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PRINCIPAL INVESTIGATOR: Richard F. Seegal, Ph.D.

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Rensselaer, New York 12144

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13. ABSTRACT (Maximum 200 Words)

The major hypothesis is that prior occupational exposure to polychlorinated biphenyls (PCBs) results in decrements in neuropsychological and neurological performance and that these deficits are related to reductions in the number of dopamine (DA) terminals in the basal ganglia. In Albany, NY 248 former capacitor workers (62 per year) will undergo neuropsychological and neurological examinations, complete a comprehensive questionnaire, have blood drawn to measure serum thyroid hormone and PCB concentrations, and undergo a non-invasive test to determine bone-lead concentrations. This latter measure will allow us to control for exposure to lead--a potential confounder. In New Haven, CT 96 subjects (24 subjects per year) will be asked to undergo brain imaging at the Institute for Neurodegenerative Disorders to determine if PCBs reduce the number of basal ganglia DA terminals. To date, 129 subjects have undergone testing in Albany and 39 have been imaged in New Haven, CT with an additional nine subjects scheduled for testing. Serum PCB concentrations are being analyzed at Mt. Sinai School of Medicine. Secure electronic databases have been created for all data. We anticipate no problems in continuing to recruit and test the number of subjects needed for studies in both Albany and New Haven to reach our annual goals.

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INTRODUCTION

The major hypotheses to be tested in this project are that high-level occupational exposure of former capacitor workers to polychlorinated biphenyls (PCBs) will result in reductions in (i) performance on neuropsychological and neurological tests that reflect the historic PCB body burden of the individual; (ii) the number of dopamine (DA) terminals in the basal ganglia that correlate with behavioral change and (iii) circulating levels of thyroid hormones.

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY, are undergoing neuropsychological and neurological exams, completing a comprehensive occupational, residential and dietary questionnaire, having blood drawn to measure serum thyroid hormone and PCB concentrations, and undergoing a non-invasive test to determine bone lead concentrations in Albany, NY. This latter measure will reduce the likelihood of confounding the neurological effects of prior PCB exposure with the neurological effects of prior lead exposure. Finally, approximately 40% of the subjects are also participating in a second portion of the study that uses brain β-CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging takes place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

In order to test the above hypotheses we have gathered a team of internationally recognized experts in the epidemiology of environmental and occupational exposure to PCBs, the neurology of movement disorders and Parkinson's Disease, the assessment of toxicant-induced deficits in neuropsychological function, measurement of serum PCB concentrations, non-invasive determination of bone lead concentrations, and brain imaging of central dopamine neurons and their relationship to movement disorders, including Parkinson's Disease.

STUDY INVESTIGATORS

Albany, NY Based Testing

Richard F. Seegal - Wadsworth Center, New York Sate Dept. of Health (NYSDOH): Principal Investigator

Edward F. Fitzgerald, Lenore J. Gensburg - Center for Environmental Health, NYSDOH Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

Stewart A. Factor, Eric S. Molho - Albany Medical Center: Neurological Assessment

Robert J. McCaffrey - University at Albany: Neuropsychological Assessment

Richard F. Haase - University at Albany: Biostatistician

Mary S. Wolff - Mount Sinai School of Medicine: Serum PCB Analyses

Andrew S. Todd - Mount Sinai School of Medicine: Bone Lead Determination

Patrick Parsons - Wadsworth Center, NYSDOH: Bone Lead Determination

New Haven, CT Based Testing

Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders: ß-CIT SPECT Brain Imaging

What has Changed This Year?

Personnel

There have been several changes during the last year. Nevertheless, we have been fortunate in finding highly talented individuals to replace those who have left—resulting in neither a loss of time nor a reduction in the number of subjects who have undergone testing.

Dr. Factor will shortly be leaving Albany to become Director of the Movement Disorder Clinic at Emory University. Dr. Donald Higgins, also a Parkinson's disease neurologist at the Parkinson's Disease and Movement Disorders Center of Albany Medical Center, will contribute his expertise to the project (see Appendix 1 for a copy of his curriculum vita).

Dr. Edward Fitzgerald continues to contribute to this project, but has moved from the Center for Environmental Health of the New York State Department to the Department of Epidemiology and Biostatistics of the University of Albany. His change of institutions, but not cities, was motivated by his desire to devote a larger portion of his efforts to research, including this project.

Ms. Gwen Mergian, the Study Coordinator, resigned and has been replaced with Ms. Sue Heckman, who previously carried out the bone lead measurements.

Ms. Lakhana Weaver has been hired (50% effort) to carry out the bone lead measurements previously conducted by Ms. Heckman.

We Are Collecting Sera for Analysis of Thyroid Hormone Function

A study of electrical workers at the La Salle Electrical Utilities Company in La Salle Illinois (Final Report to the Agency for Toxic Substances Disease Registry, May 2002) demonstrated altered thyroid hormone function following exposure to PCBs at levels similar to those seen in our subjects. We decided, based on the fact that altered thyroid hormone function may affect some of our measures, to also determine if circulating levels of thyroid hormones are altered in workers in our study.

We received IRB approval to begin collecting an additional tube of blood from each subject (one tube is for analysis of serum PCB concentrations) in order to determine T_3, T_4 and free TSH levels. We have presently collected an additional blood sample from 48 subjects. We will, in this fiscal year, request modification of the Statement of Work (SOW) and additional monies to carry out the above described analyses.

We Have Modified Our Procedures for Selecting Subjects for Inclusion in the Study

Until recently, we randomly selected subjects from computer lists that contain the names and addresses of all individuals who worked for at least three months at either the Ft. Edward or Hudson Falls, NY capacitor plants. However, examination of job description codes for prospective subjects who had not participated in the earlier study by scientists from Mt. Sinai Medical Center (*i.e.,* those with archived sera) demonstrated that approximately $1/3^{rd}$ of the subjects did not have any jobs that involved exposure to PCBs. In order to increase the likelihood that future subjects will be drawn from a sub-population of exposed workers, we have decided to limit subject recruitment to those individuals whose job codes indicate past exposure to PCBs. This approach, although different from that described in the initial application, will allow us to more adequately

address the question of whether high level exposure to PCBs alters behavior and brain dopamine function.

Progress in Fiscal Year 2004

The following narrative provides descriptions of the progress we have made in the third year of the project—a period in which we have been actively engaged in data collection.

We Have Succeeded Our Goal for Recruiting and Testing Subjects in 2004

In the past year we successfully recruited and tested sixty-seven subjects in Albany, NY. As of 23 December 2004 we have tested a total of 129 subjects with ten additional subjects still scheduled, and are thus on schedule (Table I). See also Appendix 2 for a summary of the demographics for the tracing and screening activity to date. The tests conducted in Albany include: (i) administering a residential, occupational, dietary and medical history interview; (ii) completing neurological and neuropsychological assessments; (iii) measuring bone lead concentrations and (iv) collecting blood for measurement of serum thyroid hormone and PCB concentrations.

TABLE I: Albany, NY Testing, Potential Subjects as of 24 Dec '04
n=297 (22 still in recruitment)

	YES: 139 129 Complete and 10 Scheduled		NO: 136	
GENDER				
Male	94	67.63%	74	54.41%
Female	45	32.37%	62	45.59%
AGE				
50s	54	38.85%	49	36.03%
60s	43	30.94%	30	22.06%
70s	34	24.46%	40	29.41%
80-90s	8	5.76%	17	12.50%

At completion of testing in Albany, subjects were asked if they wished to participate in the SPECT β-CIT imaging portion of the study carried out by Dr. Marek's group at the Institute for Neurodegenerative Disorders in New Haven, CT. Despite the fact that these procedures required a two day stay in New Haven and the injection of a radio-labeled tracer, we have met our goal of testing 24 subjects per year. These data are presented in Table II.

During the past year we completed testing subjects who had participated in earlier studies conducted by investigators from the Mt. Sinai School of Medicine in the late 1970's and early 1980's (*i.e.* those individuals with archived sera). Those individuals are important because we have access to their archived serum, and comparisons of current and archived serum PCB concentrations, will allow us to 'fine-tune' the algorithms needed to estimate historic serum PCB concentrations for the subjects for whom we do not have archived sera. Summary data for those subjects are presented in Appendix 3.

TABLE II: New Haven, CT Testing, Potential Subjects as of 24 Dec '04
Subjects n=129 (35 still in recruitment)

	YES: 48 39 Complete and 9 Scheduled		NO: 46	
GENDER				
Male	34	70.83%	31	67.39%
Female	14	29.17%	15	32.61%
AGE				
50s	20	41.67%	11	23.91%
60s	18	37.50%	11	23.91%
70s	9	18.75%	19	41.30%
80-90s	1	2.08%	5	10.87%

We have also begun tracing, screening and testing of subjects who had not been previously tested by investigators at Mt. Sinai in the late 1970's and early 1980's (*i.e.*, non-archived individuals). Table III provides a description of those individuals who were traced, screened and recruited. Tracing refers to the procedures carried out to identify and locate individuals who potentially could take part in the study, while screening refers to the procedures carried out by staff at the Center for Environmental Health (a part of the New York State Department of Health) to determine if the individuals are medically eligible. If found eligible, the subjects' names were sent to the Study Coordinator, who contacted them to more completely describe the test protocols and schedule their visits to Albany.

TABLE III: Subjects from Non-Archived Sera Cohort as of 24 Dec '04 (n=6488)

Tracing Results	**Entered Tracing: 1400**	
Dead	413	29.50%
Out of Area	163	11.64%
Too Young	1	0.07%
Could not be Located	17	1.21%
Eligible for Screening	**512**	**36.57%**
Still in Tracing	294	21.00%
Screening Results	**Entered Screening: 512**	
Refused	87	16.89%
Medically Ineligible	154	30.08%
Eligible for Recruitment	**205**	**40.04%**
Still in Screening	66	12.89%
Albany Testing: Recruitment Results	**Entered Recruitment: 205**	
Participated	89	43.41%
Refused	94	45.85%
Still in Recruitment	22	10.73%
New Haven Testing: Recruitment Results	**Entered Recruitment: 89**	
Participated	23	25.84%
Refused	24	26.97%
Still in Recruitment	42	47.19%

Table IV provides a summary on those subjects who have either agreed or refused to participate in the study as of 24 December 2004.

TABLE IV: Summary of Subject Participation in Albany, NY and New Haven, CT Portions of the Study from Inception to 24 Dec '04

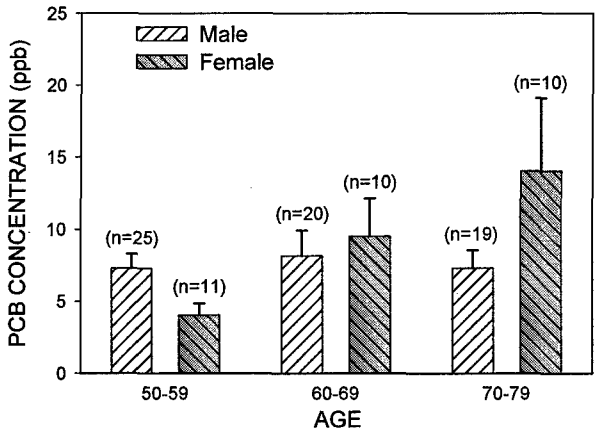
	Archived Sera Cohort (N=310)		Non-Archived Sera Cohort (N=6488)		All Subjects	
Albany Participation						
Yes, Participated	51	55%	78	38%	129	43%
Yes, Scheduled	0		10	5%	10	3%
To Be Contacted/Recruit Later	0		22	11%	22	7%
Refused	41	45%	95	46%	136	46%
TOTAL	**92**	**100%**	**205**	**100%**	**297**	**100%**
New Haven Participation						
Yes, Participated	23	45%	16	21%	39	30%
Yes, Scheduled	0		9	11%	9	7%
To Be Contacted/Recruit Later	6	12%	29	37%	35	27%
Refused	22	43%	24	31%	46	36%
TOTAL	**51**	**100%**	**78**	**100%**	**129**	**100%**

Measurement of Serum PCB Concentrations

Dr. Mary Wolf, of the Mt. Sinai School of Medicine, is analyzing serum PCB concentrations from the former capacitor workers using glass capillary gas chromatographic techniques. Data includes not only congener specific determination of current serum PCB concentrations, obtained when the subjects travel to Albany, but also, for those individuals for whom we have archived sera, reanalysis using the same analytical procedures described in the grant application. The availability of both current and archived sera PCB levels, determined in the same laboratory using the same analytical techniques, allows us to more precisely estimate historic serum PCB levels for those individuals for whom we do not have archived sera.

The data presented below represents PCB analyses from 102 individuals broken down by age (decade) and gender. It is noteworthy that the serum PCB levels remain elevated (average PCB levels in non-occupationally-exposed individuals are approximately 2-3 ppb) more than twenty-five years after occupational exposure ceased. Although we chose to present only total PCB concentrations (a sum of lightly and heavily chlorinated congeners), subsequent analyses, particularly for levels of lightly chlorinated congeners that have short half-lives, will allow us to discriminate between occupational and more recent recreational and/or residential exposures.

Figure 1. Total Current Serum PCB Levels (mean ± sem)



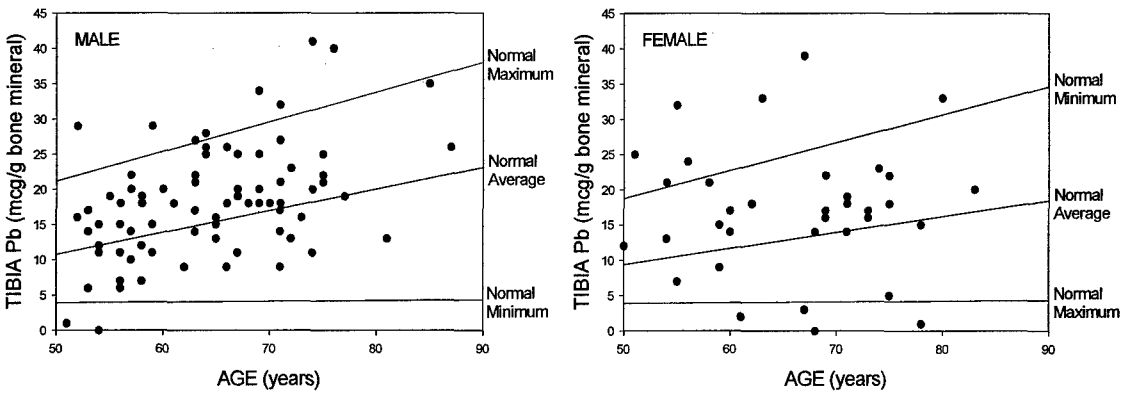
Measurement of Bone Lead Concentrations by K-Shell X-Ray Fluoresence

Mount Sinai supervised the *in vivo* measurement of lead in bone in Albany and analyzed the raw data (in electronic form) generated with the bone lead measurement system. Mount Sinai personnel also continued to provide consultation on all aspects of the X-ray Fluorescence bone lead measurement system, including regular and *ad hoc* consultation, as required, on the quality of spectra acquired, the control and use of the measurement system and the reliability of the analytical results in order to provide both the most precise and the most reliable bone-lead data possible.

Mount Sinai personnel also supervised the Albany XRF operators in the daily operation of the XRF measurement system with regard to its maintenance, calibration, optimization and quality control protocol and have provided expertise on the optimization of the measurement system with regard to operational parameters of the spectroscopy electronics (*viz.* rise time, flat-top, *etc.*).

All calibration and human measurement XRF data have been electronically transmitted to the Mount Sinai XRF Laboratory for analysis. The analyses of the data received to date have been completed. Analyses of new data are being performed as they arrive. To date, sixty study participants have had their bone lead measured and analyzed. These bone lead data are presented below.

Figure 2. Tibia Lead (Pb) Concentrations by Age and Gender



The range of values for 'maximum' and 'minimum' are based on data from 13-16 studies of XRF measurement of bone lead concentrations obtained from non-occupationally-exposed men and women (Roy *et al.*, *Appl. Radiat. Isotopes*, 48, 391-6, 1997; Gamblin *et al.*, *Appl. Radiat. Isotopes*, 45, 1035-8, 1994) and are presented here to provide a framework in which to begin to interpret the concentrations of bone lead we have determined in the former capacitor workers.

Investigators Meetings

In order to facilitate communication between these individuals who are located at the different institutions in Albany, we have met five times during the past year (March 9th, May 4th, June 4th, September 21st and December 7th). These meetings have proven to be extremely useful and allow us to avoid many of the pitfalls that might otherwise occur in the conduct of this complicated multi-institutional epidemiological study. Topics discussed included how to best report results to subjects' physicians if abnormal neurological and neuropsychological deficits are seen; issues of confidentiality and database development for reporting results for statistical analyses.

In June of last year a meeting was held in Albany that included all investigators from Albany and New Haven, as well as the epidemiology consultants, to present data that had been collected up to that time and discuss issues related to changing the procedures for identifying and testing future subjects.

KEY RESEARCH ACCOMPLISHMENTS

As in all epidemiological studies, presentation of interim results prior to the collection of the entire data set and the accompanying statistical analyses to control for potential confounders is at best misleading and at worse may result in conclusions that are fallacious. Hence, the key research accomplishments are those described in the above sections.

REPORTABLE OUTCOMES

Two abstracts that included data from this study were presented during the past year at scientific conferences. The first, entitled 'Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function' was presented in February 2004 at the Twenty-First International Neurotoxicology Conference in Honolulu, HI and the second, entitled 'PCBs, Dopamine and Cell-Death - Relevance to Human Exposure' was presented in September 2004 at the Superfund Basic Research Program Conference 'Persistent Contaminants: New Priorities, New Concerns' in Bear Mountain, NY (see Appendix 4).

CONCLUSIONS

For the second year we have met our goal for recruiting and testing subjects, both in Albany, NY and in New Haven, CT. We are proud of this progress since many of our subjects are elderly (median age = 65 years) and must travel considerable distances to undergo testing at these two sites.

We are at the mid-point in the testing of subjects (to date we have tested 129 subjects; our goal is to test 248 subjects) and can now begin to carefully review the data to determine initial trends. For example, a review of the job histories of the most recently recruited subjects indicates a need to move from random selection of subjects to a recruitment procedure that emphasizes selection of the more heavily exposed subjects. We have begun this new selection process and will continue to do so for the remaining tenure of the grant.

We have shown that current serum PCB levels are significantly elevated in former capacitor workers compared to literature values for non-occupationally exposed individuals. These findings demonstrate, given the many years since occupational exposure ceased, the extraordinarily high levels of PCBs to which these workers had been exposed.

Finally, we will begin determining whether occupational exposure has altered thyroid hormone function in these workers and use that information to statistically determine the contributions of endocrine disruption in addition to those hypothesized to occur following reductions in central dopamine function.

APPENDICES

Appendix 1: Curriculum Vita for Dr. Donald S. Higgins, Jr.

Appendix 2: Demographic Outcomes for Tracing and Screening Activity to Date.

Appendix 3: Summary of Participation for the Archived Sera Cohort.

Appendix 4: Abstracts from the International Neurotoxicology Conference, Honolulu, HI, February 2004 and the Superfund Basic Research Program Conference, Bear Mountain, NY, September 2004.

APPENDIX 1

Curriculum Vita for Dr. Donald S. Higgins, Jr.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Higgins, Donald S. Jr.	Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Illinois Wesleyan University, Bloomington, IL	B.A.	1982	Biology/Chemistry
SUNY at Stony Brook, Stony Brook, NY	M.D.	1987	Medicine
The University of Michigan, Ann Arbor, MI	Intern	1988	Internal Medicine
The University of Michigan, Ann Arbor, MI	Fellow	1989	Neuroscience
The University of Michigan, Ann Arbor, MI	Resident	1992	Neurology
The University of Rochester, Rochester, NY	Fellow	1994	Movement Disorders

A. Positions and Honors

EMPLOYMENT

1994-1995	Senior Instructor, Department of Neurology, The University of Rochester
1995-2000	Assistant Professor, Department of Neurology, The Ohio State University
1998-2000	Assistant Professor, Department of Neuroscience, The Ohio State University
2000-	Associate Professor, Department of Neurology, Albany Medical College
2000-	Associate Professor, Center for Neuropharmacology and Neuroscience, Albany Medical College

HONORS

1983	Research Fellowship, Parkinson Disease Foundation, Columbia University
1988-1989	National Research Service Award (NS07222), The University of Michigan
1992	Notter Neuroscience Research Award, The University of Rochester
1992-1994	National Research Service Award (AG00107), The University of Rochester
1993	Travel Fellowship, American Neurological Association
2002	Distinguished Leader Award, Central Ohio Chapter, Huntington Disease Society of America

SERVICE

1997-	Member, Editorial Board, Hospital Physician
1998	Clinical Sciences Special Emphasis Panel (ZRG1 SSS-G-05), Center for Scientific Review (CSR)
2000-2002	Member, Human Subjects Committee, Albany Medical College
2001	Member, Nominating Committee, Huntington Study Group
2000-	Member, Grants Review Subcommittee, Huntington's Disease Society of America
2004-	Temporary Member, Behavioral Medicine, Interventions and Outcomes Study Section, CSR
2004-	Member, Center Program and Education Advisory Committee, HDSA
2004-	Member, Clinical Protocol Working Group, Gene Therapy in Parkinson Disease

B. Selected peer-review publications (in chronological order)

1. Greenamyre, JT, Higgins, DS, Young, AB, Sodium dependent d-aspartate 'binding' is not a measure of presynaptic neuronal uptake sites in an autoradiographic assay, Brain Res 511: 310-318, 1990
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13. Hoyt, KR, McLaughlin, BA, Higgins, DS, Reynolds, IJ, Inhibition of glutamate-induced mitochondrial depolarization by tamoxifen in cultured neurons, JPET 293(2): 480-486, 2000
14. Talpade, DJ, Green, JG, Higgins, DS, Greenamyre, JT, In vivo labeling of mitochondrial complex I (NADH:ubiquinone oxidoreductase) in rat brain using [^{3}H]dihydrorotenone, J Neurochem 75(6): 2611-2621, 2000
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C. Research Support

ACTIVE

1 R01 NS40767-A01 (Shoulson – P.I.) 07/01/2002-06/30/2007
NIH; NHGRI, NINDS
Prospective Huntington At Risk Observational Study (PHAROS)
An observational study to prospectively determine, in a double-blinded controlled fashion, the rate of illness onset (phenoconversion) in individuals who are at immediate risk for inheriting the HD gene and who are unaware and wish to remain unaware of their HD gene status.
Role: Site Investigator

(Marshall – P.I.) 04/01/2003-03/31/2005
Prestwick Pharmaceuticals, Inc.
Tetrabenazine in Huntington's Disease (TETRA-HD)
A multicenter, placebo-controlled, safety, tolerability, dose-finding, and efficacy trial of tetrabenazine, an inhibitor of the vesicular monoamine transporter type 2 gene (VMAT2), in ambulatory HD patients.
Role: Site Investigator

(Higgins – P.I.) 07/01/2003 - 06/30/2005
Community Foundation for the Capital Region
Incorporation of Rehabilitation and Social Work into a Multidisciplinary Clinic for Huntington Disease
Prospective assessment of physical therapy, occupational therapy and social work services in Huntington disease.
Role: Principal Investigator

(Higgins – P.I.) 03/01/2004 – 06/30/2005
Pfizer Pharmaceuticals
Double-Blind, Placebo-Controlled Evaluation of Donepezil in the Management of Tourette Syndrome
Examination of cholinesterase inhibition as tic suppressant.
Role: Principal Investigator

(Higgins – P.I.) 03/01/2005 – 09/30/2006
Janssen Pharmaceuticals
Pilot Examination of Galantamine in the Management of Tic Disorders
Examination of cholinesterase inhibitor as therapy for tics.
Role: Principal Investigator

OVERLAP

There is no scientific overlap

APPENDIX 2

Demographic Outcomes for Tracing and Screening Activity to Date

	GROUP 1: Potential Subjects with Archived Sera		GROUP 2: Potential Subjects without Archived Sera	
	Traced to Date: 310		Traced to Date: 1106	
	n	%	n	%
DEMOGRAPHICS: OVERVIEW				
Sex				
Female	146	47.10%	446	40.33%
Male	164	52.90%	660	59.67%
Agegroup				
40s	0	0.00%	1	0.09%
50s	53	17.10%	261	23.60%
60s	55	17.74%	203	18.35%
70s	92	29.68%	270	24.41%
80s+	110	35.48%	370	33.45%
Unknown	0	0.00%	1	0.09%
DEMOGRAPHICS: BY TRACING OUTCOME				
Sex	Eligible for Screening (n=192)		Eligible for Screening (n=512)	
Female	89	46.35%	220	42.97%
Male	103	53.65%	292	57.03%
	Not Eligible for Screening (n=118)		Not Eligible for Screening (n=594)	
Female	57	48.31%	226	38.05%
Male	61	51.69%	368	61.95%
Agegroup	Eligible for Screening (n=192)		Eligible for Screening (n=512)	
40s	0	0.00%	0	0.00%
50s	45	23.44%	182	35.55%
60s	41	21.35%	130	25.39%
70s	61	31.77%	133	25.98%
80s+	45	23.44%	67	13.09%
Unknown	0	0.00%	0	0.00%
	Not Eligible for Screening (n=118)		Not Eligible for Screening (n=594)	
40s	0	0.00%	1	0.17%
50s	8	6.78%	79	13.30%
60s	14	11.86%	73	12.29%
70s	31	26.27%	137	23.06%
80s+	65	55.08%	303	51.01%
Unknown	0	0.00%	1	0.17%

All results updated 12/24/04.

	GROUP 1: Potential Subjects with Archived Sera		GROUP 2: Potential Subjects without Archived Sera	
	Traced to Date: 310		Traced to Date: 1106	
	n	%	n	%

DEMOGRAPHICS: BY SCREENING OUTCOME

Sex	Refused (n=40)		Refused (n=87)	
Female	26	65.00%	41	47.13%
Male	14	35.00%	46	52.87%
	Medically Ineligible (n=60)		Medically Ineligible (n=154)	
Female	27	45.00%	80	51.95%
Male	33	55.00%	74	48.05%
	Passed to Recruitment (n=92)		Passed to Recruitment (n=205)	
Female	36	39.13%	78	38.05%
Male	56	60.87%	127	61.95%
Agegroup	Refused (n=40)		Refused (n=87)	
40s	0	0.00%	0	0.00%
50s	6	15.00%	30	34.48%
60s	7	17.50%	19	21.84%
70s	12	30.00%	23	26.44%
80s+	15	37.50%	15	17.24%
	Medically Ineligible (n=60)		Medically Ineligible (n=154)	
40s	0	0.00%	0	0.00%
50s	12	20.00%	42	27.27%
60s	13	21.67%	42	27.27%
70s	18	30.00%	41	26.62%
80s+	17	28.33%	29	18.83%
	Passed to Recruitment (n=92)		Passed to Recruitment (n=205)	
40s	0	0.00%	0	0.00%
50s	27	29.35%	77	37.56%
60s	21	22.83%	58	28.29%
70s	31	33.70%	50	24.39%
80s+	13	14.13%	20	9.76%

All results updated 12/24/04.

APPENDIX 3

Summary of Participation for the Archived Sera Cohort

Participation Results from Archived Sera Cohort as of 24 Dec '04 (n=310)

Tracing Results	Entered Tracing: 310	
Dead	97	31.29%
Out of Area	21	6.77%
Too Young	0	0%
Could not be Located	0	0%
Eligible for Screening	**192**	**61.94%**
Still in Tracing	0	0%

Screening Results	Entered Screening: 192	
Refused	40	20.83%
Medically Ineligible	60	31.25%
Eligible for Recruitment	**92**	**47.92%**
Still in Screening	0	0%

Albany Testing: Recruitment Results	Entered Recruitment: 92	
Participated	51	55.43%
Refused	41	44.57%
Still in Recruitment	0	0%

New Haven Testing: Recruitment Results	Entered Recruitment: 51	
Participated	23	45.10%
Refused	22	43.14%
Still in Recruitment	6	11.76%

APPENDIX 4

Abstracts from
International Neurotoxicology Conference,
Honolulu, HI, February 2004 and
Superfund Basic Research Program Conference,
Bear Mountain, NY, September 2004

INTERNATIONAL NEUROTOXICOLOGY CONFERENCE 2004

Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function. RF Seegal[1], KL Marek[2], SA Factor[3], RJ McCaffrey[4], RF Haase[4] and AG Kanthasamy[5]. [1]Wadsworth Center, New York State Dept. of Health, Albany, NY; [2]Institute for Neurodegenerative Disorders, New Haven, CT; [3]Albany Medical Center, Albany, NY; [4]University at Albany, Albany, NY and [5]Iowa State University, Ames, IA.

PCBs reduce dopamine (DA) concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra of adult rodents and nonhuman primates (NHPs). This loss of function may involve inhibition of monoamine transporters, including the vesicular monoamine transporter, consequent metabolism of cytosolic DA, induction of oxidative stress and apoptosis. Indeed, in a midbrain DA cell line (N27), PCBs induce oxidative stress to a greater extent than MPP+. In order to determine whether these findings induce similar changes in humans we are studying the behavioral and structural consequences of prior long term high level exposure to PCBs in a cohort of former workers. This epidemiological study will determine if prior PCB exposure alters DA mediated behaviors, including motor function, memory and neurological function and the number of DA terminals in the basal ganglia, determined using β-CIT SPECT imaging. This epidemiological study will allow us to begin to determine whether laboratory data demonstrating the neurotoxicity of PCBs can be extrapolated to humans and may provide additional evidence concerning the role of environmental neurotoxicants in the etiology of parkinsonism (*e.g.,* dioxins and furans) on human DA function, including Parkinson's disease. Supported by grants from the US Army Medical Research and Materiel Command, NIEHS and EPA to RFS, and NIH to AGK.

SUPERFUND BASIC RESEARCH PROGRAM CONFERENCE 2004

PCBs, Dopamine and Cell Death - Relevance to Human Exposures? R.F. Seegal[1,2], A. Dreiem[1], G. Lyng[2] and AG Kanthasamy[3]. [1]Wadsworth Center, NYSDOH; [2]School of Public Health, University at Albany, Albany, NY and [3]Iowa State University, Ames, IA.

Although many epidemiological studies suggest an association between developmental exposure to polychlorinated biphenyls (PCBs) and behavioral deficits in infants and children, recent studies carried out in adults have also found an association between PCB exposure and behavioral change. Although the mechanisms for these deficits remain largely unknown, recent evidence from *in-vitro* laboratory studies of neurons in culture, as well as *in-vivo* studies of adult non-human primates (NHPs), demonstrate that PCBs alter dopamine (DA) function and neuronal viability in the mature central nervous system and may thus contribute to the aforementioned changes in behavior.

PCBs are potent inhibitors of monoamine transporters, including the vesicular monoamine transporter (VMAT) responsible for the sequestration of cytosolic DA. In turn, elevations in free cytosolic DA, due to VMAT inhibition, lead to formation of hydrogen peroxide and reactive quinones and semi-quinones. PCBs also induce reactive oxygen species and apoptotic neuronal death in a rat mid-brain dopaminergic cell line that can be inhibited by superoxide dismutase mimetics and caspase inhibitors. These *in-vitro* mechanisms may aid in explaining the long-term reductions in striatal DA concentrations and the number of DA-containing neurons seen in the basal ganglia of NHPs following long-term exposure to PCBs.

In order to determine whether similar changes occur in humans we are studying the neurological consequences of prior long-term high level exposure to PCBs in a cohort of former workers. This epidemiological study will determine if: (i) prior exposure alters DA mediated behaviors, including motor function, memory and neurological function, and the number of DA terminals in the basal ganglia using β-CIT SPECT imaging and (ii) environmental contaminants, including PCBs, are etiologic factors in parkinsonism.

Supported by grants from the US Army Medical Research and Materiel Command, NIH and EPA to RFS and NIH to AGK.