EOHSI

Environmental & Occupational Health Sciences Institute

Spring, 2008

Message from the Interim Director

Kenneth Reuhl, Ph.D.

It is an axiom of academia that if you're not building, you're slipping. There appears little middle ground between the two states—'holding ground' can only be a temporary transition between one and the other. So how is EOHSI doing?

The last year has been one of transition. The Robson Committee is completing its review of Institute procedures and policies, and will issue their report this summer. The receipt of this report will signal the beginning of a search for a permanent Director. Institute members continue to garner extramural funding and recognition for their scholarship. The Institute's core facilities continue to provide outstanding, cutting-edge support for basic and translational studies. The graduate programs continue to recruit excellent students and postdoctoral fellows. EOSHI continues to be the home for imaginative and important research in the environmental sciences. Overall, the Institute remains strong.

Nevertheless, EOHSI faces major challenges. Foremost of these is the development of a strategic vision to carry our efforts through the next 5-10 years. This vision must be flexible enough to accommodate changes in environmental health priorities yet strong enough to focus members' activities around broad themes and thereby avoid the natural centrifugal tendency of research to become diffuse and insular. Developing this future vision will require the enthusiastic participation of all EOHSI members. Critical as future planning is, it is also essential that EOHSI members view the Institute as an important element of their research program; an entity in whose success they can take satisfaction and pride. Perhaps the greatest threat to the Institute is potential deterioration of morale and camaraderie; traditionally these have been among our greatest strengths. If lost, they would take years to rebuild. Simultaneously, EOHSI leadership must continue to evaluate what the Institute can do to further the sense of 'common cause' and enhance members' research programs.

The challenges facing the Institute are recognized by all of us; in fact, we've been talking about them for some years. Solutions are complicated, and will require imagination and commitment. With the development of common goals and joint initiatives, together with strategic application of EOHSI resources to enhance members' research, the Institute will continue to be a major force on the joint campuses, within New Jersey and among the broader environmental community.

Symposium in Honor of Paul Lioy, Ph.D., Winner of the Alumni Award for Distinguished Accomplishments and Service in Physical, Mathematical and Engineering Sciences, March 7, 2008

A Symposium honoring Dr. Paul Lioy was held at the Environmental and Occupational Health Sciences Institute (EOHSI) on Friday, Marcy 7, 2008. Dr. Lioy was the recipient of the Fifth Annual Distinguished Alumni Award from the Rutgers University Graduate School. This distinguished award is given to a Rutgers alumnus who has made significant contributions in the Physical, Mathematical and Engineering Sciences. Dr. Lioy has been instrumental in establishing the strong translational research program in exposure assessment/exposure modeling at EOHSI and has given the Institute an internationally recognized presence in these disciplines.

The focus of the symposium was Exposure Science and featured three distinguished speakers. Dr. William Suk, Acting Deputy Director of the National Institute of Environmental Health Sciences, presented "Approaches to Exposure Sciences by the NIEHS" to a standing-room only audience. His presentation was following by Dr. Morton Lippmann, Professor of Environmental Medicine at New York University Medical School, who discussed "Paul Lioy's Contribution to the Science of Human Exposure Assessment". The final speaker was Dr. Bernard Goldstein, Professor of Environmental and Occupational Health and former Dean of the University of Pittsburgh's Graduate School of Public Health, who presented "The Challenges of Integrating Exposure Science and Risk Policy".

Dr. Paul J. Lioy is Professor and Vice Chair, Department of Environmental and Occupational Medicine, UMDNJ-Robert Wood Johnson Medical School (RWJMS). He is Deputy Director for Government Relations at EOHSI. He is the Division Director for Exposure Science, and, with Dr. Panos Georgopoulos, directs the Center for Exposure and Risk Modeling. In 1985, he started the first academically-based program in the world on exposure assessment research, and in 1992, he and Dr. Christopher Uchrin established the first doctoral program in Exposure Science, a joint program of UMDNJ and Rutgers University. Dr. Lioy received the International Society of Exposure Analysis Wesolowski Award for Lifetime Achievement in Exposure Analysis in 1998, and in 2003, he was the recipient of the Frank Jerome

Chambers Award for lifetime achievement in Air Pollution from the Air and Waste Management Association. In 1999, he was elected to the International Academy of Indoor Air Sciences, and the same year was elected as a Fellow of the Collegium Ramazzini, Carpi. He is one of the founders of International Society for Exposure Analysis and served as President from 1993-94. Recently, Dr. Lioy was appointed Co-Chair of the New Jersey University Consortium for Homeland Security Research and is a member of the New Jersey Domestic Security and Preparedness Planning Group. Dr. Lioy is a member of the Science Advisory

Board of the US EPA and currently a member of the Homeland Security Advisory Committee. Dr. Lioy has also been a member of the National Academy of Sciences Board of Toxicology and Environmental Studies and was Chair of the National Research Council's Committee on Exposure Assessment. Currently, Dr. Lioy is the Associate editor of Environmental Health Perspectives, and the Journal of Exposure Science and Environmental Epidemiology.

NIOSH-Funded Solvent Health Effects Study: A Collaborative EOHSI/Union Study of Exposed Workers

Nancy Fiedler, PhD

Many workers routinely use organic solvents in manufacturing and construction occupations. As early as 1970, clinicians began to observe what was to become known as chronic solvent encephalopathy among workers exposed to solvent mixtures. Despite numerous publications over the past 30 + years, the existence of solvent-induced cognitive deficits remains controversial, particularly in the United States. In light of this controversy, the National Institutes for Occupational Safety and Health requested proposals to evaluate potential cognitive effects of solvent mixtures among workers with a chronic history of exposure.

For the past three years, a multidisciplinary research team, under the direction of Dr. Nancy Fiedler, has been recruiting and testing construction painters who routinely use oil based solvent mixtures. The performance of this group is compared to unexposed controls from other construction trades such as carpenters, glaziers, and dry wall tapers. All workers complete tests of cognition from the Cambridge Neuropsychological Test Automated Battery (CANTAB, a culture free and language independent battery of tests validated as sensitive to cognitive deficits among individuals with well-characterized dementing disorders).

Complete exposure history is collected based on an extensive questionnaire developed by Dr. Cliff Weisel of the Exposure Science Division. This self-report exposure information is supplemented by historical information about paint composition and current environmental sampling all of which are used to model lifetime exposure metrics for each worker. In addition, Dr. Cheuk Tang of Mt. Sinai Medical School is conducting functional neuroimaging of subjects while they are performing cognitive tests. From neuroimaging data, patterns of neural activation that may differ as a function of chronic solvent exposure can be determined. For example, although solvent exposed individuals may be able to perform as well as their matched controls, they may be activating alternate and compensatory neural structures to achieve that performance. Finally, under Dr. Weisel's direction, susceptibility factors including genetic polymorphisms and body mass index will be used to build models of susceptibility that reach beyond those already in the literature. Results of this study will be forthcoming in 2009.

The Beijing Olympics HEART Study (Health Effects of Air Pollution Reduction Trial)

Junfeng "Jim" Zhang, Ph.D.

Unprecedented measures will be taken during the 2008 Beijing Olympics and Paralympics (July 25 – September 17, 2008) to ensure that ambient air quality in one of the world's most polluted regions (see the photo at right showing a sunny day in Beijing) will be substantially improved. The targeted reduction in fine particulate matter ($PM_{2.5}$) is ~70% from a pre-Olympics level of >100 $\mu g/m^3$. A study team consisting of UMDNJ, EOHSI, and Peking University scientists will take advantage of this unique opportunity to test the following hypotheses: (1) Biomarkers of lung and systemic inflammation, vascular endothelial dysfunction, blood coagulation, autonomic dysfunction, and oxidative stress measured in local residents will change significantly in response to this substantial air pollution reduction.

Further, these biomarkers will return to pre-Olympic levels following relaxation of air pollution controls when the Olympics are over. (2) $PM_{2.5}$, ultrafine particles, and certain PM constituents, will each be associated with specific biomarkers across the entire study period. (3) Subjects' responses to changes in pollutant exposure will vary depending on their inherited polymorphisms for molecular pathways related either directly to the biomarkers measured or to mechanisms of PM-induced oxidative stress.

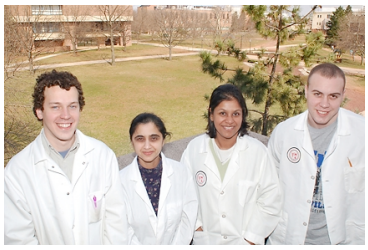
The study will be carried out in 50 male and 50 female, healthy, non-smoking medical residents who work and reside in the same hospital facility where both air pollutants and biomarkers will be measured. Each subject will be measured twice during each of the three time periods: pre-, during-, and post-Olympics.

Epidemiological evidence strongly suggests that acute and chronic cardio-respiratory diseases and events are related to exposure to air pollution, especially $PM_{2.5}$. However, specific mechanisms for these outcomes remain ill-defined and mechanistic studies have been very limited and largely confined to laboratory-based exposures that may not reflect real-life conditions. By expanding the suite of PM constituent measures, measuring multiple biomarkers and pathway-related genes simultaneously and examining a wide range of time frames (from hours to days to a few weeks) for biomarker responses, this real-world study is a comprehensive investigation of several prominently hypothesized mechanisms of PM effects. It will also provide invaluable data to improve the assessment of public health impacts of air pollution reduction.

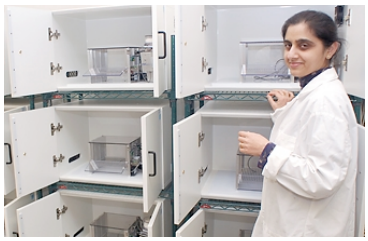
The study is funded through a Research Agreement between UMDNJ and the Health Effects Institute, an investigator-initiated research grant from NIEHS, and by several funding agencies of the Chinese Government. The team is led by Drs. J. Zhang and H. Kipen from EOHSI and Dr. T. Zhu from Peking University. The co-investigators of the study include Drs. D. Rich, S. Diehl, S. Lu, P. Ohman-Strickland, G. Wang, P. Zhu, W. Huang, X. Tang, M. Hu, M. Shao, X. Pan, X. Guo and Y. Wang.

Pathogenesis of Parkinson's Disease

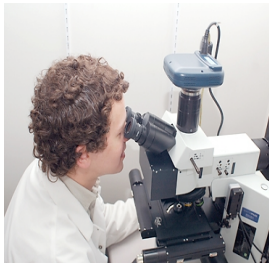
Mona Thiruchelvam, PhD



Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized pathologically by loss of nigrostriatal dopaminergic neurons and clinically by motor dysfunction. Onset of PD is typically associated with the aging population and though genetic factors play a predominant role in some instances of the disease, environmental factors such as pesticide exposures have been widely implicated in the etiology of idiopathic PD.



Data from our laboratory demonstrate that exposure to two pesticides, each known by itself to adversely impact dopamine systems, specifically, the herbicide paraquat (PQ) and the fungicide maneb (MB), produce potentiated effects when administered in combination. Combined PQ and MB engenders a pre-clinical PD model that selectively involves nigrostriatal dopamine system, producing permanent neurotoxicity with loss of dopamine neurons. This model is in line with the multiple hit hypothesis, whereby numerous insults to a given target prevents homeostatic re-regulation, increases vulnerability, and subsequently leads to the disease phenotype.



A developmental etiology for PD has been speculated, but remains largely unexplored. Studies from our laboratory provide compelling support for this speculation. Postnatal exposure to combined PQ and MB not only produces permanent and selective nigrostriatal DA neurotoxicity, but it also enhances vulnerability to subsequent pesticide exposures in adulthood and more importantly, produces progressive dopaminergic neurodegeneration with aging.

In another model, prenatal exposure to MB alone results in a markedly greater loss of dopaminergic neurons when subsequently exposed to PQ. Interestingly, most of the adverse consequences of PQ and MB exposure are gender specific, with males more susceptible than females, an observation that is consistent with the human etiology.

Current efforts are focused on identifying and understanding the target sites implicated in the neuroprotection seen in females, with the hope of developing specific neuroprotective agents. It is becoming more apparent from our studies and those of others that PD is a multifactorial disorder, with multiple risks factors such as age, gender, genetic background, environmental exposure and neurodevelopmental pertubations. Studying the interaction of the various risk factors, and correlating the experimental data with the human epidemiological data will provide important insights into the pathogenesis, progression, and potential therapeutic intervention strategies for PD.

The CounterACT Initiative at EOHSI

Jeffrey Laskin, PhD

The National Institutes of Health (NIH) awarded a five-year $19.2 million grant to Jeffrey D. Laskin and Donald R. Gerecke to support the creation of the UMDNJ/Rutgers University CounterACT Research Center of Excellence. This grant was awarded under the NIH CounterACT program(Counter measures Against Chemical Threats), a major federal effort to develop antidotes to high priority chemical threats including vesicating agents such as sulfur mustard, neurotoxic agents such as organophosphorus nerve 'gases', pulmonary agents such as chlorine gas and metabolic/cellular poisons such as cyanide. Funds for this program were originally provided to the NIH through Project Bioshield, a White House initiated national security priority to expedite research on the most promising scientific discoveries that would lead to improved medical countermeasures to protect Americans against a chemical, biological, radiological, or nuclear (CBRN) attack. It was also designed to provide the FDA with the ability to make promising treatments quickly available in emergency situations. The CounterACT program is intended to support mechanistic research aimed at identifying targets for therapeutic development and to develop candidate drugs for use in case of an attack.

The UMDNJ/Rutgers University CounterACT Research Center of Excellence is focused on sulfur mustard, a gas that has been used as a chemical warfare agent. Sulfur mustard is easy to make and transport, and therefore thought to present a likely terror threat. It is a potent vesicant known to cause significant injury to the skin, eyes, and lung. Although sulfur mustard has been studied for more than 80 years, the mechanisms mediating its actions as a vesicant remain unknown; moreover, to date, there are no effective medical countermeasures for exposure to warfare vesicants. Research at the UMDNJ/Rutgers University CounterACT Research Center of Excellence is aimed at identifying molecular targets of sulfur mustard-induced injury and developing drugs to treat individuals exposed to sulfur mustard. In collaborative studies with Battelle Memorial Institute and Lehigh University, members of the Center are optimizing lead compounds that are candidate pharmaceutical countermeasures. Studies have been initiated to evaluate the efficacy of these potential countermeasures in model systems of sulfur mustard toxicity. An active program is also up and running to develop appropriate pharmaceutical formulations of these new drugs and to evaluate their therapeutic efficacy as the Center moves these agents towards FDA approval. The Center also has important Research and Development Projects underway to identify specific mechanisms of action of sulfur mustard and potential new targets for therapeutic intervention in three major vesicant targets: the eye, the skin and the lung. Investigators on these projects work closely with a Pharmacology and Drug Development Core and a Medicinal Chemistry and Pharmaceutics Core which brings together considerable expertise in drug development that exists at EOHSI and the School of Pharmacy at Rutgers. Additional members of the Center include EOHSI members Marion Gordon, Debra Laskin and Patrick Sinko, Ned Heindel from Lehigh University, Diane Heck from Rutgers and New York Medical College and Joshua Gray from Rutgers.

News from EOHSI Centers

The EOHSI Analytical Center is Focused on Mass Spectrometric (MS) Solutions

The capabilities of the EOHSI Analytical Center are directed at identification and quantitative analysis of small molecules and metal contaminants. EOHSI houses eight mass spectrometers, all with chromatographic separation. There are four high performance liquid chromatographs ion trap MS (HPLC/ITMS) instruments dedicated to nonvolatile and polar organic compounds such as metabolites or drugs. These instruments are currently being used for analysis of perflouro compounds and Ritalin.

The method for perfluoro compound quantitation is of special interest to the New Jersey Department of Environmental Protection because many of New Jersey's water supplies are contaminated with PFOA or PFOS. The arrival of our new Thermo LTQ XL, linear ion trap MS and UPLC will allow more sensitivity and higher throughput. We will be adapting many of our current methods, such as MPP+ and paraquat in brain tissue, to utilize this new instrument. There are two GC/ITMS dedicated to semi-volatile and volatile organic compounds such as PAHs and BTEX.

The Analytical Center is currently using these instruments for quantification of PCBs and chlorinated pesticides in human serum. We have been performing total metals analysis using an inductively coupled plasma mass spectrometer (ICPMS). Work is now being performed to identify Pb in synthetic turf samples from many NJ fields. Our organometallic speciation methods are performed by coupling ion chromatography to ICPMS. These methods are internationally recognized and have been used to certify two new NIST reference standards. Microwave extraction methods for paraquat and Hg species are being utilized by investigators from other institutions and are now part of a proposed EPA method. CEM's recently donated a new single sample microwave digester in recognition of the extraction methods developed by the Analytical Center. New speciation methods and analytical protocols for estrogenic compounds are currently being developed. The EOHSI Analytical Center looks forward to continuing its support of EOHSI investigators in the future. For additional information please contact Brian Buckley at (732) 445-0204 or bbuckley@eohsi.rutgers.edu.

Please send your comments and article ideas to Paul Lioy (plioy@eohsi.rutgers.edu) and/or Betty Davis (davisbe@eohsi.rutgers.edu) at their e-mail addresses.

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