



SPECIAL ASSISTANT  
FOR  
GULF WAR ILLNESSES

OFFICE OF THE SECRETARY OF DEFENSE  
1000 DEFENSE PENTAGON  
WASHINGTON, DC 20301-1000

Admiral (Ret) Elmo R. Zumwalt  
1000 Wilson Boulevard, Suite 3105  
Arlington, VA 22209-3901

OCT 05 1999

Dear Admiral Zumwalt:

Enclosed for your use and reference is a copy of the recently completed RAND report on pyridostigmine bromide. Please treat this report as embargoed until its release on Tuesday, October 19, at the regularly scheduled Pentagon press briefing. In addition, we plan to meet with members of veterans and military service organizations that morning to provide information and answer questions.

This report provides a serious, independent review of the possible medical consequences associated with pyridostigmine bromide. We believe it also establishes a firm foundation for further work by the Institute of Medicine.

In response to the author's call for research, my staff compared the federally funded research projects on pyridostigmine bromide with the hypotheses posed by the author. We found that many of the projects underway are responsive to the recommendations; a few are complete. A listing of the author's hypotheses identified with the associated study projects is enclosed for your reference.

Please contact me or my staff if you have any questions or comments.

Sincerely,

A handwritten signature in cursive script, appearing to read "Bernard Rostker".

Bernard Rostker

Enclosures

### Federally Funded Research Projects on Pyridostigmine Bromide (PB)

#### Hypothesis 1: Stress and the Blood Brain Barrier

<u>Project #</u>	<u>Title</u>	<u>Researcher</u>	<u>Budget ( with Projected FY-99)</u>	<u>Start and Estimated Completion</u>	<u>Summary</u>
DoD-62	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice	Dr. Satu Somani	\$201,000	1997 - 1999	Effects of stress on the neurotoxic effects of PB and Sarin Exposure
DoD-59	Pyridostigmine-Induced Neurodegeneration: Role of Neuronal Apoptosis	Dr. Gary Isom	\$625,000	1997 - 2000	Neurotoxic response to PB
DoD-64	Individual Differences in Neurobehavioral Effects of Pyridostigmine	Dr. Mary Cook	\$1,918,516	1997 - 2001	Use of PB as a defense-agent
DoD-79	Time Course of Stress-induced Impairment of Blood Brain Barrier	Dr. G.J. Kant	\$100,200	? - 2000	Does PB access the blood brain barrier due to stress

#### Hypothesis 2: Individual Susceptibility

VA-5D	Effects of Genetics and Stress on Responses to Environmental Toxins	Dr. John Ottenweller	\$2,600,000 (Section of 5 Part Study)	1994 - 1997	Genetic susceptibility to stress & the toxic effects of PB - Concluded genetic susceptibility rats are more susceptible to some PB effects
DoD-11	Male/Female Differential Tolerances to Pyridostigmine Bromide	Dr. Kenneth Lasseter	\$908,000	1994 - 1998	Male/Female tolerances to PB - Concluded No gender differences
DoD-65	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment	Dr. Robert Haley	\$3,000,000	1994 - 2002	Demonstrate the specific sites and nature of neurological damage associated with symptoms comprising the case definition
DoD-21	Study of Variability in Pyridostigmine Inhibition of Blood Cholinesterases in Health Adults and Individuals with Symptoms Following Participation in Operation Desert Storm	Dr. Bhupendra Doctor	\$138,000	1995 - 1997	Differences in Blood Cholinesterase due to PB- Concluded no difference in deployed/nondeployed
DoD-60	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness	Dr. Oksana Lockridge	\$125,000	1997 - 1999	To test if Gulf War Illness is caused by chemical damage to the nerves
VA-49	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction	Dr. Richard Servatius	\$197,700	1998 - 2002	Long-term Effects of PB on Physiology/Behavior

**Hypothesis 3: Interactions**

DoD-10	Pyridostigmine Synergistic Toxicity Study	Dr. Wildred McCain	\$86,000	1994 - 1994	Toxic interactions of PB, DEET, & permethrin - Concluded toxic in extraordinarily high doses
DoD-2	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET	Dr. J. Rossi	\$90,000	1994 - 1997	Multiple Exposure to PB/Fuels/DEET - Concluded differences only when exposed to JP4 Fuel
DoD-33	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity	Dr. David Overstreet	\$354,000	1996 - 1999	Effects of acute and chronically administered PB
DoD-37	Neurobehavioral and Immunological Toxicity or Pyridostigmine, Permethrin, and DEET in Male and Female Rats	Dr. Frans van Haaren	\$939,000	1996 - 1999	Neurobehavioral toxicity and immune response produced by PB and insecticides
DoD-62	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice	Dr. Satu Somani	\$201,000	1997 - 1999	Effects of stress on the neurotoxic effects of PB and Sarin Exposure
DoD-54	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats	Dr. Carl Olson	\$415,000	1997 - 1999	Effect of low-level GB exposure on possible toxic effects produced by other chemicals, especially chemicals that have a mechanism of action similar to that of GB
DoD-61	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid	Dr. Carl Olson	\$1,586,000	1997 - 2000	Effect of low-level GB exposure on toxic effects from other chemicals/PB
DoD-55	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed effects	Dr. Herman vanHelden		1997 - 2000	Investigate the relationship between C.t-values, internal dose and adverse effects on performance in animals which will be exposed to low levels of sarin (GB)
DoD-56	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine	Dr. Barry Wilson	\$785,000	1997 - 2001	Long-term effects of low-level chemical exposures in the presence/absence of PB

DoD-72	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals	Dr. M. Abou-Donia	\$996,000	? - 2000	Examine, in an animal model, the early and delayed toxic consequences of subclinical sarin exposure given intramuscularly
DoD-81	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress	Dr. Gary Gilkeson	\$300,000	? - 2001	Exposure to DEET, PB and Stress
DoD-76	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel	Dr. Jim Riviere	\$448,369	? - 2002	Absorption and toxicity of exposure to DEET/PB/JP-8 Fuel
DoD-77	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War	Dr. Jim E. Riviere	\$760,031	? - 2002	Quantitate the dermal absorption and cutaneous toxicity of chemical mixtures that veterans may have been exposed to during the Persian Gulf War
DoD-78	Experimental Models of Gulf War Syndrome	Dr. Hugh Evans	\$2,179,097	? - 2002	Experimental models with laboratory animals to identify possible causes and therapies for the "Gulf War Syndrome"
DoD-75	Toxic Interactions of Prophylactic Drugs and Pesticides	Dr. M. About-Donia	\$1,380,157	? - 2003	Interactive effects and mechanisms of combined exposure to three compounds: pyridostigmine bromide (PB); DEET; and the insecticide permethrin
<b>Hypothesis 4: Bromism</b>					
no current research					
<b>Hypothesis 5: Multiple Chemical Sensitivity</b>					
several MCS studies but nothing related to PB					
<b>Hypothesis 6: Neuromuscular Junctions</b>					
A-6C	Neurotoxicity of Environmental Pollutants and Warfare Agents	Dr. Rosemarie Drake-Baumann	\$2,096,681 (1 section of 6 part study)	1994 - 1999	Long-term Exposure to PB
<b>Hypothesis 7: Abnormal regulation of ACh</b>					
no current research					
<b>DA application (DoD-17) does not fit the 7 hypotheses</b>					

DoD-17	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning	LTC Mary Burman	N/A	1991 - 1992	3 Survey Study - Concluded PB is Safe
--------	--	-----------------	-----	-------------	---------------------------------------