

Evaluation of alterations in inflammatory processes in Gulf War veterans affected by multisymptom conditions . . .

- A pilot study of PET study of PK11195 uptake (peripheral dibenzodiazepin receptors) in brain is being conducted in a pair of twins discordant for GW deployment and illness in collaboration with the Johns Hopkins Neuroimaging Center. Since this objective is not yet covered in the Overall Research Plan, this pilot study is being funded by private funds of the UT Southwestern Epidemiology Division.

Interest Area 8: Animal models of effects of GW exposures on inflammatory processes

Experimental studies that characterize persistent effects of Gulf war-related exposures on inflammatory processes and their biological mediators in the central nervous system and other target organs

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Neuro-inflammation

**Interest Area 9: Identification of retained markers of GW exposures
Studies that utilize technologies capable of identifying markers (e.g. retention of toxins, secondary metabolites) that persist after exposure to Gulf War-related compounds individually and in combination**

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- A study to address this objective is being designed but has not yet been approved.

Other Topics of Importance (8)

1. Studies of effects of depleted uranium
2. Studies of birth defects and other effects in children
3. Multivariate modeling in epidemiologic studies
4. Studies of effects of vaccines
5. Studies of CW-exposed populations
6. Studies of effects on immune system
7. Studies of occult infectious diseases
8. Experimental studies of GW exposure effects

Other Topic 1: Studies of effects of depleted uranium

Epidemiologic research utilizing a sample size sufficient to evaluate health outcomes of interest (e.g., rates of symptoms and multisymptom conditions, cancer, reproductive effects) among Gulf War veterans known to have been exposed to depleted uranium in comparison to veterans not exposed to depleted uranium during deployment

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is surveying by telephone random samples 14,754 GW-era veterans, stratified by age, sex, race/ethnicity, active/reserve status, deployment.
- The potential effects of depleted uranium exposure is being assessed by including a special stratum in the sample of units present at Camp Doha during the ammunition explosion and fire—a cohort that should have had the highest DU exposure. Questionnaire items provide the Capstone Study's classification of DU exposure for analysis as a risk factor.
- The sample was powered to assess rates of symptoms and multisymptom conditions.
- If cancer and reproductive effects are highly prevalent in certain subgroups defined by exposures or GW case definitions, there may be adequate power to study them.

Other Topic 2: Studies of birth defects and other effects in children

Use of innovative study designs to evaluate risk of specific types of birth defects or other conditions previously suggested to be elevated among children of Gulf war veterans

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is surveying by telephone random samples 14,754 GW-era veterans, stratified by age, sex, race/ethnicity, active/reserve status, deployment.
- The sample was also powered to study several reproductive effects, including fertility, miscarriage, gender ratios, and learning problems in children, all of which may be prevalent enough to study.
- Information on birth defects is being obtained and will be analyzed in case rates of birth defects are unusually common in certain subgroups defined by exposures or GW case definitions.
- The association of Goldenhar birth defect is being studied by a population-wide case control study, where all Goldenhar cases in era veterans were obtain by a national registry and birth denominators in deployed and nondeployed samples will be estimated from the national survey.

Other Topic 3: Multivariate modeling in epidemiologic studies

Additional utilization of available epidemiologic and clinical data to more clearly characterize associations between illnesses affecting Gulf War veterans and reported or modeled exposures, using analytic methods capable of distinguishing effects of multiple concurrent exposures and combinations of exposures

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is collecting risk factor measures by self report and by objective collateral data sources such as the Unit Location Database.
- Multivariate statistical modeling techniques will be used to assess the associations of concurrent exposures and combinations of exposures.
- Sample weights reflecting the complex stratification design and effects of sample attrition will be used to obtain population estimates of prevalences and risk factor associations.

Other Topic 4: Studies of effects of vaccines

Studies of chronic symptoms and health characteristics of military personnel known to have received individual and combinations of vaccines administered to 1990-91 Gulf War veterans, particularly studies of Gulf War-era veterans for whom reliable vaccine information is available

ORP Objective #1: National Survey and Serum/DNA Bank

- The immunization question set of U.S. Military Health Survey asks veteran participants to find the immunization (shot) record and have it available during the interview. This will allow separate analysis of immunization effects in the subset with shot records, if the group is large enough.

Other Topic 5: Studies of CW-exposed populations

Studies of chronic symptoms and other health characteristics of populations known to have been exposed to chemical weapons

- This is not yet included in the Overall Research Plan, but a study of pesticide-exposed agricultural workers is being planned. Japanese researchers are conducting similar studies Japanese citizens with chronic illness after documented sarin exposure in the 1995 sarin attacks and have obtained findings similar to neuroimaging findings in ill Gulf War veterans (Yamasue et al. *Ann Neurol* 2007).

Other Topic 6: Studies of effects on immune system

Comprehensive evaluation of humoral and cellular immune parameters among Gulf War veterans with multisymptom conditions, including parameters that may differ among illness and/or exposure subgroups

- This is not yet included in the Overall Research Plan, but pending the outcome of the pre-clinical studies of the effects of GW exposures on immunologic systems in mice, studies will be designed and carried out on the serum, plasma and/or DNA being banked from the national survey.

Other Topic 7: Studies of occult infectious diseases

Use of diverse methods, including serological testing, polymerase chain reaction testing, and lymphocyte challenge tests, to determine whether Gulf War veterans with multisymptom conditions are affected by undetected infectious conditions (e.g. leishmaniasis)

- This is not yet included in the Overall Research Plan, but this is a likely objective for use of serum, plasma and/or DNA being banked from the national survey or future data collection projects (e.g., biomarker study of 80 population-representative sample).

Other Topic 8: Experimental studies of GW exposure effects

Experimental studies that characterize molecular, cellular, systemic, and behavioral effects of compounds to which Gulf war veterans were exposed (e.g., individual and multiple vaccine combinations, depleted uranium, oil fire smoke, jet fuel) individually, and in combination with other exposures of potential concern

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
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VA Research Advisory Committee ***Research Priorities –January 2006***

Gulf War Research: General Principles

Presently addressing 6 of 6

Highest Priority Areas of Interest for Gulf War Illness Research

Presently addressing 9 of 9

Other Topics of Importance

Presently addressing 5 of 8

