



# Environmental Factor

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March 2009

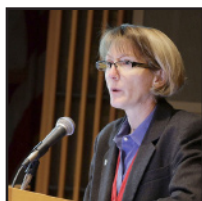
## NIEHS Spotlight



### Council Looks to Integrating Stimulus Funding with NIEHS Mission

A receptive NIEHS National Advisory Environmental Health Sciences Council (NAEHSC) welcomed new

NIEHS Director Linda Birnbaum, Ph.D., at its spring meeting on February 19 ...[read more](#)



### NTP Board Peer Reviews Draft Cancer Reports

National Toxicology Program (NTP) reports on five of the nine compounds being considered for listing in the 12th Report on Carcinogens (RoC)

were for the first time peer reviewed by the NTP Board of Scientific Counselors (BSC) February 24 in Rodbell Auditorium. ...[read more](#)



### NIEHS Gears Up for SOT

Each year, one of the Institute's major national meetings is the annual gathering of members of the Society of Toxicology (SOT). ....[read more](#)



### Suk Represents NIEHS at President's Cancer Panel Meeting

NIEHS took a seat at a meeting of the President's Cancer Panel (PCP) with a presentation by NIEHS Center for

Risk and Integrated Sciences Director Bill Suk, Ph.D., on January 27 in Phoenix. ...[read more](#)

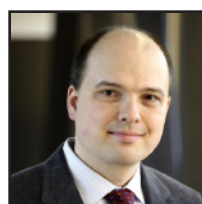
## Science Notebook



### Estrogen and Hormone Replacement in Menopause

The use of estrogen and hormone replacement therapy (HRT) to treat menopausal symptoms in women has caused confusion in the general public

and cardiology research circles. ...[read more](#)



### ONES Awardee Speaks at NIEHS

In a lecture on February 6, NIEHS grantee Sven-Eric Jordt, Ph.D., discussed the latest developments in his basic research on the

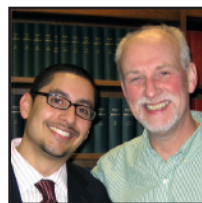
mechanisms of transient receptor potential (TRP) channels. ...[read more](#)



### Research Finds New Cause of Ozone Wheezing and Potential Treatments

Researchers at NIEHS and Duke University have discovered a cause of airway irritation and wheezing after

exposure to ozone, a common urban air pollutant. ....[read more](#)



### Glutathione Synthetase Linked to Arsenic Susceptibility in Fruit Fly Model

NIEHS grantee Iain Cartwright, Ph.D., an associate professor at the University of Cincinnati College of Medicine,

his former student, Jorge Muñiz Ortiz, Ph.D., and two co-authors recently reported a surprising genetic twist regarding arsenic susceptibility in the February 2009 issue of *Toxicological Sciences*. ....[read more](#)

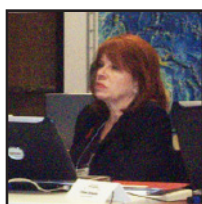
## NIEHS Spotlight



### NIEHS Grantees Speak at Global Health Symposium

Veteran NIEHS Grantees Peter Thorne, Ph.D., and Joseph Graziano, Ph.D., were among the global health experts giving keynote talks at the

Managing Toxic Risks for Global Health symposium February 20 at Duke University. ...[read more](#)



### Columbia University Hosts Research Translation Workshop

Four years after the addition of a research translation component to the NIEHS Superfund Basic Research

Program (SBRP) in 2005, the leaders of the SBRP research translation cores gathered at a workshop on February 11-13 to assess their progress. ...[read more](#)



### Former Postdoc Featured in TV Special

When former Postdoctoral Fellow John Fortune, Ph.D., left NIEHS in 2005, he knew he was taking an important step that would change

his career path. ....[read more](#)



### Schroeder Appointed EHP Science Editor

In December 2008, Jane Schroeder, D.V.M., Ph.D., joined the staff of *Environmental Health Perspectives* (EHP) as its new science editor,

providing scientific expertise and oversight for virtually every aspect of the NIEHS journal. ...[read more](#)



### Duke Bioethicist Reflects on Personal Genomics

In 1989 and 1990 when Robert Cook-Deegan, M.D., was a consultant to the director of what was then the NIH National Center for Human Genome

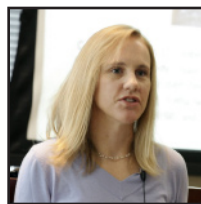
Research, James Watson, few people could have predicted how the evolution and democratization of genomics would impact society. ....[read more](#)

## Science Notebook



### Study Explores the Mechanisms of Age-Related Neurodegeneration

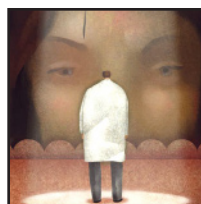
A new study by researchers at NIEHS sheds light on the mechanisms involved in the accumulation of a neurotoxic protein, amyloid-beta<sub>42</sub> (Aβ<sub>42</sub>), which is implicated in Alzheimer's disease (AD) and other age-related neurodegeneration. ....[read more](#)



### Endocrine Disrupting Effects of BPA on Puberty and Estrogen Cycles

On February 18, Sigma Xi hosted a lunchtime talk by NIEHS grantee Heather Patisaul, Ph.D., on

her latest findings about the effects on brain and ovarian function of developmental exposure to Bisphenol-A (BPA). ...[read more](#)



### This Month in EHP

The March 2009 issue of *Environmental Health Perspectives* is now available on-line, highlighting issues surrounding regulation of hazardous substances, non-cancer

toxicity assessment, mobile phones and cancer, pesticide mixtures, proteasome inhibition by organotins and children's exposure to dust lead. ...[read more](#)

### Upcoming Distinguished Lecture with Mike Levine

The 2008–2009 NIEHS Distinguished Lecture series will welcome its next guest speaker March 10 at 11:00 a.m. in Rodbell Auditorium. Geneticist Mike Levine, Ph.D., will discuss "Transcriptional Precision in the *Drosophila* Embryo"... ...[read more](#)

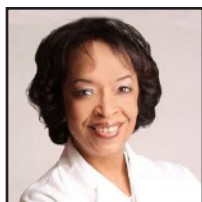


### Samson and Hollingsworth to Speak at Duke in March

Leona Samson, Ph.D., and recent Outstanding New Environmental Scientist (ONES) awardee John Hollingsworth, M.D., are scheduled to lecture in March

at the Duke University School of Medicine. ...[read more](#)

## NIEHS Spotlight



### Higginbotham Challenges Students at NIH Black History Event

The talk was for everyone at NIH — and by videocast for people at NIEHS — but the target audience on February

18 was clearly the students when ophthalmologist Eve Higginbotham, M.D., delivered a talk in celebration of Black History Month. ....[read more](#)



### Colwell to Speak at Eighth Spirit Lecture

The NIEHS Spirit Lecture Series, the hallmark event in NIEHS Women's History Month celebrations since 2002, will welcome environmental

microbiologist and scientific administrator Rita Colwell, Ph.D., on March 27. ....[read more](#)

## Inside the Institute



### Fellowship and Food – The Keystone of Satellite Cohesion

Food was the centerpiece at two recent events at the new NIEHS satellite offices in the Keystone building.

....[read more](#)



### Institute Celebrates African-American Culture

The NIEHS Diversity Council joined with the RTP Chapter of Blacks In Government (BIG) to sponsor a novel African-American Cultural Celebration

in Rodbell Auditorium and the NIEHS Cafeteria February 26 for Black History Month Observance. ....[read more](#)

## Science Notebook



### NCSU to Host Grantee Peter Thomas

NIEHS grantee Peter Thomas, Ph.D., is scheduled to present a seminar March 26 on “Characteristics of a Putative

Steroid Membrane Receptor,” as part of the North Carolina State University (NCSU) Department of Biology Seminar Series. ....[read more](#)

## Extramural Research

### Extramural Update

NIEHS and U.S. Environmental Protection Agency (EPA) announce the release of two linked funding opportunities – the Children's Environmental Health and Disease Prevention Centers (P01) RFA-ES-08-002 and the Formative Centers (P20) RFA-ES-08-004. Applications are due April 30, 2009 and will be reviewed in July by a special emphasis panel convened by the NIEHS Scientific Review Branch. ....[read more](#)

### Extramural Papers of the Month

- [Clean Air Extends Life Expectancy](#)
- [Variations in Human Gut Microbiome Linked to Obesity](#)
- [MicroRNAs Modulate Smoking Damage](#)
- [New Treatment Found for Ozone-Caused Wheezing](#)

## Intramural Research

### Intramural Papers of the Month

- [Maternal Obesity Increases the Risk of Neonatal Death](#)
- [The Involvement of UV Radiation in the Development of Dermatomyositis](#)
- [Fibroid Growth Differs Among Black and White Women](#)
- [The Role of Activation-Induced Deaminase in Lupus](#)

## Calendar of Upcoming Events

- **March 9**, in Rodbell Auditorium, 10:00 – 11:00 — LMG Fellows-invited Guest Lecture with Roger Woodgate, Ph.D., speaking on “Translesion Synthesis”
- **March 10**, in Rodbell Auditorium, 11:00 – 12:00 — Distinguished Lecture Seminar Series featuring a lecture on “Transcriptional Precision in the Drosophila Embryo” by Mike Levine, Ph.D.
- **March 12**, in Rodbell Auditorium, 8:30 – 4:00 — 2009 North Carolina Environmental Stewardship Initiative Members Meeting
- **March 12**, in Rall D350, 11:00 – 12:00 — Kevin Weinfurt, Ph.D., addressing the topic of “Disclosing conflicts of interest in clinical research: Attitudes of investigators, IRB Members, and research subjects”
- **March 12 (offsite event)**, at Wilson Hall on the NIH Campus in Bethesda, 11:00 – 12:00 — NIH Women’s History Month Seminar featuring Sharon Hrynkow, Ph.D., speaking on “Women Taking the Lead to Save Our Planet” with closing remarks by Linda Birnbaum, Ph.D., and live [videocast](#)
- **March 13**, in Rodbell Auditorium, 10:00 – 4:00 — Welcoming Ceremony for NIEHS Director Linda Birnbaum, Ph.D., with distinguished lectures by Grace LeMasters, Ph.D., Jim Riviere, Ph.D., and Jack Keene, Ph.D.
- **March 13 - 17 (offsite event)**, in Washington — American Academy of Allergy, Asthma and Immunology Annual Meeting
- **March 15 - 18 (offsite event)**, in Baltimore — Society of Toxicology Annual Meeting
- **March 23 - 24**, in Rodbell Auditorium, 8:00 – 5:00 — Board of Scientific Counselors review of the Laboratory of Pharmacology & Chemistry and the Laboratory of Experimental Pathology
- **March 24 (offsite event)**, in the RTP-EPA Auditorium, 1:30 – 3:00 — Women’s History Month Celebration featuring Anne Taylor
- **March 26 (offsite event)**, in 101 David Clark Labs at North Carolina State University, 4:00 – 5:00 — Department of Biology Seminar Series on “Characteristics of A Putative Steroid Membrane Receptor” by Peter Thomas, Ph.D.
- **March 27**, in Rodbell Auditorium, 10:00 – 11:00 — Spirit Lecture/Frontiers of Environmental Sciences Lecture Series with Rita Colwell, Ph.D., speaking on “Climate, Oceans, Infectious Diseases, and Human Health: The Saga of Cholera”
- **March 27 (offsite event)**, in 147 Nanaline Duke Bldg. at Duke University, 11:00 – 12:00 — Duke Biochemistry Series Lecture with Leona Samson, Ph.D.
- **March 30**, in Rodbell Auditorium, 10:00 – 11:30 — LMG Fellows-invited Guest Lecture by Daniel Bogenhagen, M.D., on “Mitochondrial Biogenesis and Heredity”
- **March 30 (offsite event)**, Alfred Lerner Hall at Columbia University, 9:00 – 5:00 — Translating Science to Policy: Protecting Children’s Environmental Health
- **March 31 (offsite event)**, in 143 Jones Bldg. at Duke University, 4:00 – 5:00 — Duke Department of Immunology Seminar Series with John W. Hollingsworth, M.D., speaking on “Ambient Environmental Exposures and Pulmonary Innate Immunity”
- View More Events: [NIEHS Public Calendar](#)

# NIEHS Spotlight

## Council Looks to Integrating Stimulus Funding with NIEHS Mission

By Eddy Ball

A receptive NIEHS National Advisory Environmental Health Sciences Council (NAEHSC) welcomed new NIEHS Director Linda Birnbaum, Ph.D., at its spring meeting on February 19 — where she shared her vision for the Institute and outlined what she sees as the highest priorities before turning to budgetary issues. During the discussion following Birnbaum's report, members explored with her the challenges of spending the NIEHS share of the \$10.4 billion NIH from the American Recovery and Reinvestment Act. The economic stimulus funding is intended to support the integrated mission of the Institute to improve human health, while at the same time saving existing jobs and creating new ones.

NAEHSC was the first council to meet after President Obama signed the measure into law two days earlier, and the lively discussion centered on many of the same issues that will likely confront other NIH councils in the weeks and months ahead. Members of the NAEHSC expressed interest in sharing ideas with the NIEHS leadership on the best ways to allocate approximately \$169 million in two-year stimulus funding.

Putting the money to work quickly in a way that both stimulates job creation and does not create a long-term commitment of basic funding is one aspect of what Birnbaum referred to as she encouraged council members to help her discover “how NIEHS can be bigger than the sum of its parts.”

As Birnbaum explained, during her first four weeks at NIEHS, she has aggressively searched for ways to bring together the human resources of the Institute and its partners by boosting employee morale, filling key leadership positions, and building or re-building relationships with other agencies, NIH institutes and centers, and the extramural community.

Speaking of the challenges she sees for environmental health scientists, Birnbaum said, “We need both the best individual- and the best team-science to address the complex diseases and the complex environmental impacts that we're dealing with... [and] we need to get a better handle on how we integrate all this information in order to prevent disease in our population.”



*Birnbaum pondered the latest news on the stimulus funding. “At this point, it is such a fast moving target that what we heard a week ago from Building One [at NIH] is not what we're hearing today,” she said. (Photo courtesy of Steve McCaw)*



*As Acting Director of the NIEHS Division of Extramural Research and Training (DERT), Gwen Collman, Ph.D., was a frequent contributor to the discussion of stimulus funding. (Photo courtesy of Steve McCaw)*

Birnbaum told members that she welcomes advice from council on additional ways to promote synergy, maximize resources and expand translation of research results. She offered a broad definition of translation that combines “bench to public health” and better understanding of how animal research impacts human disease with the traditional “bench to bedside” theme.

Birnbaum’s message underscored the synergy she intends to facilitate by promoting non-traditional collaborations. “It’s not enough to look at a single type of cell or a single type of organ system,” she argued. “We’re going to have to look at the whole individual, and this is going to require a lot of cross-disciplinary activity.”

Keeping the director’s priorities in mind, along with their own concerns and perceived needs, Council members took the initial steps in recommending priorities for Recovery Act funding. Birnbaum admonished the members to bear in mind that there is “no expectation of more than two years of supplemental funding.”

As Birnbaum noted during the discussion, “We’re getting updates [on the Recovery Act] as we speak.” She added, “Everything is going to be very quick.... You can expect to see requests for solicitations and information about the areas of interest that we have out on the street by the end of the month.”



*Member George Leikof, Ph.D., was one of several concerned by how quickly new grants will need to be bid and processed. “I think it should be done by September of this year to have any impact at all,” he noted. (Photo courtesy of Steve McCaw)*



*Member Ken Ramos, Ph.D., center, seemed to express Council sentiment as he observed, “The May meeting will be a challenging meeting in terms of the logistics for the number of decisions that are going to have to be made.” Sitting beside him was Kevin Stephens, M.D., J.D. (Photo courtesy of Steve McCaw)*



*“This is an opportunity to help young investigators,” commented Liebler, center, seated with Wani and member Stephani Hines, right. “I would urge, in the strongest terms terms, that that be made a high priority.” Birnbaum said it was one of the priorities she has in mind. (Photo courtesy of Steve McCaw)*



*Three of the new members follow the director’s report on their electronic Council Books. Shown left to right are Phan, McCabe and Lemasters with DERT staff seated behind them. (Photo courtesy of Steve McCaw)*

## New Faces and More Openness at Council Meeting

The February 19 meeting included five new members to fill the seats of retiring members on the Council and enhanced access to deliberations for people unable to attend the public sessions in person.

The meetings, except for closed sessions to consider grant proposals, have always been open to members of the public — as long as they could physically attend. At this meeting, for the first time a streaming video gave anyone with an internet connection access to the public portion of the meeting. Except for confidential information about grants, the Council Book, a compilation of reports by NIEHS leaders, was made available online prior to the meeting. Videos of proceedings and presentations at the meeting will be posted on the NIEHS website as an effort to better meet the spirit, as well as the letter, of the Sunshine Act.

New Council members in attendance included the following:

- University of Cincinnati Professor of Epidemiology [Grace LeMasters, Ph.D.](#), who is director of an NIEHS training grant on Molecular Epidemiology in Children's Environmental Health
- Oregon Health and Science University (OHSU) Professor of Molecular and Medical Genetics [Stephen Lloyd, Ph.D.](#), a senior scientist in the OHSU Center for Research on Occupational and Environmental Toxicology
- University of Michigan Professor of Molecular and Cellular Pathology [Sem Phan, M.D., Ph.D.](#)
- Dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California San Diego [Palmer Taylor, Ph.D.](#)
- Executive Director of the non-profit advocacy organization Improving Kids' Environment [Janet McCabe](#)

Birnbaum also presented certificates of appreciation to two retired members of council whose terms were extended to ensure a quorum of voting members at the meeting — Dan Liebler, Ph.D., of Vanderbilt University and Altaf Wani, Ph.D., of Ohio State University. She also recognized the contributions of three retiring members not present at the meeting — Kate Dixon, Ph.D., of the University of Arizona, Bruce Freeman, Ph.D., of the University of Pittsburgh and Lisa Greenhill of the Association of American Veterinary Medical Colleges.

## NTP Board Peer Reviews Draft Cancer Reports

*By Robin Mackar*

### Report on Carcinogens (RoC)

National Toxicology Program (NTP) reports on five of the nine compounds being considered for listing in the 12th Report on Carcinogens (RoC) were for the first time peer reviewed by the NTP Board of Scientific Counselors (BSC) February 24 in Rodbell Auditorium. Four of the chemicals, including *ortho*-nitrotoluene, used in the synthesis of some dyes; aristolochic acids, a family of acids used in herbal medicine; captafol, previously used to control fungal diseases in fruits, vegetables and other plants; and riddelliine, a toxic plant component, underwent a thorough, but relatively quick review by the BSC. The majority of the day was spent discussing the weight of evidence presented in the styrene draft substance report.

Styrene is a highly flammable liquid used worldwide in the production of polymers that are incorporated into products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers and carpet backing. The NTP's preliminary policy decision for listing styrene is that styrene is *reasonably anticipated to be a human carcinogen* based on limited evidence in humans, sufficient evidence of carcinogenicity in experimental animals and supporting mechanistic data.

“This is the first time we’re bringing draft substance profiles from the RoC for peer review to the Board,” said Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy and Review, during her presentation to the BSC. She outlined the new multi-step scientific review process for the RoC and presented the board’s charge, which is to determine whether the scientific information cited in each draft substance report is technically correct, clearly slated and supports the NTP’s preliminary decision regarding its listing in the RoC. She explained the status of the remaining four RoC candidate substances — cobalt-tungsten carbide powders and hard metals, metalworking fluids, certain glass wool fibers, and formaldehyde — and told the board they would likely be peer reviewing those substances in the next year.

Wolfe also highlighted the multiple opportunities for public input into the process, which was evident at the board meeting. Eight public commenters were provided ample opportunity to offer oral remarks or make presentations regarding the styrene draft substance profile, in addition to providing written comments for the record. Board members also had an opportunity to discuss and deliberate the comments with the public presenters. Representatives from industry included George Cruzan from ToxWorks who spoke on behalf of the Styrene Information Center and James Bus, Ph.D., from Dow Chemical speaking on behalf of the American Chemistry Council Ethylbenzene Panel. They and others shared reasons why they did not agree with the NTP draft listing. A non-scientist voice was also heard from Jay Merrell, who spoke on behalf of Industrial Dielectrics, a business his father started in 1966 that uses styrene-polyester resin to make highly engineered molding compounds. Merrell urged the NTP to do its work carefully, but not to needlessly frighten people about this compound.

The public comments followed a scientific presentation on each compound made by NTP staff. In the case of styrene, RoC Director Ruth Lunn, Dr. P.H., discussed the critical papers and data used by the NTP to recommend listing styrene as *reasonably anticipated to be a human carcinogen*. Her analysis included human, animal and mechanistic data.



Wolfe provided a thorough overview of the new RoC process, which substantially increases opportunities for public input. (Photo courtesy of Steve McCaw)



New NIEHS/NTP Director Linda Birnbaum, Ph.D., second to right, participated actively in the two-day meeting and presented her vision for the NIEHS/NTP as well as budget updates. Sitting with her left to right are John Bucher, Ph.D., NTP Associate Director, Novak and NTP lead scientist for the technical reports, Michelle Hooth, Ph.D. (Photo courtesy of Steve McCaw)



The NTP recommended listing aristolochic acids as *known to be human carcinogens* based on sufficient evidence from studies in humans and supporting mechanistic data. Captafol, o-nitrotoluene, and riddelliine are recommended to be listed as *reasonably anticipated to be human carcinogens*.

Each compound reviewed had two to six lead BSC or ad hoc reviewers. Other BSC members also participated in the discussion of each profile. Overall, the BSC provided editorial and thoughtful comments and input on each draft report that the NTP will use to finalize its policy decision regarding the compound's listing in the RoC. The BSC meeting was aptly chaired by Kenneth Portier, Ph.D.

### Technical Reports on NTP 2-Year Cancer Bioassays

The following day, the NTP BSC Technical Reports Review Subcommittee completed its independent public peer review of six draft NTP technical reports. These reports are used by regulatory authorities worldwide for developing risk assessments and regulations to establish “safe” levels of chemicals in the environment.

The agents studied included goldenseal root powder, a dietary supplement ingredient; androstenedione, a dietary supplement banned in 2004 for over-the-counter sales;  $\beta$ -myrcene, an ingredient used in the production of scents and flavorings; 2,3',4,4',5-pentachlorobiphenyl (PCB 118), a dioxin-like compound evaluated as part of NTP's program on dioxins; 3,3',4,4'-tetrachloroazobenzene, a contaminant found in herbicides; and tetralin, an industrial solvent. An overview of each report was presented by an NTP study scientist, followed by the committee's peer review. An additional presentation by NTP pathologist Mark Cesta, D.V.M., following the overview of the  $\beta$ -myrcene report provided more detail about the histopathologic features of the non-neoplastic renal diseases that were seen in the rat studies. All of the agents presented were found to have carcinogenic activity in the rodent models. The draft reports are available [online](#). The technical report reviews were chaired by Raymond Novak, Ph.D.

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*James Sherley, M.D., Ph.D., center, was one of the newly appointed members attending a BSC meeting for the first time. Michael Pino, D.V.M., Ph.D., sat to Sherley's left. (Photo courtesy of Steve McCaw)*



*This was also the first public peer review of a technical report for Chad Blystone, Ph.D., above left. He was the study scientist for the androstenedione technical report and is an IRTA fellow recently hired in the Toxicology Branch as part of NTP's Applied Toxicology and Carcinogenesis postdoctoral training program. Grace Kissling, Ph.D., NTP biostatistician conversed with Blystone at the meeting. (Photo courtesy of Steve McCaw)*



*Cesta shown at a recent training class put his new skills to work as he presented pathology slides to the BSC. (Photo courtesy of Steve McCaw)*

# NIEHS Gears Up for SOT

*By Eddy Ball*

Each year, one of the Institute's major national meetings is the annual gathering of members of the Society of Toxicology (SOT). With the appointment of Linda Birnbaum, Ph.D., as NIEHS and National Toxicology Program (NTP) director — the first toxicologist to hold that leadership position — the SOT 48th Annual Meeting and ToxExpo March 15–19 in Baltimore will be an especially high-profile one for NIEHS.



In addition to its booth and scientific presentations and posters, this year the NIEHS will engage in three important activities as part of its presence at the meeting:

- Meet the Director of NIEHS and NTP — NIEHS Director and former SOT Director Linda Birnbaum will talk about her plans for leading NIEHS and NTP in its fifth decade of promoting the environmental public health of the United States and the world through research directed at preventing and treating disease. Birnbaum, who was also president-elect of the International Union of Toxicology, will speak at a luncheon March 18.
- NTP Criteria for Hazard Identification in Non-Cancer Studies — Discipline leaders Paul Foster, Ph.D., and Dori Germolec, Ph.D., will conduct an exhibitor-hosted session March 17 on how the NTP will reach conclusions on its non-cancer studies in reproductive, developmental and immune system toxicology.
- Division of Extramural Research and Training — Leaders and grant administrators will expand their outreach efforts to current and potential grantees at a special Brown Bag Luncheon on March 17 and in the Grants Room March 17 and 18.

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## Suk Represents NIEHS at President's Cancer Panel Meeting

*By Eddy Ball*

NIEHS took a seat at a meeting of the President's Cancer Panel (PCP) with a presentation by NIEHS Center for Risk and Integrated Sciences Director Bill Suk, Ph.D., on January 27 in Phoenix. Suk was part of a program on "Nuclear Fallout, Electromagnetic Fields and Radiation Exposure" — the final meeting in the four-part 2008-2009 PCP meeting series devoted to the topic of "Environmental Factors in Cancer."

The 2008–2009 PCP series involved a review of the general lines of evidence that show environmental exposures are important in cancer etiology. The panel addressed the role of "avoidable" or "preventable" factors, along with the magnitude of the role of environment.

Suk's presentation outlined the broader definition of "environment" that informs the Institute's environmental public health initiatives on many scales, ranging from microscopic to global. "For this workshop," he said at the beginning of his presentation, "we are interested in environmental health at the community level and particularly how decisions in this region can have impacts, positive or negative, on the health and well-being of people in this community."

As he discussed the gene/environment interactions that are involved in the risk for complex disease, Suk outlined the contributions that the environmental health sciences can make to improving public health in relation to fallout, electromagnetic field and radiation exposures. These include the development of advanced technologies for measuring exposures and assessing the body's responses to the environment with the goal of using the information to design new preventive and therapeutic strategies.

“While early detection strategies are critically important because they allow treatment to begin early in the course of disease,” Suk said of the environmental health sciences' approach to disease, “true cancer prevention strategies aim to reduce the incidence of cancer by lessening the number of stressors that cause disease.”

Suk concluded by challenging his colleagues to view the topic of “Environmental Factors in Cancer” on a global scale as an emerging epidemic of non-communicable disease. He pointed to the dramatic increase in cancer rates in developing countries and underscored the importance of understanding the heightened susceptibility of children worldwide to cancers linked to environmental factors.



*SBRP Director and former Acting Deputy Director Bill Suk (Photo courtesy of Steve McCaw)*

Authorized by the National Cancer Act in 1971, the PCP is funded through the National Cancer Institute's Division of Extramural Activities. With the input of scientists, advocates and representatives of government agencies, the three-member panel issues reports on various aspects of cancer, annually and biannually, to fulfill its mission to monitor the development and execution of the activities of the National Cancer Program in direct [reports](#) to the President of the United States.

Over the years, the panel has examined quality of life for cancer patients, access to care issues, and lifestyle risk factors related to cancer. Earlier [meetings](#) in the 2008–2009 series explored the issues of industrial and manufacturing exposures, agricultural exposures, indoor/outdoor air pollution and water contamination.

Along with Suk and a number of distinguished grantees attending meetings in the series, the Institute's leadership was also represented by NIEHS Associate Director Chris Portier, Ph.D., at the September 16, 2008 meeting in East Brunswick, N.J.

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## **NIEHS Grantees Speak at Global Health Symposium**

*By Eddy Ball*

Veteran NIEHS Grantees Peter Thorne, Ph.D., and Joseph Graziano, Ph.D., were among the global health experts giving keynote talks at the Managing Toxic Risks for Global Health symposium February 20 at Duke University. Along with five other experts, Thorne and Graziano explored the goals of clean air, pure water and safe food in preventing disease and improving environmental health at the daylong symposium.

Sponsored by the [Duke Integrated Toxicology and Environmental Health Program](#), the NIEHS-funded [Duke Superfund Basic Research Center](#) and the [Duke Global Health Institute](#), the symposium was chaired by Professor Ed Levin, Ph.D., director of the Training Core of the Duke University Superfund Research Center.

[Thorne](#), a University of Iowa College of Public Health professor and director of the NIEHS-funded Environmental Health Sciences Research Center there, launched his exploration of “Bioaerosol Exposures and Asthma: Effects of a Changing Climate,” with an account of his experiences during the “500-year” flood that ravaged Iowa along the Iowa River and Cedar River in the summer of 2008 — the second of its kind since 1993. Along with his work in New Orleans post-Katrina, Thorne said, the Iowa flood strengthened his conviction that “anthropogenic climate change [can] lead to more problems with flooding and indoor moisture levels such that we can expect a significant effect on asthma and allergy.”

As Thorne explained, what the floods leave behind — including human sewage, animal waste, chemicals and toxic algae — creates microbial airborne hazards that can impact respiratory health through infectious bacteria and virus, inflammatory agents and mold allergens. Along the Gulf and in Iowa, the after-effects of the floods included an upsurge in asthma, allergy, and persistent chronic cough with flu-like symptoms related to contamination of indoor air with allergens and pathogens.

Models of the climate in the future point to an increase in such events and a friendlier environment for the triggers of respiratory disease. A wetter, warmer world with higher CO<sub>2</sub> levels could mean an increase in mold- and pollen-producing biomass and a longer exposure season, as well as a greater vulnerability to extreme weather events that raise moisture levels.

Such weather events, triggering threats to health, happen all too frequently in south Asia, where [Graziano](#) and colleagues performed the fieldwork that underpinned his presentation, “Exposure Consequences and Remediation of Arsenic and Manganese in Bangladesh.” [Graziano](#) is an associate dean for Research as well as a professor and the interim chair of the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health.

Graziano heads a binational group that pursued a multi-faceted, decade-long Superfund-supported research agenda in Bangladesh. The investigators studied 12,000 people to establish the extent of arsenic exposure from drinking water in shallow tube wells, the mechanisms of arsenic metabolism, the myriad direct and inter-generational health effects, and measures to protect residents from continued exposures to very high levels of arsenic. Based on the results of mapping wells and testing arsenic levels, the cross-disciplinary group crafted a novel strategy for remediation. The investigators later extended their research to elevated manganese concentrations found in the water from the wells, including those that are arsenic free.



*Levin, left, the lead organizer and chair of the event, introduced Diamond, the first speaker of the day. Diamond discussed the role of cultural myth in what she argued is an “unsustainable” global economic and environmental situation. (Photo courtesy of Steve McCaw)*



*Listening closely to speaker Eve Diamond was Heather Stapleton, Ph.D., a Duke professor and [2008 Outstanding New Environmental Scientist \(ONES\)](#) awardee. Sitting to her right was NIEHS Senior Science Advisor Sally Tinkle, Ph.D. (Photo courtesy of Steve McCaw)*

The intervention involved drilling deeper wells to tap cleaner water below the arsenic and manganese reserves nearer the surface — work financed by an anonymous donor — encouraging people to switch wells when they could and launching an aggressive educational outreach campaign to translate study findings into preventive strategies. The team also discovered that folate supplementation facilitates arsenic methylation and elimination, thereby lowering blood arsenic levels.

In addition to Thorne and Graziano, the [program](#) included talks by Miriam Diamond, Ph.D., of the University of Toronto, Dan Costa, Ph.D., of the U.S. Environmental Protection Agency (EPA), Duke environmental economist Subhrendu Pattanayak, Ph.D., Jason Carver, of the U.S. Department of Agriculture, and Jeff Herndon, Ph.D., of the U.S. EPA.



Graziano described his very first trip in 1999 to a severely affected village in Bangladesh as “a life-altering experience” that convinced him “we have to work on this.” (Photo courtesy of Steve McCaw)



In his talk, Thorne, center, said of the 2008 flood in Iowa, “When you think it can’t get any worse, it does.” He is shown listening to the presentation by Graziano. (Photo courtesy of Steve McCaw)



Pattanayak, above, reported on his group’s World Bank-funded outreach program to educate people in rural India about the benefits of improving sanitation and water quality through well constructed and maintained latrine facilities. (Photo courtesy of Steve McCaw)



NIEHS Director Linda Birnbaum, Ph.D., center, shared a humorous moment during the question-and-answer session following Graziano’s talk. She was flanked by Levin, right, and graduate student Matthew McElwee, left, who works in the NIEHS Comparative Genomics Group. (Photo courtesy of Steve McCaw)

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# Columbia University Hosts Research Translation Workshop

*By Rebecca Wilson*

Four years after the addition of a research translation component to the NIEHS Superfund Basic Research Program (SBRP) in 2005, the leaders of the SBRP research translation cores gathered at a workshop on February 11-13 to assess their progress.

Columbia University SBRP hosted the workshop, “Translating SBRP Triumphs into Public Health Progress: Understanding and Implementing Effective Research Translation,” which was held at the Lamont-Doherty Earth Observatory.

An estimated fifty participants from across the country gathered to discuss the different approaches their programs are taking to fulfill their research translation mission, share best practices and build on networking opportunities. In addition to members of the research translation cores, community stakeholders and members of the regulatory community were also in attendance. According to Beth Anderson, NIEHS-SBRP program analyst, the workshop “provided the participants with many opportunities to learn about each other’s activities, to identify opportunities to collaborate, and to set the stage for ongoing interactions among the group.”



*Telfer, center, joined meeting participants Martha Keating, from the Community Outreach Core at Duke University, left, and Kathleen Gray, from the Community Outreach Core at UNC-Chapel Hill, in the on-line discussion following a keynote presentation. (Photo courtesy of Beth Anderson)*

After introductory remarks by Columbia University SBRP grantee Joseph Graziano, Ph.D., and Anderson, the workshop explored four themes. In each session, the theme was introduced by a keynote speaker and was followed by an interactive, facilitated on-line discussion. The keynote sessions and group discussions were followed by break-out sessions.

The first session, “Partnerships,” opened with a presentation by Mark Maddaloni, Ph.D., a risk assessor from EPA Region 2, which is responsible for environmental protection in New York, New Jersey, Puerto Rico, the United States Virgin Islands and seven tribal nations. Maddaloni discussed his approach to partnering with different populations and his experiences working with local school systems to address the potential problems of lead contaminants present in Astroturf and other man-made turfs.

The discussion of the second topic, “Two-Way Communication,” began with a presentation by Jana Telfer, from the Center for Disease Control’s Agency for Toxic Substances and Disease Registry (ATSDR) Office of Communications, on ways to foster communication in times of crisis. She advised that truth, openness and empathy are necessary for establishing rapport with the public and that a speaker should clarify what is known as well as what is unknown in a situation.

Theresa Pardo, Ph.D., of the Center for Technology in Government (CTG) at the University of Albany, opened the discussion for the third theme, “Building Technical Capacity.” She talked about how knowledge networks are formed and operate. Pardo then outlined a multi-pronged approach to find solutions to communication gaps that are often present between groups of stakeholders.

The final theme, “Science-to-Action,” was addressed in a presentation by Elizabeth Yeampierre, who talked about a federated network of environmental justice organizations across the country. Yeampierre also shared her experiences in working with communities to utilize science in their advocacy of decision-making processes and mobilize communities to effect change.

The workshop provided participants with many opportunities to learn about each other’s activities, to identify opportunities for collaboration and to lay the foundation for ongoing interactions among the group.

(Rebecca Wilson is an environmental health information specialist for MDB, Inc., a contractor for the NIEHS Superfund Basic Research Program and Workers’ Education and Training Program.)

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## Former Postdoc Featured in TV Special

*By Eddy Ball*

When former Postdoctoral Fellow John Fortune, Ph.D., left NIEHS in 2005, he knew he was taking an important step that would change his career path. What he couldn’t have known was that in February 2009 he would appear on national television as one of the real-life heroes showcased in a National Geographic Channel special on the “[Hi-Tech War on Terror](#),” speaking as a specialist in the application of innovative technology to protect people and infrastructure in the event of terrorist attacks.

During his four years at NIEHS, Fortune was a member of the [DNA Replication Fidelity Group](#) headed by Principal Investigator Tom Kunkel, Ph.D., which is known for its pioneering work in DNA replication and mutagenesis. He was a talented young biologist with degrees from Duke and Vanderbilt and a growing list of publications in peer-reviewed journals.

Today, Fortune works at the Department of Homeland Security (DHS) as a program manager in the Science and Technology Directorate’s Infrastructure and Geophysical Division. He oversees twelve programs, including “[Resilient Tunnel](#),” which was featured in “Hi-Tech War on Terror.” The segment showed Fortune and scientists from West Virginia University testing fireproof inflatable devices that can be installed at intervals in subway and traffic tunnels to block fires from accidents and explosions.

The journey from the bench to the television set began when Fortune landed an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellowship. He accepted an assignment at DHS that turned into something he hadn’t expected at all. “I went in thinking of my background in biology,” Fortune recalls, “and [18 months later] ended up working on transportation infrastructure.”



*Fortune, shown during one of his lighter moments as an NIEHS trainee, now takes technology a little more seriously in his position at DHS. He’s also had to swap his lab-casual shorts and sandals for a suit and tie. (Photo courtesy of Tom Kunkel)*

Looking back on his circuitous path to DHS, where he is far more likely to talk of material stress and thermodynamics than mismatch repair and double-strand breaks, Fortune credits his experiences at NIEHS with helping prepare him for the transition. As a trainee, he took advantage of career development experiences at NIEHS and elsewhere, especially in regard to communication and presentation skills. “It was a great experience,” he said of his time at NIEHS, “and I am much indebted to Tom [Kunkel] for the opportunities and support provided during my time there.”

Fortune transferred the kind of divergent, “outside-the-box” thinking he applied at the bench designing experiments to his new challenges in explosives protection and surveillance. He also built on his curiosity, his ability to be flexible and his willingness to tackle “steep learning curves” — in terms of both his technical work and the “different world” of government service, where his earlier lessons in collaboration and communication have proven invaluable.

“At NIEHS, trainees are exposed to some of the workings of government, which is very helpful,” Fortune said, “but it’s a different world here, and there is some culture shock in the beginning that’s very hard to anticipate.” These days Fortune finds himself “balancing different responsibilities at the same time” as he deals with budgets, new cutting-edge developments, politics and other competing responsibilities.

Although he misses the slower pace and less congested environment of the Triangle, Fortune said he’s enjoying his exposure to different aspects of science and constantly learning new things. For those who like the idea of an alternate career path, Fortune recommends networking to get a feel for the culture of those who work in the field. Even the busiest people, he notes, such as congressmen and executives, are often willing to spend time with curious and motivated people.

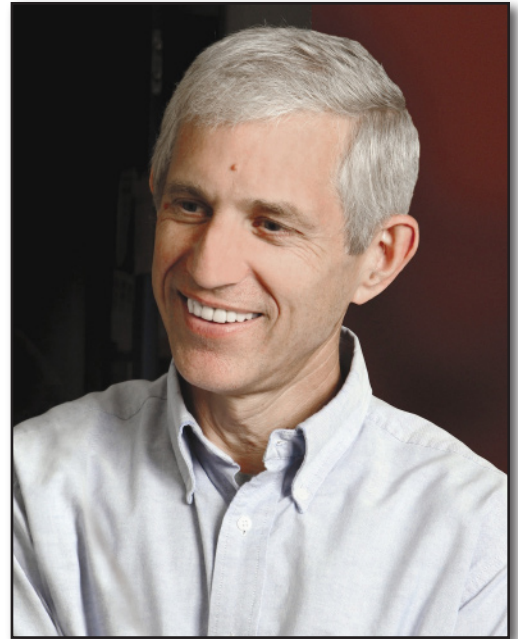
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## Schroeder Appointed EHP Science Editor

*By Eddy Ball*

In December 2008, Jane Schroeder, D.V.M., Ph.D., joined the staff of [Environmental Health Perspectives \(EHP\)](#) as its new science editor, providing scientific expertise and oversight for virtually every aspect of the NIEHS journal. Schroeder promises to bring a truly cross-disciplinary approach to her duties at the journal — rooted in her experiences as a veterinarian, environmental public health specialist, University of North Carolina at Chapel Hill (UNC-CH) epidemiologist, award-winning educator and mentor, and reviewer for epidemiology and cancer journals.

“Jane is an excellent fit for EHP,” commented Editor in Chief Hugh Tilson, Ph.D. “She combines the scientific rigor of a specialized investigator with an insatiable curiosity about all the scientific fields represented in the journal’s content and among its editorial board and board of associate editors.”



*Kunkel, above, described Fortune as “a particularly fine example... of how trainees can use their fundamental strengths to succeed in what many would consider a non-traditional career path.” (Photo courtesy of Steve McCaw)*



“My duties include reviewing news articles, press releases and the scientific content of the papers we’ve accepted,” Schroeder said. “I’m also involved in the process of selecting papers for peer review and with choosing papers for press releases and feature articles.” Working with Tilson and the editorial staff, Schroeder will help shape the directions the journal takes and the themes of individual issues, as well as the [online modules](#) the journal offers science educators.

Schroeder explained that she considers an important part of her role keeping abreast of developments and trends in the environmental health sciences and “mak[ing] sure that people stay aware of EHP as the premier environmental health journal when they are ready to publish their findings.” She pointed to the journal’s enviable impact factor of 5.64, making it the first among 160 environmental science journals and second among 100 public, environmental and occupational health journals with its English and [international editions](#) for readers in more than 190 countries.

Looking to the future of EHP, Schroeder noted that within the next few months the journal will begin offering podcasts on the website, highlighting featured papers and research breakthroughs from upcoming issues as well as interviews with leading figures in the environmental sciences including toxicologist and NIEHS Director Linda Birnbaum, Ph.D. “I’ll also be expanding the conferences we attend,” she said, “to include, among others, meetings of epidemiologists such as the Society for Epidemiologic Research.”

Schroeder began her career in biomedicine as a veterinarian with her doctorate from the University of California Davis. After practicing small animal medicine and surgery for eight years, she transitioned into public health by earning a Master of Public Health in environmental and occupational health from the Rollins School of Public Health at Emory University in the mid-1990s. The public health experience, she said, sparked an interest in epidemiology that inspired her to pursue a doctorate and later to teach and research as a professor of epidemiology at the School of Public Health at UNC-CH.

Along the way, Schroeder received a long list of honors for her scholarship, research and teaching. She also held postdoctoral fellowships at UNC-CH from the National Cancer Institute and in the Epidemiology Branch at NIEHS. In the course of 16 years as a graduate student and professor at UNC, she conducted several studies and served as the principal investigator on grants from NIH and other sources devoted to better understanding uterine fibroids and several types of cancer, including non-Hodgkin’s lymphoma and prostate cancer.

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*“It’s a great time to be at the center of something like EHP,” Schroeder said of her new position, “and to be able to impact the field of environmental health science. I feel like a kid in a candy store.” (Photo courtesy of Steve McCaw)*

# Duke Bioethicist Reflects on Personal Genomics

By Eddy Ball

In 1989 and 1990 when Robert Cook-Deegan, M.D., was a consultant to the director of what was then the NIH National Center for Human Genome Research, James Watson, few people could have predicted how the evolution and democratization of genomics would impact society. Nearly 20 years later, during a lunchtime lecture at Duke Hospital in Durham in January, Cook-Deegan shared some of his thoughts about the new field of consumer genomics in a talk titled “Personal Genomics: Do We Need Doctors Anymore?”

Today, [Cook-Deegan](#) is the director of the Center for Genome Ethics, Law & Policy (GELP) in the Institute for Genome Sciences & Policy at Duke University, where the ethical and legal implications of the genomic revolution occupy much of his time. GELP houses the Center for Public Genomics, which is a Center of Excellence co-funded by the U.S. Department of Energy and the National Human Genome Research Institute.

“I’m going to talk about the complex interactions between the public sector and the private sector,” Cook-Deegan said as he began his talk. “I’m also going to be talking about a phenomenon that began about a year and a half ago — so-called ‘personal genomics’ — and some of the issues that arise in business models that incorporate genomic technologies into the transport of information to consumers.”

As Cook-Deegan pointed out, genomics has advanced at an unprecedented pace in a very short period of time. The field was founded when the Supreme Court upheld the patent on a living organism in *Diamond v. Chakrabarty* (1980). The term “genomics” was coined in the late 1980s to describe the practice of conducting molecular analysis of DNA and RNA on a larger scale than human genetics previously had.

The cost of genomic profiling, Cook-Deegan said, has dropped precipitously from the approximate \$100 million it cost to do Craig Venter’s genome in 2007, and a company called Complete Genomics projects that genome mapping will be available for as little as \$5000 by the end of 2009. The dramatic reduction in cost and an equally dramatic increase in the power of available technologies are opening up commercial opportunities in consumer genomics.



*“This is an incredibly powerful technology that’s entering our culture, and we don’t know what it’s going to do,” Cook-Deegan said, “any more than in 1994 we knew what the World Wide Web was going to do.” (Photo courtesy of Steve McCaw)*



*Answering a question from NIEHS Bioethicist David Resnik, J.D., Ph.D., center, about distinguishing between the recreational and medical uses of personal genomic information, Cook-Deegan conceded that there is no “bright line,” but added, “There are no bright lines anywhere in medicine.” (Photo courtesy of Steve McCaw)*

“At the beginning of this era, the 1980s, what everybody was doing was trying to find genes that we knew were broken because we knew there was an inherited pattern,” Cook-Deegan explained. “What has happened in the meantime is that we’ve gone upscale.... We can sample a million different genotype changes in a single experiment.... Now what we are talking about are people’s whole genomes being available for analysis.”

The growth of consumer genomics for “recreational” purposes such as ancestry studies and social networking, Cook-Deegan argued, has outstripped the ability of ethics and law to deal with its social ramifications. “We have an oversight and regulatory mechanism that is primarily framed around how we think about testing for Mendelian conditions in high-risk families,” he said, “but that’s not really what this is.”

Cook-Deegan proposed that society might be better served by treating consumer genomics as a loosely regulated “open source,” similar to Google and Wikipedia, to let users in the marketplace experience its network benefits while fine-tuning weaknesses. “We [often] put up policies to keep bad things from happening [with a new technology], but we completely forget that we may be blocking all the future benefits.”

As inadequate as the current decentralized legal model is for dealing with consumer genomics, the answers are not simple. “I don’t know where we’re going to land,” he admitted. “I don’t even know where I’m going to land in thinking about regulation.”

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## Higginbotham Challenges Students at NIH Black History Event

*By Eddy Ball*

The talk was for everyone at NIH — and by videocast for people at NIEHS — but the target audience on February 18 was clearly the students when ophthalmologist Eve Higginbotham, M.D., delivered a talk in celebration of Black History Month. Higginbotham, who is dean of the Morehouse School of Medicine, spoke on the “Quest for Black Citizenship in the Americas – Inspiring Future Leaders” at the National Library of Medicine’s Lister Hill Center in Bethesda.

NIH Acting Director Raynard Kington, M.D., Ph.D., made opening remarks and predicted that the talk would provide “inspiration for the future generation.” Lecture host Paul Sieving, M.D., Ph.D., director of the National Eye Institute, followed Kington with an introduction of Higginbotham and her many accomplishments as a physician, leader and advocate for minority participation in science. Sieving described [Higginbotham](#), the first woman to head a major university ophthalmology department, as a “friend for a number of years” and a teacher and mentor “who practices what she preaches.”

Closely related to her award-winning work in glaucoma, which strikes African Americans in disproportionate numbers, are Higginbotham’s research interests in the area of health disparities. Her experience in that field, including a 2008 review co-authored with former Surgeon General David Satcher, M.D., informed much of her talk. She urged her audience to maintain focus and “keep your



*“Poor health literacy is a stronger predictor of individual health than age, ethnicity and nearly every other factor,” Higginbotham told the students as part of her appeal that they strive to correct health disparities. (Photo courtesy of Morehouse School of Medicine and NIHOD OEO)*

goals in mind” — both as a way of realizing personal dreams and as a way of impacting the disparities in health and healthcare experienced by minorities in the U.S. and the poor health literacy that affects the wellbeing of as many as 90 million Americans.

“We’re all bound together to try to make a difference in medicine and make sure we overcome these health disparities,” Higginbotham said. To reinforce her message, she invoked the spirit of Martin Luther King, Jr., who once said, “Of all the forms of inequality, injustice in health is the most shocking and the most inhumane.”

Achieving a more diverse scientific population, she explained, will not only give minorities their long deferred opportunities in medical research. It will also help the scientific and medical communities better understand the challenges of health disparities. “Diversity of background brings a diversity of perspective,” she argued, improving the overall state of health and healthcare in the U.S.

NIH Deputy Director for Intramural Research Michael Gottesman, M.D., offered closing remarks at the event. He referred to the number of special programs, scholarships and fellowships that NIH offers to help young scientists and promised to work for even more opportunities. “Can we do better?” he asked. With a reference to the famous words of America’s first African American President, he answered enthusiastically, “Yes, we can!”

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## Colwell to Speak at Eighth Spirit Lecture

*By Eddy Ball*

The NIEHS Spirit Lecture Series, the hallmark event in NIEHS Women’s History Month celebrations since 2002, will welcome environmental microbiologist and scientific administrator Rita Colwell, Ph.D., on March 27. Colwell’s talk, “Climate, Oceans, Infectious Diseases, and Human Health: The Saga of Cholera,” will begin at 11:00 a.m. in Rodbell Auditorium.

Colwell will address the issue of climate change by focusing on the interaction of humans with the cholera bacteria and the implications for global environmental health. She will also explore the ways the patterns of other climate-driven diseases are expected to change as the impact of global warming becomes more evident.

Colwell is well known in scientific circles for her work in biology and ecology as well as for her tenure as the first woman to serve as the director of the U.S. National Science Foundation (NSF) from 1998 to 2004. She is a prolific author, with 17 books and 700 scientific articles to her credit. Colwell also produced the award-winning 1982 film *Invisible Seas*.

During her career as a researcher and administrator, Colwell has received nearly 50 honorary degrees and a long list of top honors from her scientific colleagues, including the National Medal of Science in 2007. In addition to heading NSF, she also served as president of the American Association for the Advancement of Science (AAAS), the American Society for Microbiology and, currently, the American Institute of Biological Sciences.

After leaving NSF, Colwell joined Canon U.S. Life Sciences as chief scientist and was later voted chairman of the company. She also accepted appointments as a distinguished professor at the University of Maryland at College Park and Johns Hopkins University Bloomberg School of Public Health.



*2009 Spirit Lecturer Rita Colwell*

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# Science Notebook

## Estrogen and Hormone Replacement in Menopause

By Robin Arnette

The use of estrogen and hormone replacement therapy (HRT) to treat menopausal symptoms in women has caused confusion in the general public and cardiology research circles. By the early 90s, the concept that estrogen and other hormones had a beneficial effect on the heart and its blood vessels was widely appreciated, based on two decades of animal and pre-clinical data. However, in 2003, the [Women's Health Initiative \(WHI\)](#) study of a large cohort of older women declared that estrogen was bad for women who were postmenopausal. Now, the pendulum has swung back to the idea that hormone therapy is beneficial to the heart, depending on *when* the therapy is administered.

Distinguished Lecturer Michael E. Mendelsohn, M.D., a specialist in Cardiovascular Disease (CVD) at Tufts University and the New England Medical Center says, "The 2006 WHI analysis showed that older women were at increased risk for heart disease following HRT, whereas younger women were, in fact, protected." Mendelsohn presented a seminar February 10 at NIEHS titled "Estrogen Action in the Cardiovascular System." In his seminar, Mendelsohn explained why he and others in the field believe that current data support the hypothesis that women who are going through menopause or recently postmenopausal receive a protective effect with HRT. The talk was hosted by Mendelsohn's friend and collaborator Kenneth Korach, Ph.D., chief of the NIEHS Laboratory of Reproductive and Developmental Toxicology.

When all of the published data on the topic were reviewed in 1992, the results consistently showed a 30–35 percent reduction in the relative risk of cardiovascular events and cardiovascular morbidity and mortality in menopausal women who took estrogen. A decade later, however, the WHI study completely changed this paradigm. "It reported that the postmenopausal women in the study experienced a substantially increased risk of coronary heart disease," Mendelsohn recalled. "There was an absolute uproar in the lay press, and NHLBI stopped the estrogen-only arm of the trial early."



*Mendelsohn is the first recipient of the Elisa Kent Mendelsohn Professorship of Molecular Cardiology and Medicine at Tufts University School of Medicine and executive director of the Molecular Cardiology Research Institute at the New England Medical Center. (Photo courtesy of Steve McCaw)*



*Korach, who monitored the question-and-answer session, was one of the investigators who developed animal models and, in collaboration with Mendelsohn, helped resolve the issue regarding estrogen and its therapeutic effects in the development of cardiovascular disease. (Photo by Steve McCaw)*

Mendelsohn explained that the women in the WHI were mostly well past menopause (greater than 10 years) and had not taken HRT previously. Work from his lab and others, especially that of Thomas B. Clarkson, D.V.M., of Wake Forest University, led to the development of the “timing hypothesis,” which likely explains the inconsistency. It states that normal blood vessels retain beneficial hormone responses such as vasodilatation, decreased inflammatory activation and decreased lesion progression, while vessels with advanced atherosclerosis do not.

Estrogen receptors, alpha (ER $\alpha$ ) and beta (ER $\beta$ ), exist in most cells, but Mendelsohn focused his talk on their role in vascular endothelial and smooth muscle cells, the cells that line blood vessels. The binding of estrogen to estrogen receptors in the endothelial cell causes the cell to generate nitric oxide, which activates a signaling system in the adjacent smooth muscle cell. “There are two classes of effects for estrogen on the blood vessel — rapid and longer-term,” Mendelsohn said. “The rapid effects dilate the blood vessel, while the longer-term effects decrease the response to vascular injury and the rate at which atherosclerosis accrues.”

Although estrogen took a beating in the press early-on, Mendelsohn said that a recent article published in the *Wall Street Journal* was one of several signs that things were changing. He said, “Melinda Beck’s ‘[The Seven Things You Should Know About Hormones](#)’ reflects a growing consensus that the risks and benefits of HRT are different for younger and older women. This news is heartening for those of us who have been watching this evolve since the early 90s.”

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## ONES Awardee Speaks at NIEHS

*By Eddy Ball*

In a lecture on February 6, [NIEHS grantee](#) Sven-Eric Jordt, Ph.D., discussed the latest developments in his basic research on the mechanisms of transient receptor potential (TRP) channels. He also offered insight into potential applications of his findings in protecting people from tear gas and other warfare and industrial agents and, possibly, in preventing or treating symptoms of asthma and allergies.

His talk, titled “Sensory TRP Channels in Respiratory Reflex Control and Inflammation,” was a part of the NIEHS Laboratory of Respiratory Biology (LRB) Lecture Series and was hosted by Principal Investigator Stephanie London, M.D.

A professor in the [Department of Pharmacology at the Yale University School of Medicine](#), Jordt is a member of the first group of [Outstanding New Environmental Scientists \(ONES\)](#) awardees. He also enjoys the distinction of being the first NIEHS extramural grantee (see [story](#)) to receive one of the prestigious Presidential Early Career Awards for Scientists and Engineers (PECASE). In his opening remarks, Jordt expressed his appreciation for the “phenomenal support I have received from NIEHS.”



*Several LRB investigators attended the talk by Jordt, above — as did NIEHS Health Science Administrator Annette Kirshner, Ph.D., who administers one of Jordt’s grants. (Photo courtesy of Steve McCaw)*

As Jordt explained, TRP channel receptors are part of an early warning system of sensory neurons during injury and chronic painful conditions that trigger tears, sneezing, neurogenic inflammation, pain and respiratory constriction in the upper airways upon exposure to noxious agents, temperature and environmental toxicants with irritant activities. In his early work with TRPs, Jordt discovered one — transient receptor potential ankyrin 1 (TRPA1) — that proved to be especially promising for preventive and therapeutic applications.

Through a process of elimination in a series of systematic experiments that included wild type and knockout mice, Jordt discovered that TRPA1 was essential for mammalian hypersensitivity reactions to a wide range of irritants. These included mustard oil, chlorine and acrolein, an oxidized hydrocarbon present in cigarette smoke, exhaust fumes and smoke from other sources.

As his work progressed, Jordt was able to add to the list of noxious industrial and warfare-agent compounds that are TRPA1 agonists. He found that several other major threats to respiratory health also activate TRPA1, including chlorine, tear gases, and isocyanates, such as the methyl isocyanate released during the industrial accident in Bhopal, India that caused more than 3000 immediate deaths and thousands more afterwards.

In a [study](#) using a TRPA1 antagonist, HC-030031, Jordt and his colleagues showed that they were able to prevent the acute sensory irritation caused by exposures to isocyanates and tear gases. They speculated further that “TRPA1 antagonists may also be useful for post-exposure treatment, reducing sensory irritation and, potentially, preventing adverse long-term health effects elicited by neurogenic inflammatory mechanisms.”

Jordt’s tear gas research is part of the trans-NIH [CounterACT \(Countermeasures Against Chemical Threats\) Research Network](#), an initiative led by the National Institute of Neurological Disorders and Stroke (NINDS) involving grants from NIEHS and seven other institutes. His lab has received additional support from the American Asthma Foundation, Health Effects Institute and Connecticut Department of Health.

Jordt’s talk at NIEHS was the second he gave during his visit last month to the Raleigh-Durham-Chapel Hill area. On February 5, he made a presentation as part of the Ion Channel Research Unit Seminar Series at Duke University in Durham.

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## Research Finds New Cause of Ozone Wheezing and Potential Treatments

*By Robin Mackar*

Researchers at NIEHS and Duke University have discovered a cause of airway irritation and wheezing after exposure to ozone, a common urban air pollutant. Using an animal model, the researchers were also able to identify several ways to stop the airways from narrowing. These findings help identify potential new targets for drugs which may eventually help physicians better treat emergency room patients suffering from wheezing, coughing and shortness of breath.

“We found that it is not the ozone itself that causes the body to wheeze, but the way the lungs respond to ozone,” said [Stavros Garantziotis, M.D.](#), principal investigator in the NIEHS Laboratory of Respiratory Biology and lead author of the [paper published online](#) in the *Journal of Biological Chemistry*.



*Lead author Stavros Garantziotis shown in his office at NIEHS (Photo courtesy of Steve McCaw)*

“Animals exposed to ozone produced and released high amounts of a sugar known as hyaluronan,” said [John Hollingsworth, M.D.](#), a pulmonologist who is an assistant professor in the Department of Medicine at Duke University Medical Center and senior author of the paper. “We found hyaluronan to be directly responsible for causing the airways to narrow and become irritated. We believe this may contribute to asthma symptoms in humans as well.”

The researchers found several proteins that can mediate the hyaluronan effect and can be used as treatment targets. They were also able to block the airway responsiveness by binding the native hyaluronan away, as well as by administering a slightly modified form of hyaluronan. “Although more research is needed before these findings can be translated to humans, we are optimistic these treatment options could prove beneficial to patients,” said Hollingsworth.

“This finding has real-life therapeutic implications,” said Garantziotis. The researchers point out that there are approximately 4,500 hospital admissions and 900,000 school absences each year attributed to ozone exposure, especially on high-ozone alert days. “We identified several new approaches to the treatment of ozone-induced airway narrowing.”



*Senior author John Hollingsworth after his talk at the ONES Award Lecture in December 2008. (Photo courtesy of Steve McCaw)*

Ozone has been estimated, in an Environmental Protection Agency analysis, to cost the United States \$5 billion a year as a result of premature deaths, hospitalizations and school absences. Inhalation of ozone can lead to irritation of the airways and increased wheezing, particularly in children and adults who have asthma and chronic obstructive lung disease. Ozone is formed in the inner atmosphere in the presence of sunlight from pollutants emitted from vehicles and other sources. Exposure occurs when people inhale air containing ozone.

“This collaborative effort exemplifies the powerful advances we can continue to make to improve human health by teaming the innovativeness of our in-house researchers with our grantees,” said Linda S. Birnbaum, Ph.D., NIEHS director. “This is also a good example of how NIEHS is helping to bring a pool of creative, talented young scientists to the field of environmental health sciences.”

An [NIEHS grantee](#), Hollingsworth is an NIEHS Outstanding New Environmental Scientists (ONES) grant award recipient (see [story](#)). The ONES program identifies outstanding scientists who are in the early, formative stages of their careers and who intend to make a long-term career commitment to research in the mission areas of the NIEHS.

*Citation:* [Garantziotis S](#), [Li Z](#), [Potts EN](#), [Kimata K](#), [Zhuo L](#), [Morgan DL](#), [Savani RC](#), [Noble PW](#), [Foster WM](#), [Schwartz DA](#), [Hollingsworth JW](#). Hyaluronan mediates ozone-induced airway hyperresponsiveness in Mice. 2009. J Biol Chem [Epub ahead of print] doi:10.1074/jbc.M802400200. [Summary](#).

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# Glutathione Synthetase Linked to Arsenic Susceptibility in Fruit Fly Model

By Brian Chorley

NIEHS grantee Iain Cartwright, Ph.D., an associate professor at the University of Cincinnati College of Medicine, his former student, Jorge Muñiz Ortiz, Ph.D., and two co-authors recently reported a surprising genetic twist regarding arsenic susceptibility in the February 2009 issue of *Toxicological Sciences*. He and his research team discovered evidence that polymorphism in the *Drosophila* glutathione synthetase (GS) gene, which encodes an enzyme responsible for the final step in glutathione synthesis, may be a more likely explanation for differential arsenic sensitivity and exposure risk than previously thought.

In an editorial appearing in the same issue, Environmental Protection Agency (EPA) Research Toxicologist David Thomas, Ph.D., lauded the [study's](#) significant contribution to unraveling the arsenic-glutathione connection. "Additional information [of this kind] on the relation between the GS genotype and the phenotype for response to As may help to reduce some of the uncertainties in the risk assessment for this metalloid and assist regulators in their task of protecting public health."

Arsenic is a metalloid that forms various compounds readily in nature. At high dosage, arsenic is extremely toxic to many organisms and has been used as an active ingredient in insecticides and herbicides. For example chromated copper arsenate (CCA), an arsenic compound, was once heavily used as a wood preserver because of its toxicity to insects, bacteria, and fungi. Subsequently, due to potential environmental and human health impact concerns, CCA has been banned from use in the U.S. and other countries.

Naturally occurring arsenic contamination in well water used by Bangladesh and neighboring countries is a current health concern that has the potential to affect tens of millions of people. Chronic ingestion of arsenic has been linked to numerous diseases such as cancer, diabetes, and respiratory ailments; however, epidemiological evidence has demonstrated that arsenic sensitivity varies from individual to individual and population to population. This variation suggests there may be a strong genetic component to arsenic toxicity.

*Drosophila*, or the fruit fly, is a common model for genetic research for which Cartwright is certainly an advocate. "The use of simpler, but genetically highly amenable, model eukaryotic systems in toxicology has much to recommend it, both from a cost-effective and time-critical perspective," he explained.

By measuring egg-hatching rates in progeny of two different *Drosophila* strains that were respectively resistant and sensitive to arsenic and using a combination of genetic analysis techniques, Cartwright's team narrowed their focus to a region in the X-chromosome. This region of the X-chromosome coded a gene of particular interest, glutathione synthetase - an enzyme involved in glutathione biosynthesis. It has been known since the beginning of the early 1920's that glutathione could protect from arsenic toxicity, and it was used as an antidote



First author Muñiz Ortiz, left, posed with Cartwright, his mentor and the principal investigator on the study. Muñiz Ortiz now works with the EPA. (Photo courtesy of Iain Cartwright and the University of Cincinnati)

to the arsenical war gas Lewisite. Since these initial observations, several studies have demonstrated that glutathione protects by facilitating both breakdown and transport of arsenic out of the cell.

What is surprising about Cartwright's finding is that glutathione synthetase is not considered the rate-limiting step for glutathione biosynthesis and that partial deficiency in this enzyme is not thought to compromise glutathione production. The research team used an RNA interference technique to demonstrate, however, that flies exhibiting partial reduction of this enzyme, showed significantly increased arsenic susceptibility. A possible explanation, suggested by the researchers, is that a stressed system may struggle to meet the demand of glutathione, thereby allowing other points of control, such as glutathione synthetase, to potentially limit overall biosynthesis rates.

“Given the intense interest in inter-individual variability in response to arsenic in studied human populations exposed to arsenic-laden water,” Cartwright commented, “this work adds an additional dimension to the metabolic and biosynthetic pathways deserving scrutiny as potential arbiters of differential susceptibility based on genetic polymorphism.”

(Brian Chorley, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

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## Study Explores the Mechanisms of Age-Related Neurodegeneration

By *Shweta Trivedi*

A new study by researchers at NIEHS sheds light on the mechanisms involved in the accumulation of a neurotoxic protein, amyloid-beta<sub>42</sub> (Aβ<sub>42</sub>), which is implicated in Alzheimer's disease (AD) and other age-related neurodegeneration. According to the investigators, their report is the first to demonstrate the role of raft aggregation-induced phagocytosis specifically in the brain macrophage or microglia and to elucidate the brain-specific mechanisms influencing its activation.

The investigators, working in the NIEHS Laboratory of Neurobiology (LN), explored a process known as raft aggregation that is essential for efficient phagocytosis, or the removal of cellular debris, in brain cells. The researchers also identified specific components of raft aggregation that they conclude could be “manipulated or used as targets for therapeutic intervention in the treatment of neurodegeneration.”

The [study](#), by first author and Postdoctoral Fellow Dixie-Ann Persaud-Sawin, Ph.D., Lynna Banach and [Neurotoxicology Group](#) head and Principal Investigator Jean Harry, Ph.D., was published in the February issue of the journal *Glia*.

Phagocytosis is critical for the clearance of potentially harmful proteins and the maintenance of brain homeostasis. A defect in this scavenging of debris in the brain may lead to excessive deposits of



*Persaud-Sawin, above, is also lead author with Harry on a report published online in December 2008 on a detergent-free method of isolating rafts from mouse tissue. (Photo courtesy of Steve McCaw)*

$A\beta_{42}$  — a protein associated with the development of proteinopathies and neurodegeneration that are the hallmark characteristics of AD. This deposition triggers microglial activation and increased production of proinflammatory cytokines, higher levels of amyloid precursor protein (APP) — triggering even more deposition of  $A\beta_{42}$  — and transcription of apolipoprotein E (APOE).

The process of phagocytosis involves the identification of debris material and the initiation of molecular and morphological changes that result in receptor recruitment and formation of a phagocytic cup for clearing the material from the microglia. Harry's group is interested in exploring the mechanism by which rafts may regulate microglial phagocytosis for insight into the development and progression of neurodegenerative disease.

Rafts are liquid-ordered microdomains in the membrane of a cell made up of specific proteins — the most important being the raft structural protein Flotillin1 (Flot1) and the cell-surface glycoprotein CD36 — cholesterol and sphingolipids, such as GM1 ganglioside. Rafts are involved in the orchestration of important cell signaling cascades and cell processes, among them apoptosis, cytokine signaling and phagocytosis. Although previous studies have demonstrated that rafts are critical in phagocytosis by peripheral macrophages, the unconventional phagocytosis that functions in the specialized macrophages found in the brain had not previously been well characterized.

To test their hypothesis that phagocytic activity in microglia employs raft activation similar to that seen in peripheral macrophages, the team treated cells directly with  $A\beta_{42}$  and induced  $A\beta_{42}$  production in rodent microglia cultures with celecoxib, a COX-2-selective non-steroidal anti-inflammatory drug (NSAID). Prolonged treatment allowed the researchers to evaluate changes in the effects on raft integrity and microglial phagocytosis with  $A\beta_{42}$  accumulation over time and to determine an  $A\beta_{42}$  threshold that is comparable to levels found in human patients with early to mid-stage AD.

Utilizing filipin, a cholesterol-sequestering agent, to induce loss of Flot1 and disrupt rafts, the authors demonstrated that shifts in that protein to non-raft fractions led to inhibition of raft aggregation and phagocytosis. They also determined that high  $A\beta_{42}$  disrupted raft localization of CD36, which is critical for normal phagocytic function.

“Along with identifying these candidate proteins for follow-up investigation, this study has important implications for the clinic,” observed Persaud-Sawin, “and may provide clues as to why NSAID treatment in AD and other inflammatory neurodegenerative diseases has not been more successful.”



*One goal of the lab headed by Harry, above, is to explore factors that may enhance regenerative ability in the adult or aging nervous system. (Photo courtesy of Steve McCaw)*



*Former Neurotoxicology Group member Lynna Banach, shown with a new friend, is now involved in marine animal research in Georgia. (Photo courtesy of Jean Harry)*

In their conclusion, the authors speculated about how their novel approach to studying raft aggregation could possibly help investigators gain insight into other neurodegenerative conditions. “Prion diseases such as Creutzfeld-Jacob disease (CJD) and bovine spongiform encephalopathy require rafts for protein processing,” they said, “and the over-expression of  $\alpha$ -synuclein in Parkinson’s disease can upregulate the raft-related caveolar protein, caveolin 1 and activate microglia.”

*Citation:* [Persaud-Sawin DA, Banach L, Harry GJ. 2009. Raft aggregation with specific receptor recruitment is required for microglial phagocytosis of Abeta42. \*Glia\* 57\(3\):320-335.](#)

(Shweta Trivedi, Ph.D., is a postdoctoral fellow in the Laboratory of Respiratory Biology Environmental Genetics Group)

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## Endocrine Disrupting Effects of BPA on Puberty and Estrogen Cycles

*By Negin Martin*

On February 18, Sigma Xi hosted a lunchtime talk by [NIEHS grantee](#) Heather Patisaul, Ph.D., on her latest findings about the effects on brain and ovarian function of developmental exposure to Bisphenol-A (BPA). Patisaul, an assistant professor in the department of Biology of North Carolina State University, was a recipient of a 2007 [Outstanding New Environmental Scientist \(ONES\)](#) award from NIEHS.

[Patisaul’s research](#) combines approaches from behavioral biology, neuroendocrinology and molecular biology to study the effects of various environmental toxins on physiological function, focusing on how endocrine disruptors affect female reproductive physiology. Positive correlation between the increasing rates of early puberty and infertility in Western women and the rising levels of circulating BPA, which mimics estrogen, prompted her to investigate the effect of exposure to the compound on the reproductive system. Patisaul’s [phytoestrogen data](#) was published in the journal *Neurotoxicology*; her Bisphenol data is currently in review.



*“If we understand the mechanics of what these compounds do,” Patisaul maintained, “we can do a better job of predicting how they will affect human or wildlife populations.” (Photo courtesy of Steve McCaw)*

BPA is a chemical commonly incorporated in polycarbonate plastics and epoxy resin used to make products such as baby and water bottles, tubing and medical devices, sports equipment, household electronics, plastic toys, lining of cans, and milk and juice cartons. According to Patisaul, BPA resembles mammalian estrogen and thyroid hormone and is suspected of being hazardous to human health. Patisaul explained that the Centers for Disease Control (CDC) estimates that the widespread use of BPA in everyday household products for the last 50 years has led to detectable levels of BPA in 95% of Americans — with levels of circulating BPA in newborns and small children under two years of age predicted to be as much as 11 times higher than adults.

Patisaul used rats as a model system to investigate whether neonatal exposure to BPA can lead to advanced puberty and possible infertility. She exposed neonatal rats briefly to the 50 micrograms /kilogram (kg) per day dose of BPA considered safe by the Food and Drug Administration (FDA) and a higher dose of 50 milligrams/kg/day. Rats treated with the low doses of BPA showed signs of early puberty similar to rats exposed to excessive estrogen. Moreover, the BPA exposed rats had irregular cycles that ended with premature infertility.

Estrogen and chemicals that mimic its structure can exert their effect on the brain by controlling hormonal secretion. In her study, Patisaul compared the function of hypothalamic neurons in the brains of BPA-treated rats and untreated rats. Specialized neurons in hypothalamus, she explained, are responsible for the secretion of gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Hypothalamic neurons of the BPA-treated rats functioned normally and hence their ability to trigger secretion of hormones responsible for maintaining menstrual cycle was unchanged.

However, a closer look at the ovaries of the BPA rats revealed marked alterations in ovarian morphology and malformed follicles. Patisaul summarized her findings by stating “short, low dose, physiologically relevant levels of exposure to BPA during very early stages of development — neonatal period in rats and gestational period around the second trimester in humans — can result in advanced puberty and the impaired ability to maintain regular estrogen cycles into adulthood.”

Patisaul concluded her talk by revisiting government policies regarding BPA. She emphasized the need to investigate further the effects of BPA on human health. The FDA policy of “no action required” and the established safe dose of 50 micrograms/kg/day of BPA came under criticism by the audience.

(Negin Martin, Ph.D., is a research fellow in the NIEHS Membrane Signaling Group. She was recently chosen as a 2009 Science Communication Fellow with Environmental Health Sciences.)

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Along with people from NIEHS and other organizations, *American Scientist* staffers, such as Assistant Book Review Editor Anna Lena Phillips, left, and Senior Editor Fenella Saunders, attended the talk. (Photo courtesy of Steve McCaw)



Also in the audience were UNC-Chapel Hill student Alexander H. Trowbridge, right, and David Schneider, senior editor at *IEEE Spectrum*. (Photo courtesy of Steve McCaw)



Organizers were pleased with the turn out for the talk. It was one of the best attended in this year's series. (Photo courtesy of Steve McCaw)

# This Month in *EHP*

By Eddy Ball

The March 2009 issue of *Environmental Health Perspectives* is now available on-line, highlighting issues surrounding regulation of hazardous substances, non-cancer toxicity assessment, mobile phones and cancer, pesticide mixtures, proteasome inhibition by organotins and children's exposure to dust lead.

- **Outside Looking In: Understanding the Role of Science in Regulation** – Exploring the inconsistencies of regulation, even when reviewers use the same evidence to make their decisions
- **Building on Success: Assessment Categories for Experimental Noncancer End Points** – Previewing new National Toxicology Program standardized criteria for assessing toxicity to the immune system, reproductive system and developing organism
- **Mobile Phones and Cancer** – Weighing the issues surrounding risk assessment of the ubiquitous cell phone's impact on health and calling for more information on long-term use
- **Pesticide Mixtures Produce Synergistic Toxicity** – Examining evidence that when pesticides combine, the risk to aquatic species is greater than previously thought
- **The Proteasome Is a Molecular Target of Organotins** – Characterizing the mechanisms and downstream events of exposure to compounds used in antifouling boat paints, polyvinyl chloride stabilizers, agricultural pesticides and industrial catalysts
- **Dust Lead in Homes of U.S. Children** – Identifying factors associated with childhood residential dust lead exposure in homes that meet Federal standards but still may put children at risk
- **Children's Blood Lead Levels and Dust Lead** – Modeling blood lead levels based on dust lead levels on floors in homes and concluding that reducing levels below Federal standards would protect more children



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## Upcoming Distinguished Lecture with Mike Levine

*By Eddy Ball*

The 2008–2009 NIEHS Distinguished Lecture series will welcome its next guest speaker March 10 at 11:00 a.m. in Rodbell Auditorium. Geneticist Mike Levine, Ph.D., will discuss “Transcriptional Precision in the *Drosophila* Embryo” during a talk hosted by Laboratory of Molecular Carcinogenesis Principal Investigator [Karen Adelman, Ph.D.](#), who is head of the Transcriptional Responses to the Environment Group.

Levine is a professor of Genetics, Genomics and Development in the Department of Molecular and Cell Biology at the University of California, Berkeley. His lab studies gene networks that control animal development and disease, specifically in the early *Drosophila* embryo, the immune response in *Drosophila* larvae, and the differentiation of the notochord and heart in the sea squirt, *Ciona intestinalis*.

Levine’s talk will focus on the effects of polymerase II (Pol II) pausing and what he calls “shadow enhancers” in the expression of developmental control genes expressed during *Drosophila* embryogenesis. Shadow enhancers are secondary enhancers that produce patterns of gene expression that overlap those produced by the primary enhancers.

His lab’s preliminary studies suggest that these mechanisms are used to produce rapid, synchronous bursts of gene expression in the early *Drosophila* embryo. Levine proposes that transcriptional synchrony helps ensure the coordination of genetic networks during embryogenesis.

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## Samson and Hollingsworth to Speak at Duke in March

*By Eddy Ball*

[Veteran grantee](#) Leona Samson, Ph.D., and recent [Outstanding New Environmental Scientist \(ONES\) awardee](#) John Hollingsworth, M.D., are scheduled to lecture in March at the Duke University School of Medicine.

Samson, who is the director of the Center for Environmental Health Sciences at Massachusetts Institute of Technology, will speak March 27 at 12:00 p.m. in 147 Nanaline Duke Building. Her presentation, “Complex Responses to DNA damaging Agents,” is hosted by Professor of Biochemistry Ken Kreuzer, Ph.D., and is part of the Duke Biochemistry Seminar Series.

[Samson](#) investigates alkylating agents, an abundant class of chemical DNA damaging agents in the environment that are toxic, mutagenic, teratogenic and carcinogenic. The repair of DNA alkylation damage provides tremendous protection against the toxic effects of these agents. Samson’s aim is to understand the biology, biochemistry and genetics of the numerous DNA repair pathways that act upon DNA alkylation damage.



*In 2008, Samson, above, spoke at NIEHS as part of the [Laboratory of Molecular Genetics Fellows Invited Guest Lecture series](#) and in Research Triangle Park as a guest lecturer at the [Fall Meeting of the Genetics and Environmental Mutagenesis Society \(GEMS\)](#). (Photo courtesy of Leona Samson and MIT)*

A professor in the Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine at Duke University Medical Center, [Hollingsworth](#) will speak March 31 at 4:00 p.m. in 143 Jones Building. His talk, “Ambient Environmental Exposures and Pulmonary Innate Immunity,” is part of the Duke Department of Immunology Seminar Series.

Hollingsworth studies the complex interaction between the innate immune system and the common inhaled toxicant, ozone. Current studies are focused on both understanding the role of innate immunity in environmental airway disease and how exposure to ambient ozone can modify subsequent innate/adaptive immune response in the lung.

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*Hollingsworth, above, spoke at a meeting of the 2008 ONES awardees in December 2008. He is senior author on a [paper](#) featured in this issue. (Photo courtesy of Steve McCaw)*

## NCSU to Host Grantee Peter Thomas

*By Eddy Ball*

NIEHS [grantee](#) Peter Thomas, Ph.D., is scheduled to present a seminar March 26 on “Characteristics of a Putative Steroid Membrane Receptor,” as part of the North Carolina State University (NCSU) Department of Biology Seminar Series. Hosted by NCSU Department of Zoology Professor Russell Borski, Ph.D., the talk will begin at 4:00 p.m. in 101 David Clark Labs on the NCSU [campus](#).

Thomas is a professor at the University of Texas at Austin Marine Science Institute (UTMSI), which is located in Port Aransas on the southern Texas Gulf coast. His research group studies fish reproductive physiology and marine environmental toxicology and stressors. His NIEHS grant is an extension of his earlier research on endocrine disruption in two marine perciform models of teleost reproduction, spotted seatrout and Atlantic croaker.

Thomas is studying the mechanisms of nonclassical steroid actions mediated by a novel family of putative membrane progesterone (P4) receptors (mPRs) his group recently discovered in human cells and their functional significance in health and disease. With his current studies, Thomas plans to characterize previously unrecognized multiple signaling cascades initiated by progesterone activation of mPRs that are likely involved in functional progesterone withdrawal in women at term, shifting the balance from a quiescent state to a contractile one. This activation of mPRs has implications in terms of preterm birth — a major medical problem that occurs with 12 percent of births.

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*NCSU guest lecturer and NIEHS grantee Peter Thomas (Photo courtesy of Peter Thomas and the University of Texas)*



# Extramural Update

## NIEHS and U.S. EPA Children's Environmental Health Centers Program – Renewed and New Funding Opportunities



NIEHS and U.S. Environmental Protection Agency (EPA) announce the release of two linked funding opportunities – the Children's Environmental Health and Disease Prevention Centers (P01) [RFA-ES-08-002](#) and the Formative Centers (P20) [RFA-ES-08-004](#). Applications are due April 30, 2009 and will be reviewed in July by a special emphasis panel convened by the NIEHS Scientific Review Branch. The earliest anticipated start date is September 1, 2009 for the P01 program and December 1, 2009 for the P20 program.

NIEHS and EPA intend to award a total of up to \$9 million each year for five years to fund up to five Children's Environmental Health and Disease Prevention Centers (P01s) and intend to award a total of up to \$3 million each year for three years to support up to four Formative Centers (P20s).

Applications funded from [RFA-ES-08-002](#) will form a multidisciplinary program of basic and applied research to examine the effects of environmental factors on children's health and wellbeing. Research conducted through the Centers should include substantive areas of science in children's health while incorporating innovative technologies and approaches and links to the environment. The revised program encourages strong links between disciplines in the basic, applied, clinical and public health sciences to prevent disease and promote health in all children.

The new Formative Centers program [RFA-ES-08-004](#) runs in parallel with the P01 program and solicits applications under the P20 mechanism. This opportunity will allow development of new research teams and connections with communities and other stakeholders. The program will obtain preliminary data on childhood diseases and disorders where the evidence of an environmental contribution has yet to be fully established or appreciated.

Together these funding opportunities give increased flexibility to create a more dynamic network of Centers that will pursue research about the complex interaction of environmental, social and genetic factors that predispose children who experience harmful exposures to a myriad of medical and behavioral conditions over their lifetimes.

Contact: [Dr. Kimberly Gray](#)

## Background of the Children's Environmental Health Centers

In 1998, NIEHS and U.S. EPA launched the Centers for Children's Environmental Health and Disease Prevention Program, also known as the Children's Environmental Health Centers (CEHCs). The CEHCs currently examine the interaction between key environmental exposures and a range of child health outcomes, including overall growth and development, asthma and respiratory health, and neuro-developmental disorders such as autism. Collectively, these Centers comprise a national network of scientific and community leaders, health care providers and government officials — with the common goals of preventing and reducing childhood diseases in the research areas under study and translating the findings to the affected communities and the broader public. The two agencies have been equal partners in promoting and sustaining this program throughout the last decade.

In 2007, NIEHS and EPA separately convened two independent evaluations of the CEHC Program. The NIEHS group evaluated the use of the program project mechanism as a research mechanism to facilitate children's environmental health over the past decade while the EPA-established workgroup, comprised of members of the Children's Health Protection Advisory Committee (CHPAC) and Board of Scientific Counselors (BOSC), assessed the program's effectiveness in translating research results into public health decisions. Results and materials related to both evaluations can be found at the following websites:

- [2007 NIEHS evaluation of the Centers](#)
- [2007 Public comments on NIEHS evaluation of the Centers](#)
- [2007 CHPAC-BOSC evaluation of the Children's Centers](#)

# Extramural Papers of the Month

By Jerry Phelps

## Clean Air Extends Life Expectancy

New NIEHS-supported research findings published in the *New England Journal of Medicine* suggest that improvements in air quality have increased average life expectancy in the U.S. by approximately five months. The researchers tracked particulate matter air pollution in 51 major metropolitan areas from 1978 through 2001 and compared those data to death records and census data. On average, life expectancy increased by 2.72 years with about 15 percent of that increase due to improved air quality. Cities that had the greatest air quality improvements saw the greatest gains in life expectancy. Overall, a reduction of 10 micrograms per cubic meter in the ambient air concentration of particulate matter was associated with an estimated increase in average life expectancy of 0.61 years.

The study signals that efforts to curtail the small, toxic particles known as PM<sub>2.5</sub> produced by power plants, factories, cars, and trucks and inhaled by city-dwellers had significant health benefits over those two decades. Clean-air advocates and public health specialists have touted the findings and have said that even stronger standards for air pollutants are needed and justified.

Research over the past few decades, much of which has been particulate matter air pollution, has found that the foreign matter inflames lung tissue and increases the plaque that forms in arteries, contributing to heart and lung disease.

*Citation:* Pope CA 3rd, Ezzati M, Dockery DW. 2009. Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 360(4):376-386.

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## Variations in Human Gut Microbiome Linked to Obesity

A study partially funded by NIEHS and published in the journal *Nature* has found that the gut microbial population in humans is unique to each individual with substantial differences between obese and lean people. The researchers analyzed the gut microbiomes of lean and obese, fraternal and identical female twins and their mothers. They found that the collection of bacteria is similar in related individuals, but not identical. The study participants are part of a long-standing study of Missouri-born twins designed to decipher the influence of the environment versus genetics on many aspects of human health.

Peter Turnbaugh, lead author of the study, sequenced the microbial DNA of a subset of obese and lean twin pairs. He found that the obese individuals had an increase in nearly 300 bacterial genes primarily responsible for extracting calories from food and processing nutrients. These findings support earlier work in mice that established a connection between obesity and energy harvested from the diet by gut bacteria.

Family members were more likely to harbor similar communities of bacteria; however the degree of similarity was the same for identical and fraternal twins regardless of whether they lived together or in different regions of

the U.S. This finding suggests that early environmental exposures play a key role in determining which bacteria colonize our intestinal tracts.

*Citation:* Turnbaugh PJ, Hamady M, Yatsunencko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. 2009. A core gut microbiome in obese and lean twins. *Nature* 457(7228):480-484.

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## MicroRNAs Modulate Smoking Damage

A multidisciplinary study conducted at Boston University identified 28 microRNAs that are differentially expressed in bronchial airway epithelial cells from smokers compared to non-smokers. These microRNAs regulate gene expression changes occurring in people who smoke and who get smoking-related diseases, according to the study's senior author Avrum Spira, M.D.

The investigators harvested samples of cells from 10 smokers and 10 non-smokers. The majority of the microRNAs were down-regulated in smokers — suggesting that restoration of expression to more normal levels could protect smokers from smoking-related diseases, such as emphysema and lung cancer. Mir-218 was identified as a key microRNA for controlling a group of genes involved in protection of lung tissues from oxidative damage.

The investigators speculate that mir-218 is crucial in preventing lung injury and thus the potential development of lung disease. Mir-218 activity could also be used as a marker for lung injury and might be useful in predicting which people are more likely to develop lung diseases as a result of smoking.

*Citation:* Schembri F, Sridhar S, Perdomo C, Gustafson AM, Zhang X, Ergun A, Lu J, Liu G, Zhang X, Bowers J, Vaziri C, Ott K, Sensinger K, Collins JJ, Brody JS, Getts R, Lenburg ME, Spira A. 2009. MicroRNAs as modulators of smoking-induced gene expression changes in human airway epithelium. *Proc Natl Acad Sci U S A* 106(7):2319-2324.

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## New Treatment Found for Ozone-Caused Wheezing

A collaborative team of researchers at NIEHS and Duke University has discovered a cause of airway inflammation and irritation in response to breathing ozone, a common air urban air pollutant. Ozone exposure causes constriction of breathing passages making normal respiration much more difficult. This is a dangerous condition in people with breathing abnormalities, such as chronic obstructive pulmonary disease and asthma.

Using an animal model, the research team found increased amounts of a sugar known as hyaluronan and found the compound to be directly responsible for the airway constriction and irritation. The researchers think hyaluronan may also contribute to asthma symptoms in humans.

Adding to the importance of this work, the researchers identified several proteins that can alter the hyaluronan effect and that might be useful treatments for asthma. They were able to block the hyaluronan effect by

administering a natural protein that binds to hyaluronan and thus prevents it from causing the airway irritation. The researchers conclude that pharmacologic modification of hyaluronan is a potential strategy for treatment of reactive airway disease.

The senior author of the study, John Hollingsworth, M.D., is a recipient of an Outstanding New Environmental Scientist award from NIEHS.

*Citation:* [Garantziotis S, Li Z, Potts EN, Kimata K, Zhuo L, Morgan DL, Savani RC, Noble PW, Foster WM, Schwartz DA, Hollingsworth JW](#). 2009. Hyaluronan mediates ozone-induced airway hyperresponsiveness in mice. *J Biol Chem* [Epub ahead of print]. [Story](#).

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## Intramural Papers of the Month

*By Robin Arnette*

### Maternal Obesity Increases the Risk of Neonatal Death

Researchers from NIEHS, Creighton University School of Medicine and the University of Nebraska Medical Center have found that during pregnancy, obese women had an increased risk of neonatal death and overall infant death. The team studied the association between maternal obesity and the risk of infant death by using the 1988 U.S. National Maternal and Infant Health Survey (NMIHS) data. The finding may represent a way to reduce infant mortality.

The National Center for Health Statistics conducted the NMIHS to study factors related to poor pregnancy outcome. The survey included a nationally representative sample of 9953 women who gave birth to live infants. Out of this sample size, 3309 of the women had late fetal deaths, while 5532 had infant deaths. After childbirth, the mothers were mailed questionnaires about reproductive history, life style, prenatal care, delivery, postpartum conditions, and neonatal and infant health. Medical records were obtained from prenatal care providers and hospitals.

The results indicated that obese women had a higher risk for neonatal death from pregnancy complications or disorders relating to short gestation and unspecified low birth rate. However, in non-obese women low weight gain may pose an increased risk of infant death.

*Citation:* [Chen A, Feresu SA, Fernandez C, Rogan WJ](#). 2009. Maternal obesity and the risk of infant death in the United States. *Epidemiology* 20(1):74-81.

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# The Involvement of UV Radiation in the Development of Dermatomyositis

The autoimmune disease dermatomyositis (DM) often causes a person's own antibodies to be directed toward Mi-2, an ATPase that serves as the core subunit of the nucleosome remodeling deacetylase (NuRD) complex. Exposure to ultraviolet (UV) radiation correlates with increased Mi-2 autoantigen and is implicated in the etiology of the disease although the exact mechanism remained unknown.

Researchers at NIEHS have determined that irradiating cell culture systems with UV increased protein expression levels of Mi-2, maximized Mi-2 levels one hour after irradiation and maintained its protein expression levels for up to 16 hours. The research team also found that following UV treatment, the Mi-2 mRNA was translated more efficiently through a regulatory element within the 5'-UTR region. Under these conditions the Mi-2 protein did not localize to DNA damage sites, suggesting an alternative mechanism to its autoantigenic activity.

The discovery represented a possible mechanism for the development of DM specific autoimmunity and provided a possible new regulatory action for Mi-2 and the NuRD complex.

*Citation:* [Burd CJ](#), [Kinyamu HK](#), [Miller FW](#), [Archer TK](#). 2008. UV radiation regulates Mi-2 through protein translation and stability. *J Biol Chem* 283(50):34976-34982.

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# Fibroid Growth Differs Among Black and White Women

Fibroids, benign tumors of the uterus, are the leading cause of hysterectomies in the U.S. Black women suffer more severe symptoms and are at higher risk for hysterectomy than whites. A collaborative study between NIEHS and UNC, with support from Integrated Laboratory Systems, followed fibroid growth using MRIs. The researchers tracked the changes in size of 262 tumors from 72 women and found several surprises. Even though most of the women had multiple fibroids, each tumor grew at its own rate, and a large tumor was not necessarily a fast growing one. The study only followed pre-menopausal women, but, surprisingly, some of the tumors from young women in the study shrank. Fibroid growth rates did not differ between black and white women under age 35, but the tumor growth rate for black women over 35 did not slow with age as it did for white women.

Important implications of this study are: 1) large tumors can no longer be assumed to be rapidly growing tumors, 2) further study of the mechanisms that result in tumor shrinkage in premenopausal women may provide new strategies for treatment development, and 3) the absence of a growth-rate decline with age for tumors in black women may help explain the higher symptom burden they experience.

*Citation:* [Peddada SD](#), [Laughlin SK](#), [Miner K](#), [Guyon JP](#), [Haneke K](#), [Vahdat HL](#), [Semelka RC](#), [Kowalik A](#), [Armao D](#), [Davis B](#), [Baird DD](#). 2008. Growth of uterine leiomyomata among premenopausal black and white women. *Proc Natl Acad Sci USA* 105(50):19887-19892.

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# The Role of Activation-Induced Deaminase in Lupus

Lupus is an autoimmune disease in humans in which the body produces autoantibodies against itself that cause inflammation, pain and damage to various parts of the body. The MRL/lpr mouse is a good rodent model for lupus because it shares many characteristics of the disorder, specifically, the development of autoantibodies to double-stranded (ds) DNA.

Researchers at NIEHS studying MRL/lpr mice have determined that decreased levels of activation-induced deaminase (AID) in heterozygotes, a protein that triggers class switch recombination (CSR) and somatic hypermutation (SHM), resulted in a dramatic drop in the levels of high affinity anti-dsDNA antibodies. This event correlated with a significant decrease in the severity of lupus nephritis. The findings represent an important step in lupus research.

The research team studied the frequency of SHM and the rate of CSR in AID<sup>+/-</sup> MRL/lpr mice using ELISA, flow cytometry analysis and affinity assays.

*Citation: Jiang C, Zhao ML, Diaz M. 2009. Activation-induced deaminase heterozygous MRL/lpr mice are delayed in the production of high-affinity pathogenic antibodies and in the development of lupus nephritis. Immunology 126(1):102-113.*

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# Inside the Institute

## Fellowship and Food – The Keystone of Satellite Cohesion

By Eddy Ball

Food was the centerpiece at two recent events at the new NIEHS satellite offices in the Keystone building. On January 26, organizers from the various divisions represented at Keystone staged a Meet and Greet for staffers. On February 2, Keystoneers had an opportunity to attend a Food Fair to sample the NIEHS cafeteria selections now available for lunchtime purchase from special vending machines on the first floor.

Both events were designed to give residents of the new office facility a chance to develop a sense of community in their new environment through the time-honored tradition of breaking bread. Each of the three floors has developed its own identity, but since the building lacks a central commons area, there is little opportunity for busy employees to explore the other floors.

Meet and Greet, sponsored by an *ad hoc* committee headed by Dona McNeill, stocked snack tables in each of the three break rooms in Keystone. Volunteers on each floor brought in items from the three major food groups — sugars, starches and salt — for employees who gathered to sample and socialize following the director’s town meeting in Rodbell Auditorium. Many passed from floor to floor — each with a distinctive lineup of goodies — to reconnect with old friends and make new ones.

The Food Fair, organized by Diane Crawford and staffed by cafeteria employees, took place in the first floor break room at Keystone — a venue that proved to be tight quarters for the turnout. Soon after Crawford sent a message reminding Keystoneers of the free treats, the line stretched half the length of the hallway, and people with plates overflowing rubbed shoulders as they crowded into the narrow space.



On the second floor, employees enjoyed a “greener” fare of veggies and dip to buffer the starches and salt. DERT’s Heather Henry, right foreground, prepared a bagel while EHP’s Arnold Greenwell picked up cheese and crackers as OM’s Chris Long watched. (Photo by Eddy Ball)



he sweets were a hit at Keystone’s Meet and Greet, and it didn’t take long for the trays on the third floor to empty. DERT’s Kim Gray, above, seemed to ponder the price she paid for her procrastination as she looked over what was left. (Photo by Eddy Ball)



*Cafeteria employee Lakisha Register, right foreground, was on hand with colleague Julius Enoch, in white, and manager Liz Cartano, right background, to answer questions about the menu. The samples included salad items, wraps, quiches, fruits and vegetables that Keystoneers can now purchase on-site. (Photo by Eddy Ball)*



*Combine free food and good publicity, and the outcome was a crowded hallway full of smiling, hungry staffers eager to see what their future would hold. Within minutes of Crawford's reminder, the first floor was transformed from an empty corridor to a long line of people talking and laughing as they waited. (Photo by Eddy Ball)*

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# Institute Celebrates African-American Culture

*By Eddy Ball*

The NIEHS Diversity Council joined with the RTP Chapter of Blacks In Government (BIG) to sponsor a novel African-American Cultural Celebration in Rodbell Auditorium and the NIEHS Cafeteria February 26 for Black History Month Observance.

As promised, the event featured entertainment by musicians, dancers, actors and mime performers, a sampling of foods from Africa, America and the Caribbean, and exhibits showcasing African-American history and culture.

The event drew a near capacity crowd to Rodbell Auditorium and the cafeteria. Afterwards, several attendees remarked that it was one of the most spirited celebrations of its kind ever at NIEHS.



*The current president of RTP BIG, Nafyys Rice, was the event's master of ceremony. Rice is a student at North Carolina Central University and a substitute teacher. (Photo courtesy of Steve McCaw)*





The NIEHS Choir sang three selections during the first part of the celebration — including the moving anthem by James Weldon Johnson, “Lift Every Voice and Sing.” (Photo courtesy of Steve McCaw)



The celebration was a family affair as well. Larrhonda Foushee, above, daughter of NIEHS Project Officer Jennie Foushee, performed as part of the Millennium Revival Center Mime Group. Shavia Westmoreland, daughter of NIEHS Administrative Technician Myra Westmoreland, was one of the group of Enloe High School students who read their poetry. (Photo courtesy of Steve McCaw)



From left to right, NIEHS staffers Lakesia Register, Wanda Holliday and Lorenzo Davis performed a scene from the award-winning play, “A Raisin in the Sun.” Edward Mosely, not shown, was also a member of the ensemble. (Photo courtesy of Steve McCaw)



Toward the end of the first part of the ceremony, a genuinely surprised NIEHS biologist Veronica Godfrey, center, received a plaque of appreciation for her service as president of RTP BIG. Flanking her are Nafiyas Rice, left, and BIG member and NIEHS stem cell biologist Annette Rice. (Photo courtesy of Steve McCaw)



*The NIEHS Community Choir shifted from solemn to energetic when it moved to the cafeteria. Contract computer support specialist Jewel Brown, above, led the singers in a rendition of “Oh, Happy Day” that had members of the audience singing and even dancing along. (Photo courtesy of Steve McCaw)*



*NIEHS Secretary Dee Anderson’s moving poem, “America Made a Change,” celebrated the election of the country’s first African-American President. (Photo courtesy of Steve McCaw)*



*For part two of the celebration, the crowd nearly filled the NIEHS Cafeteria, where dance, poetry, good food and more music were the order of the day — as were the many standing ovations performers received. (Photo courtesy of Steve McCaw)*

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