Your Health & the Environment

NEWS FROM THE UNIVERSITY OF ROCHESTER

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What is a toxic environment?

By Dr. Bernard Weiss

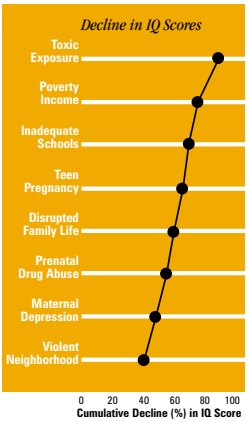
Scientists in our Environmental Health Sciences Center exploit the tools of contemporary molecular biology to create novel organisms such as mice with unique genetic properties. These genetically-modified mice are tested for how they differ in their response to toxic chemicals from ordinary mice. Our scientists carry out such a strategy because they know that toxicity is not just a property of the chemical, but, like the infectivity of a bacterium, a property shared jointly with the host.

Human hosts differ not only in genetic endowment, but in their histories and experiences and social settings. Such variations in the host complicate our understanding of toxic risks. Environmental differences are particularly important during the early years because of their strong influence on our vulnerability to toxic exposures. Lead is a toxic hazard that exemplifies these complications.

Lead poisoning in children has been a scourge since antiquity. We no longer see many cases in the U.S. that require medical treatment, thanks to alert public heath authorities and to programs and organizations such as our own Get the Lead Out (GLO) initiative and the efforts of the Coalition Against Lead Poisoning. Instead, we now see it in more insidious forms because the exposure levels are lower and their expression more elusive. For example, lead toxicity may take the form of lowered IQ scores, or a tendency to suffer from attention deficits. We don't see these forms of toxicity directly; we detect them with instruments such as intelligence or other diagnostic tests. However, such diagnostic tests reflect not only the direct biological effects of lead but all the other factors that determine IQ and behavior. What we typically do in our research is to compensate statistically for these other factors to try to obtain a "pure" estimate of the effects of lead or whichever other chemical is the subject of our scrutiny.

We know that exposure to lead is not random. Certain communities are more at risk than others—communities that inhabit older, often decaying housing contaminated by lead paint, a legacy of the time when it was still legal to apply it in dwellings. But decaying housing is correlated with low income, unstable families, and menacing neighborhoods. All these factors influence IQ scores.

These perplexities are increasingly recognized. Some researchers have asked, "Can we really separate the effects of lead [or other toxic chemicals] from these other factors that almost seem glued to them? Can we really isolate the effects of lead from its social environment?" Some of us, in fact, are coming to believe that it is an unrealistic or even impossible task. We point to the principle of Effect Modification, by which we mean that the association of lead exposure with IQ score varies across the magnitude of some other factor.



We possess an abundance of information about social class and health—wealth equals health: lower incomes foster more disease and shorter lives. They mean reduced educational opportunities for children; more days missed from school because of illness; less adequate nutrition; more family disruption. All conspire to diminish IQ scores. To help visualize how such stress factors might work together, I've drawn the accompanying figure. Each stressor contributes to a

Continued on back page.

Opanashuk Lab: PCB and Dioxin Neurotoxicity Throughout the Lifespan

Dr. Lisa Opanashuk

Assistant Professor of Environmental Medicine

Dr. Lisa Opanashuk and the members of her lab are interested in identifying environmental risk factors that may contribute to developmental disabilities and neurodegenerative processes associated with aging. Their overall research theme centers on discovering vulnerable cellular targets and molecular mechanisms of neurotoxicity in the brain during development and later in life. The immature nervous system is particularly sensitive to damage produced by toxicant exposures. One reason for this increased sensitivity is that the blood brain barrier, which serves to protect the brain by limiting penetration of chemicals, does not completely form until six months of age. Another reason is that brain development occurs during a protracted time period and neurological damage may occur following toxicant exposure during a number of developmental time points, including gestation and lactation. The aging nervous system is also more vulnerable to environmental toxicant exposure due to its diminished ability to defend against injury and a reduced capacity to compensate for disrupted neurological function. Thus, understanding both the cellular and molecular mechanisms of environmental neurotoxicity increases our ability to mitigate or even prevent neurological damage throughout an individual's lifespan.

In collaboration with investigators both in the Environmental Health Sciences Center and the University of Rochester's Interdepartmental Neuroscience Program, Opanashuk's current research is focused on defining cellular, gene and protein targets of neurotoxicity following exposure to PCBs or dioxin throughout an organism's lifespan. These compounds have been associated with cognitive, auditory and motor neurological abnormalities following exposure during development or adulthood. PCBs and dioxin are both members of the polyhalogenated hydrocarbon family of compounds. Exposure to either is a profound health hazard because these compounds have a wide environmental distribution and persist in ecosystems. Furthermore, these chemicals also accumulate and remain present in human tissues for extended periods of time.

Two graduate students, Mary Williamson and Donna Lee, are accomplishing the majority of research in the Opanashuk laboratory. Mary has been working to identify various cellular, gene, and protein targets of developmental dioxin neurotoxicity. She has identified a vulnerable neuronal population and she is currently working to further understand the adverse impact of dioxins on the developing brain. Donna's project focuses on determining whether exposure to PCBs damages dopaminergic neurons in the brain region that deteriorates in Parkinson's disease patients. She is currently studying the mechanisms by which PCBs injure dopamine neurons. Her future objective is to establish whether PCB exposure predisposes the nervous system to become more vulnerable to oxidative damage that results from either toxicant exposure or the normal aging process.

Both Donna and Mary provide a description of their research on the following page. Additional projects, with the help of research associate Bryan Thompson, endeavor to identify the molecular mechanisms underlying developmental dioxin/PCB neurotoxicity during neural precursor cell development and on auditory function.

Donna Lee:

5th yr. Graduate Student
Toxicology Ph.D. Program
B.A. University of California-
Santa Cruz 1999
Advisor: Dr. Lisa Opanashuk

Despite being banned in 1977, polychlorinated biphenyls (PCBs)[1] remain ubiquitous in the environment due to their improper disposal and resistance to degradation. PCBs can be taken up by marine animals from the environment. These chemicals preferentially bioaccumulate and biomagnify in higher trophic levels of the food chain, including humans. Unfortunately, PCBs are not only a threat to natural ecosystems. A recent article in the journal Science reported that farmed salmon contained higher levels of PCBs, dioxins, and pesticides than wild salmon. Thus, the consumption of PCB contaminated fish, both wild-caught and farm-raised, raises important public concerns related to adverse health effects.

Both developmental and adult exposures to PCBs have been connected to several neurological deficits in humans. My research interests stem from evidence suggesting that PCBs may play a role in neurodegeneration. For example, a study in the late 1990's reported that brains of Parkinson's disease (PD) patients contained elevated levels of PCBs. PD, a chronic and progressive movement disorder that afflicts at least one million Americans, is characterized by the death of dopaminergic neurons[2] within the substantia nigra area of the brain. Although the etiology of PD is not well defined, this disorder most likely arises from a combination of genetic and environmental factors. This linkage of PCBs with a neurodegenerative disease highlights the need to understand the mechanisms by which relevant and persistent environmental toxicants may contribute to such disorders.

Oxidative stress[3], resulting from excessive production of unpaired and highly reactive electrons, is thought to be one of the factors in the development of PD and in neurodegeneration in general. Dopamine neurons are particularly sensitive to oxidative stress and PCBs have been shown to adversely impact dopaminergic pathways[4]. My project focuses on elucidating the mechanisms by which PCBs activate oxidative stress-related pathways that may compromise dopamine neurons and ultimately disrupt neuronal function and lead to neuron death. This research will also examine whether PCB exposure causes the dopaminergic system to be more vulnerable to oxidative damage because of the exposure to toxicants which produced free radicals as compared to normal aging. Furthermore, the results from these studies will help to determine whether PCBs are potential risk factors for neurodegenerative processes associated with PD and guide the development of prevention or treatment strategies to combat adverse health effects.

Mary Williamson

5th yr. Graduate Student
Toxicology Ph.D. Program
B.A. SUNY Stony Brook 1996
Advisor: Dr. Lisa Opanashuk

2,3,7,8-tetrachlorodibenzodioxin (TCDD), commonly referred to as dioxin, is a widespread and persistent environmental contaminant known to exert toxicity in many species. Some Vietnam veterans were exposed to dioxin through military use of the herbicide Agent Orange. However the primary route of dioxin exposure occurs through food consumption. In fact, detectable levels of dioxin are found in most people due to the ingestion of fish, meat, and dairy products. Because of its lipophilic[5] nature, dioxin can be transferred to developing offspring during gestation and lactation. Because TCDD is associated with teratogenic effects[6] in the nervous, immune, and reproductive systems, exposure to this extremely potent toxicant raises important public health concerns. The developing brain is an especially vulnerable target for dioxin neurotoxicity.

Epidemiological studies have reported cognitive and locomotor impairments in children exposed to dioxin during the fetal and neonatal periods. Because perinatal TCDD exposure has been associated with some neurological abnormalities consistent with improper cerebellar function, the focus of my project is to characterize the biological effects of dioxin exposure during the development of the cerebellum, a brain region that is important for learning and executing coordinated movements. In addition, there is also some evidence that the cerebellum may participate in cognitive functions. My research goals have centered on identifying the precise cellular and molecular targets of dioxin-mediated neurotoxicity. I have determined that dioxin accelerates the normal differentiation program of cerebellar granule neurons by disrupting the spatial and temporal expression of genes that regulate normal cerebellar development. These observations could potentially contribute to functional abnormalities associated with developmental TCDD exposure.

This research will advance our current understanding of the molecular events underlying neurodevelopmental disabilities associated with perinatal dioxin exposure. Our findings should help guide the design of treatment strategies aimed to prevent nervous system damage associated with dioxin and related environmental toxicant exposure.

Key Terms

1. Polychlorinated biphenyls (PCBs): Due to their non-flammability, chemical stability, high boiling point and electrical insulating properties, PCBs were used in hundreds of industrial and commercial applications. More than 1.5 billion pounds of PCBs were manufactured in the United States prior to cessation of production in 1977.

2. Dopaminergic neurons: The neurons responsible for controlling the initiation of movement, resting muscle tone and targeted movement. It is these cells that undergo degeneration in Parkinson's Disease.

3. Oxidative Stress: Oxidative stress exists when there is an excess of free radicals over antioxidant defenses. As a consequence, free radicals attack and oxidize other cell components such as lipids, proteins, and nucleic acids. This leads to tissue injury and in some cases, the influx of inflammatory cells to the sites of injury.

4. Dopaminergic pathways: These are pathways in the brain which transmit the neurotransmitter dopamine from one region of the brain to another.

5. Lipophilic: "Fat-loving" molecules (or parts of molecules), having a tendency to dissolve in fat-like solvents.

6. Teratogenic effects: Damage to a fetus, by such things as infectious agents, maternal health factors, or environmental chemicals.

My Environment, My Health, My Choices
Partners with Monroe High School on School-Wide Environmental Health Theme

The University of Rochester's Environmental Health Sciences Center (EHSC) and Monroe High School, in the City of Rochester, have launched a partnership focused on environmental health that will engage students, school-wide, in interdisciplinary projects, courses, and activities exploring the link between health and the environment.

Monroe High School is participating in the *My Environment, My Health, My Choices* project, led by Dina Markowitz, Ph.D. and funded by the National Institute of Environmental Health Sciences. Monroe teachers will work with environmental health and curriculum development experts at the university to develop innovative projects for all subject areas.

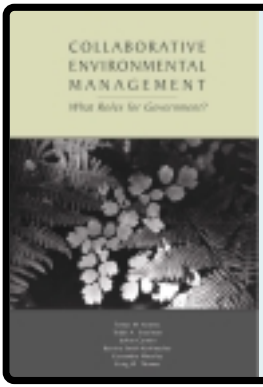
"The Rochester City School District is fortunate to have as a partner the University of Rochester School of Medicine & Dentistry," said Rochester Superintendent of Schools Dr. Manuel J. Rivera. "This project opens up a world of resources to our students. It is another example of the power of collaboration in enriching the education of Rochester children."

The $1.3 million, seven-year project has already been operating for four years and has involved 11 schools in the greater Rochester area. The EHSC teamed with four high schools in the first phase of the project and seven middle and high schools in the second phase. The third and final phase will involve a partnership with Monroe High School alone. The project will provide funding for a variety of programs including field trips, mini-grants, professional development for teachers, and school presentations by environmental health experts.

Monroe teachers Liza Steffen and Larissa Boettcher (who both teach interdisciplinary classes for English-learners), and Ellen Sedor (who teaches science) have been involved in the project since June 2003, as part of a phase 2 team. The newly announced partnership expands the project to the entire school and builds on the experience of the original three-teacher team.

The team of Steffen, Boettcher and Sedor has created lessons for students addressing the links between environmental health and water. They used innovative lessons to involve a mix of students including students in English as a Second Language classes. One project involved a fictional scenario involving middle school students and the Genesee River. Students conducted research about water pollution, investigated the potential reasons for the problem, and participated in a variety of activities linked to environmental health, including solving an environmental health mystery created by the teachers.

Information about *My Environment, My Health, My Choices* is available online at: www.envmed.Rochester.edu/envmed/ehsc/outreach/myenvironment.html



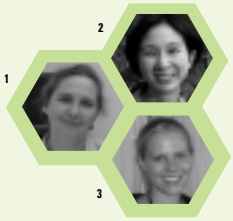
Collaborative Environmental Management:
What roles for government?

Resources for the Future Press. 2004.
By Tomas Koontz, Toddi Steelman, JoAnn Carmin, Katrina Smith Korfmacher, Cassandra Moseley, and Craig Thomas.

Community outreach coordinator Katrina Smith Korfmacher, Ph.D. is co-author of a new book about collaborative environmental management. While collaboration has become a popular approach to environmental policy, planning, and management, questions remain about the roles that governments play in collaboration. This book analyzes a series of cases to understand how collaborative processes work in practice. It discusses the choices and challenges faced by governmental institutions and actors as they try to realize the potential of collaborative environmental management. While most of the cases deal with natural resources like watersheds, farmland preservation, and species protection, the concepts inform the work of our community outreach partnerships in environmental health on a daily basis!

We would like to provide this newsletter to you electronically. If you are interested, please send your email address to Kate_Kuholski@URMC.rochester.edu.

Community Outreach and Education Programs:
Welcome to Our Newest Staff Members



Deirdre Bonnell, MS Ed. (1)
On sabbatical from her teaching position at Rochester's Wilson Magnet High School, Deirdre Bonnell, MS Ed. has joined the Life Sciences Learning Center for the 2004/05 school year. She is not a newcomer to the LSLC, however, as she has taught in its summer programs for 8 years and has contributed to the Laboratory Skills Development Program by involving her students in LSLC lab activities during the school year. She has taught at the secondary level for 10 years, with 8 years of teaching biology within the Rochester City School District. Deirdre is looking forward to a creative year of teaching in the lab, working with colleagues in the schools and collaborating with the LSLC staff on new research projects.

Dr. Shaw-Ree Chen, PhD (2)
Dr. Shaw-Ree Chen joined the Department of Environmental Medicine on September, 2004 as a Research Assistant Professor in the Center for Science Education and Outreach. She has her PhD in Biochemistry from the University of Washington, where she studied the molecular events that underlie early zebrafish development. While in Seattle, she also participated in the Science Education Partnership, which partnered graduate students at the University of Washington and the Fred Hutchinson Cancer Research Center with teachers in Washington state. Thus began her interest in science education and outreach, and led to her involvement with our Life Sciences Learning Center. One of Shaw-Ree's main interests is in developing computer simulations and programs that can bring complex concepts in molecular biology to life.

Kate Kuholski (3)
After her internship with Dr. Katrina Smith Korfmacher this spring, Kate Kuholski became a full-time member of our Community Outreach and Education Programs in June 2004 as a project manager. Kate manages the field component of the Get the Lead Out (GLO) project. She also provides assistance for some of our other programs, such as the "My Environment, My Health, My Choices" environmental health curriculum development program and the Life Sciences Learning Center's Laboratory Skills Development Program. Kate received her B.S. in environmental management from Rochester Institute of Technology in May 2004. When she attended RIT, Kate also did internships at an environmental consulting firm as well as a civil/environmental engineering firm. Kate enjoys applying her technical background to the Community Outreach and Education Programs.

Toxicology Training Program News

Joyce Morgan (4)
Our long-time Toxicology Training Program coordinator, Joyce Morgan retired this summer, leaving Rochester and moving to Florida. Joyce joined the Environmental Medicine Department in 1979, and became the Administrative Assistant and Coordinator of the toxicology program in 1998.

Muriel Stanley (5)
The Department of Environmental Medicine welcomes Muriel Stanley as our new Toxicology Training Program Coordinator. Muriel has been with the University of Rochester for many years, working in the Rush Rhees Library, Academic Advising Office, Neurosurgery, University Health Services and the Community and Preventative Medicine Department before finding her niche in Environmental Medicine. In her spare time, she is a quilt maker and a weekend hiker. Muriel has two children attending college in the greater Rochester area. She looks forward to working with our graduate students and faculty.

Congratulations to the following Toxicology graduate students who were recently awarded their Ph.D.'s:

- **Christine Hammond,** Advisor: Ned Ballatori, Ph.D. Thesis title: "Mechanisms and Physiological Significance of Glutathione Export During Apoptosis."
- **Christopher Helt,** Advisor: Michael O'Reilly, PhD. Thesis title: "Activation and role of the p53/p21 pathway during hyperoxic stress."
- **Gary Minsavage,** Advisor: Thomas Gasiewicz, Ph.D. Thesis title: "Identification and characterization of phosphorylated sites that are required for aryl hydrocarbon receptor (AhR) DNA binding and transactivation." Gary was awarded the National Research Council Research Associate Position and is utilizing this award as an associate at the United States Army Medical Research Institute of Chemical Defense.
- **Christine Palermo,** Advisor: Thomas Gasiewicz, Ph.D. Thesis title: "Identification and Mechanism of Action of Aryl Hydrocarbon Receptor Inhibitors in Green Tea Extract."
- **Amber Wyman,** Advisor: Thomas Gasiewicz, Ph.D. Thesis title: "Effect of TCDD on Murine Hematopoietic Stem Cells." Amber is a post-doctoral fellow in a tumor immunology lab at the Fred Hutchinson Cancer Research Center.

Welcome to the new Toxicology Training Program graduate students:

Xianglu Han: Jining Medical University, B.S. 1996/University of Georgia, M.S. 2004
Jonathan Holz: Washington University, B.S. 2004
Brent Kobielush: Bethel College, B.S. 2004
Michael Madejczyk: Alfred University, B.S. 1999
Jamie O'Brien: University of Rochester, B.S. 2004
Van Thai: University of Rochester, B.S. 2001
Zhengyu Yin: Anhui Medical University, B.S. 1995/Fudan University, M.S. 2003

What is a toxic environment?

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lowering of IQ score by six points. They cumulate to yield a score about half the average of 100. This is not an unrealistic model. The Rochester Longitudinal Study, an investigation that began in the 1970s and still continues, examined ten different risk factors, somewhat overlapping with those pictured here, and found that each added an additional decrement. The greater the number of risk factors experienced by the child, the lower the IQ score.

What especially fascinates those of us who engage in laboratory research is how these dilemmas from human research translate into findings from animal experiments. For nearly 50 years we've known that the early environment and experiences of rats and mice, our standard species, determine how they function as adults. Picking up an infant rat and stroking it for a few minutes on several occasions before it is even weaned makes it more tolerant of adult stress; the tolerance shows up in how it behaves in strange environments and in its secretion of stress hormones. Conversely, separating it repeatedly from its nest and mother for several hours makes it more vulnerable to stress and more prone to maladaptive adult behaviors. These results mirror what we know about human development.

We also have known for over 50 years that raising young rats and mice in special "enriched" environments can make them more adept at solving cognitive tasks and even promote the growth of brain cells. These enriched environments take the form of large enclosures with many playmates and lots of toys, in contrast to the usual laboratory cages that many researchers now consider "deprived" conditions. More recently, we have learned that enriched environments can help rats and mice overcome the damage inflicted on brain development due to exposing their mothers before their birth to excessive amounts of alcohol or lead. Effect Modification, indeed.

These findings tell us that we deceive ourselves in the laboratory by assuming that testing animals raised under conventional conditions yields a "pure" evaluation of toxic potential free of the complexities that obscure human research. We can't ignore the history of the host.

Nor can we ignore the wider implications of our knowledge. What we've acquired from both human and laboratory research is not just a body of scientific findings. Our Environmental Health Sciences Center is committed to translating science into beneficial actions, and into laying the foundations of public policy if we pursue translation to its ultimate goal. Such a goal is broader than our Get Out the Lead initiative. GLO is only the first step—a worthwhile, frustrating, difficult, and often exhausting beginning—to solving the roots of the lead problem. Like other chemical hazards in our environment, especially those that threaten brain development, lead presents a problem in which risk is piled upon risk upon risk. It is a challenge that calls for redressing a whole edifice of inequities where science is inseparable from policy. It's what happens when you sit back and ask what your data really mean.

Bernard Weiss, Ph.D. is Professor of Envirnmental Medicine and Pediatrics. His research focues on neurotoxicology and behavior.

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University of Rochester
Environmental Health Sciences Center
575 Elmwood Avenue
Box EHSC
Rochester, NY 14642

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