



April 2007



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# NIEHS Spotlight

## NIEHS Introduces Innovative Weekly Lecture Series

By Eddy Ball

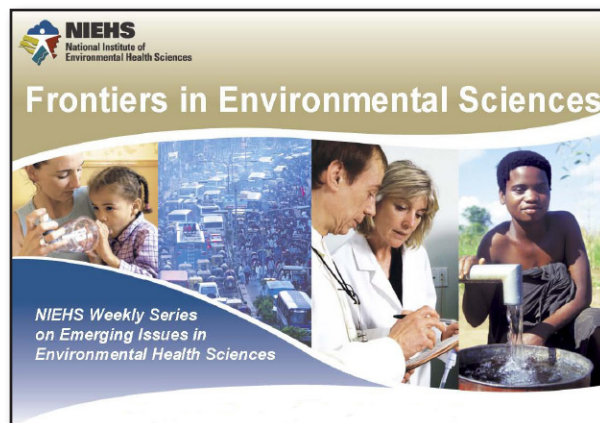
On March 9, NIEHS launched its newest lecture program with the first talk in the Frontiers in Environmental Sciences (FES) series in Rodbell Auditorium. The Institute has introduced this latest lecture program with the intention of fostering a spirit of interdisciplinary communication among researchers at NIEHS, engaging them in discourse about the environmental science mission they all share. With a few exceptions, talks in the weekly lecture series will take place on Friday mornings from 9:00 am to 10:00 am.

Like its sister NIH institutes and centers, NIEHS has long sponsored a diverse mix of regularly scheduled scientific talks. However, unlike the lectures and special presentations sponsored by research divisions, programs and individual laboratories, the FES series will cross organizational borders by featuring talks sponsored by scientists and administrators throughout the Institute.

The inaugural lecture featured a talk by Daniel Baden, Ph.D. Baden is the William R. Kenan, Jr. Distinguished Professor of Marine Sciences and director of the Center for Marine Science at the University of North Carolina at Wilmington (UNCW). He has been an NIEHS grantee continuously since 1979.



*Portier opened the series on March 9, launching an initiative by the Office of the Director to enhance exchange of information and ideas throughout the Institute. The new lecture program will maximize its resources by focusing on Triangle-area researchers, many of them grantees. (Photo courtesy of Steve McCaw)*



### March Lectures

- March 9: Daniel Baden, Ph.D., UNC-Wilmington, “From Beach to Bedside: Effects of Inhaled Florida Red Tide Brevetoxins.” Hosted by Gwen Collman, Ph.D.
- March 16: Nancy Monteiro-Riviere, Ph.D., NCSU, “Nanomaterials: Is Toxicology Really an Issue?” Hosted by Nigel Walker, Ph.D.
- March 23: Douglas Crawford-Brown, Ph.D., UNC-CH, “Where Do You Want to Live? Designing Sustainable Communities as a Health and Environmental Strategy.” Hosted by Chris Portier, Ph.D.
- March 30: Fernando Pardo-Manuel de Villena, Ph.D., UNC-CH, “On the Origin of the Laboratory Mouse: Lessons from the NIEHS Resequencing Project.” Hosted by Bill Schrader, Ph.D.

The host for the first lecture in the series was Gwen Collman, Ph.D., chief of the DERT Susceptibility and Population Health Branch. In 2006, DERT awarded Baden a five-year competitive renewal to further delve into the acute and chronic effects of inhaling toxic particles generated by red tides on Florida's west coast.

Director of the Office of Risk Assessment and the series' coordinator Chris Portier, Ph.D., delivered the series' inaugural remarks. "This seminar series is intended as a time for the Institute to get together and listen to a talk that is of broad, general interest," Portier explained, "and then, maybe, stimulate some discussion amongst ourselves of what this means to our own research and how it fits into the broader scheme of environmental health sciences."

When NIEHS Director David A. Schwartz, M.D., announced the weekly series, he described it "as an opportunity for the federal scientific community to interact, share ideas, and strengthen our overall sense of community." The series, he said, will focus on speakers who are now or have been NIEHS grantees and will feature primarily local scientists — taking advantage of the abundant scientific resources in the Triangle.

A unique element of the new series, according to Kristina Thayer, Ph.D., deputy director of the Office of Risk Assessment Research, is the [FES website](#) that will archive recordings for many of the lectures when the speakers give permission. The site offers webcasts and podcasts beginning the afternoon of a lecture for people who are not able to attend. The website will also post PowerPoint presentations of the talks and provide an opportunity for many people, both inside and outside the Institute, to view the lectures. RSS feeds are under development and will be available soon.

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## Epidemiology Branch Hosts Annual Advisory Meeting

*By Eddy Ball*

On February 22 and 23, the NIEHS Epidemiology Branch convened the 14th annual meeting of the [Agricultural Health Study](#) (AHS) National Advisory Panel (NAP) in Rodbell Auditorium. The meeting gave an audience of scientists, educators, concerned citizens and pesticide manufacturers' representatives an opportunity to hear about the progress and future plans of the study.

AHS is a research effort by scientists at NIEHS, the National Cancer Institute (NCI) and the

### Tentative Schedule of Upcoming Lectures in April

- April 6: William Kaufmann, Ph.D., UNC-CH, Topic TBA. Hosted by Chris Portier, Ph.D.
- April 13: David Armstrong, Ph.D., NIEHS, "Endocrine Disruption of Thyroid Hormone Signaling and Its Implications for Human Health." Host TBA.
- April 20: James Swenberg, D.V.M., Ph.D., UNC-CH, Topic TBA. Hosted by James Huff, Ph.D.
- April 27: Richard Di Giulio, Ph.D., Duke, Topic TBA. Hosted by Chris Portier, Ph.D.



*In his overview, meeting facilitator Michael Alavanja asked panel members, "Do you endorse our plan?...[Do] you think we're on the right track, that we're doing the right things? And do you have suggestions for modifications?"*  
*(Photo courtesy of Steve McCaw)*

Environmental Protection Agency (EPA) working with collaborators at the University of Iowa and the Battelle Centers for Public Health Research and Evaluation in North Carolina. The National Institute for Occupational Safety and Health and the National Center on Minority Health and Health Disparities also have provided support for the study, and individual studies routinely have included extramural scientists as collaborators or principal investigators.

The goals of AHS are to investigate the effects of environmental, occupational, dietary and genetic factors on the health of the agricultural population. Through more than 82 publications in peer-reviewed journals, AHS has translated its epidemiological findings into information that agricultural workers can use in making decisions about their health and the health of their families.

The study is in the final two years of its third phase of funding. AHS is currently performing Phase III follow-up phone interviews and preparing add-on epidemiological studies of select populations from its more than 89,000 subject cohort in Iowa and North Carolina. Although some in the cohort are now near or in retirement, at the time of their enrollment (1993-1997), subjects were active private and commercial pesticide applicators and the spouses of these applicators.

Fact sheets produced by the study have influenced pesticide certification and educational programs in both Iowa and North Carolina, where applicators have become more sensitive to the importance of protective equipment and proper application practices. Cohort updates provide subjects in the study with summaries of research findings and help to keep retention rates high.

The meeting began with an overview by AHS Project Officer Michael Alavanja, Dr. P.H., of NCI, who underscored the statistical power of the AHS cohort. According to Alavanja, AHS researchers have documented over 900,000 person years of observed health history,

## AHS – Revisiting Past Research Findings and Taking New Directions

During both enrollment and through follow-up interviews every five years, AHS participants provide detailed information about their lives and pesticide use. During Phase II (1999-2003), participants in the AHS provided buccal (inside cheek) cell samples in saliva. Carefully stored since collection, these cell samples will now provide researchers with tissue for DNA analysis. Testing of the original buccal cell samples and, in some cases, newly collected samples is an important component of an ongoing prostate cancer study at NCI.

- Prostate Cancer – Michael Alavanja, Dr. P.H., will explore possible gene-environment interaction in prostate cancer. Alavanja's earlier research with subjects who had developed prostate cancer found an association between pesticide use and cancer, but only among men with a family history. Comparing the genetic polymorphism data from those cancer patients and men who do not have the disease may help researchers pinpoint specific genes that are affected by the environment to trigger prostate cancer.
- Asthma - Jane Hoppin, ScD., will build upon earlier findings that farmers have a greater risk of developing asthma, but that growing up on a farm offers protection against allergic disease. In a proposed study of 4000 farmers and their wives, Hoppin will conduct pulmonary function testing, collect blood for DNA and other analyses, and collect dust to look at non-pesticide related factors for disease.
- Parkinson's Disease– Freya Kamel, Ph.D., was a lead author on earlier investigations into the association between pesticide use and Parkinson's Disease in the AHS cohort. Kamel and others from the AHS are collaborating with The Parkinson's Institute on the Farming and Movement Evaluation (FAME) Study, a study nested in the AHS cohort, which conducted in-home movement assessments and collected blood and dust to look at potential Parkinson's disease determinants.
- Predictors of Early Puberty – Dale Sandler, Ph.D., will be the lead researcher on the Growth and Puberty Study among Young People in Iowa (GAP). Sandler will study the associations between exposure to hormonally active chemicals by children between the ages of 7 and 15 in farm families and several health conditions related to endocrine disruption. The study will involve recruiting the children of AHS cohort members and utilize non-invasive measures of hormones in saliva and urine.

including over 5,000 incident cancer cases and more than 5,000 deaths. Response rates to follow-up interviews remain high, due primarily to the careful design and timing of questionnaires.

Following reports on field station activities in North Carolina and Iowa, NCI Staff Scientist Joe Coble, ScD., reported on modifications to the pesticide exposure algorithm, which assigns numerical weights to the various behaviors, such as glove use and application methods, associated with exposure intensity. New pesticides and changes in practices make modifications necessary, Coble explained, but there are also opportunities to incorporate additional factors and molecular data. Panel members discussed whether the project should continue to add variables to the metric— and risk distorting it — or leave it as it is — and possibly miss an important variable.

The remainder of the meeting was devoted to reports by lead researchers on add-on studies evaluating links between pesticide and other farming exposures and prostate cancer, asthma, Parkinson’s disease and puberty among the children of cohorts (see sidebar for more detail). Some of these initiatives present researchers with recruitment and informed-consent challenges, as well as the need to incorporate molecular assessments.

As the AHS looks forward to the completion of Phase III in 2008 and beyond, its scientists are asking questions about several key matters, including incorporating studies of additional diseases into the project, the handling of biological specimens, the impact of new practices in pesticide applications, secondary exposures and the growing number of minorities involved in agriculture. AHS wants to expand the translation of its research into public health, consumer protection and occupational safety programs, and policy and to enhance communication with the clinical community.



*Shown from left, Marsha Dunn, Coordinating Center Director; Westat, Beate Ritz, M.D., of UCLA, and AHS Co-principal Investigator Jane Hoppin, ScD., of the NIEHS Epidemiology Branch watched from the head of the table as Alavanja enumerated the accomplishments of the first three phases of the AHS. (Photo courtesy of Steve McCaw)*



*AHS Principal Investigator Dale Sandler, Ph.D., of the NIEHS Epidemiology Branch, described the study design and recruitment challenges of the GAP add-on study. (Photo courtesy of Steve McCaw)*



Staff Scientist Freya Kamel, Ph.D., of the NIEHS Epidemiology Branch and NCI Research Fellow Laura Beane-Freeman, Ph.D., listened to the proceedings from their places at the NAP table. Daniel Goldstein, M.D., Director of Medical Toxicology for Monsanto, sat in the row behind the main table. (Photo courtesy of Steve McCaw)



The panel included two members with more than an academic interest in pesticide safety. Farmers Bryant Worley, left, of North Carolina and Dennis Schwab of Iowa have first-hand knowledge of pesticide application practices among their colleagues. Panel Member Annette G. Greer, not shown, represented North Carolina farm spouses, and testified to the positive impact that participating in the AHS has had on her life. (Photo courtesy of Steve McCaw)



Advisory Panel Member Linda Naeve and Iowa Field Station Director Chuck Lynch, M.D., Ph.D., took advantage of a break to view the posters on display. (Photo courtesy of Steve McCaw)

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# NIEHS Welcomes Aspiring Environmental Stewards

By Eddy Ball

Rodbell Auditorium took on a more “Old North State” flavor than usual on March 8 as NIEHS hosted the 2007 N. C. [Environmental Stewardship Initiative \(ESI\)](#) meeting and member recognition. The ESI program is operated by the state Department of Environment and Natural Resources (DENR) Division of Pollution Prevention and Environmental Assistance (DPPEA). Attendees included business people from throughout the state, representatives of local governments and community organizations, students from Duke’s Stanford Institute of Public Policy and a contingent of state employees.

As an ESI Environmental Partner since 2005, the Institute is striving to become what is called a Rising Environmental Steward, the next step in the process of achieving full Environmental Steward status. Working under Health and Safety Branch (HSB) Chief Scott Merkle, HSB Environmental Compliance Specialist Bill Steinmetz is overseeing efforts by the Institute to reach “self-declaring performance” in accordance with ISO 14001 (see sidebar), a standard of environmental management excellence recognized worldwide.

NIEHS Associate Director for Management Marc Hollander welcomed meeting attendees, explained a little about what goes on at NIEHS and underscored the Institute’s commitment to “getting better at being green.” Hollander credited the lake, lush vegetation, and resident ducks and geese as some of the “environmentally friendly stuff” that makes it so pleasant to work on the 375 acre campus. “We’re committed to stewardship on this campus,” Hollander declared. “We accept it as a community [because] public health and environmental health cannot be separated.”

DPPEA Division Director Gary Hunt and DENR Secretary Bill Ross returned to the “public health and environmental health” theme several times as they explained the ESI program and recognized new Rising Environmental Stewards. Key to ESI membership is a commitment to go beyond compliance with environmental regulations through development of a proactive Environmental Management System (EMS). According to Ross, this commitment means that members adopt a “triple bottom line,” which gives weight to environmental and social considerations, as well as profit.

Like the new Rising Environmental Stewards, other North Carolina businesses have reaped the benefits of adopting responsible environmental management practices. According to one of the event’s featured speakers, Smithfield’s Vice President of Environmental and Corporate Affairs Dennis Treacy, striving to optimize



*In the course of welcoming attendees, Hollander invited them to have lunch at the NIEHS cafeteria. “It’s very money friendly,” he joked. “It’s one of our ways of keeping ‘green.’” (Photo courtesy of Steve McCaw)*



*At the beginning of the meeting, Hunt introduced his colleagues at DENR. Unlike the heady scientific discourse that normally fills Rodbell Auditorium, the talk at this meeting was more likely to be of waste reduction, biodiesel, permaculture and grey water systems. (Photo courtesy of Steve McCaw)*

environmental management has saved the company millions in annual operating costs, dramatically reduced litigation and legal costs, salvaged the firm's less than stellar reputation, expanded its customer base and given Smithfield a greater sense of security in the marketplace.

The day-long workshop included a presentation on "Stewardship: Moving Forward, the EPA Perspective" by Dan Fiorino, director of the Performance Incentives Division at EPA. Another presentation highlighted ESI members Degussa-Stockhausen, a specialty chemical manufacturer in Greensboro, and the U.S. Coast Guard Support Center in Elizabeth City. The meeting closed with a program update and information presentation by DPPEA administrators and a session on working with mentors to help newer members benefit from the experiences of Environmental Stewards and Rising Environmental Stewards.

During one of the morning's presentations by Eric Henry of Burlington's T. S. Designs, Inc., a poster child for doing sustainable green business in North Carolina, Merkle and Steinmetz got a good-natured reminder of the work ahead at NIEHS. After describing the way T. S. Designs has looked at every aspect of its operations, from reducing electrical usage with solar panels and light tubes to replacing most of its lawn with trees and permaculture, Henry pointed to the lights in the ceiling of Rodbell. "This lighting is incandescent," he noted. "I know it's like picking low-hanging fruit, but this room really should have fluorescent lights or light tubes."



Ross presented plaques to eight new Rising Environmental Stewards — International Paper, Michelin Tire, Smithfield Hams, Telecris Biotherapeutics, Advanced Tubing Technology, Degussa-Stockhausen, Firestone Fibers and Textiles, and Smithfield Transportation. (Photo courtesy of Steve McCaw)

## Environmental Stewardship at NIEHS — From Grass-Roots Activism to a Proactive Program of Environmental Management

When Scott Merkle joined NIEHS in 1988, responsible environmental management was in the hands of a relatively few socially conscious employees. Today, Merkle has a full-time Environmental Compliance Specialist working in HSB and an EMS team of specialists led by Bill Steinmetz identifying and solving problems throughout the Institute. The team includes Radiation Safety Officer Bill Fitzgerald, Mechanical Engineer Greg Holland, Safety Officer Chris Hunt, Hazardous Waste Manager Paul Johnson and Employee Services Support Specialist Dick Sloane, all of whom report to Steinmetz.

As part of its program to become a full-fledged Rising Environmental Steward, NIEHS is developing a comprehensive [Environmental Management System](#) to achieve "self-declaring performance" in regard to international standards. [The International Standards Organization \(ISO\)](#) has developed more than 350 protocols for the monitoring of such aspects as the quality of air, water and soil, as well as noise and radiation. These standards also serve in a number of countries as the technical basis for environmental regulations.

In an increasingly global economy, ISO certifications are extremely attractive to American businesses involved in international trade and useful for setting beyond-compliance standards. ISO 9000 quality management and 14000 environmental management certifications require applicants to document their practices and submit to outside inspections to verify compliance. As an agency under the DHHS umbrella, NIEHS will not apply for formal certification, but will perform in a manner that meets the strict requirements of ISO 14000.

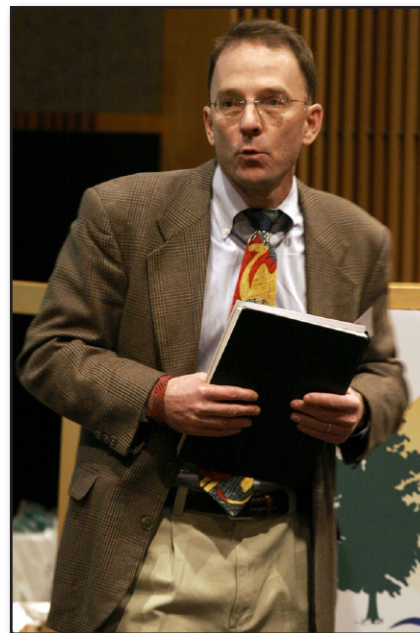
As part of the Environmental Stewardship Initiative, the Institute will submit to regular outside audits by DPPEA field staff as part of the approval process for its continued membership. The program's Environmental Management System model is based on the ISO 14001 rules. Participants must meet specific requirements, including assigning qualified staff to environmental management, keeping detailed, current records of compliance, and performing audits and issuing reports of the organization's environmental management activities.





Merkle, left, and Steinmetz head up the environmental management team at NIEHS. One of the team's recent accomplishments involved recycling cafeteria grease through an arrangement with a local alternative fuel producer. (Photo courtesy of Steve McCaw)

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After NAFTA nearly ruined the business, Henry helped T. S. Design become a green apparel printer selling certified organic cotton t-shirts, made and printed with non-toxic dyes in the US, largely in North Carolina "I always tell people that when I start selling t-shirts in China, then maybe I'll think about making t-shirts in China." (Photo courtesy of Steve McCaw)

## Institute in Top Ten for Postdocs

By Eddy Ball

*The Scientist*, a magazine focused on the life sciences, announced this month that NIEHS has again ranked high in the publication's annual "Best Places to Work for Postdocs" survey. NIEHS was the only NIH institute ranked in the top ten. The survey asks postdoctoral fellows to rate their institutions in 11 categories, including mentoring, communication and opportunities for networking and career development.

Not surprisingly, most respondents valued quality of training and career preparation highest among the categories — a category listed as a major strength along with pay in evaluations of NIEHS. The Institute ranked seventh this year after ranking number five in 2006 and number three in 2004 and 2005.

NIEHS was one of five 2006 top ten to make the top ten this year. Of the institutions included in the top 40 in 2007, 26 are new to the



Intramural Research Training Award Fellow Amy Inselman (Photo courtesy of Steve McCaw)

list, suggesting that growing awareness of the value of nurturing postdocs is intensifying competition. This year marks the first time that private sector organizations have made the top ten with Genentech in San Francisco placing fourth and the Fred Hutchinson Cancer Research Center in Seattle ranking tenth.

*The Scientist* article featured the comments of Laboratory of Reproductive and Developmental Toxicology Fellow Amy Inselman, Ph.D., on her experiences at NIEHS. “The people, from the principal investigators to the support staff, are knowledgeable and willing to lend a hand any way they can,” Inselman wrote in her survey response. “Collaborations are easy to build, and we have a wide array of resources available (from equipment to career guidance) that will help us transition to the next level.”

During their typical two- to five-year stay at NIEHS, postdoctoral fellows are offered numerous opportunities to participate in professional development activities and explore career options. NIEHS sponsors regular workshops to help fellows improve their presentation, writing and speaking skills, as well as develop effective strategies for negotiating and resolving conflicts. Their mentors help them to build their CVs by encouraging research that leads to publication, often with the fellows as lead authors.

NIEHS also received good marks in the survey for its remuneration. Fellows receive compensation at National Research Service Award stipend levels and individual or family group health coverage at no cost through the Foundation for Advanced Education in the Sciences. The cost of living in the Triangle helps the stipend go farther than comparable compensation in places with higher costs of living.

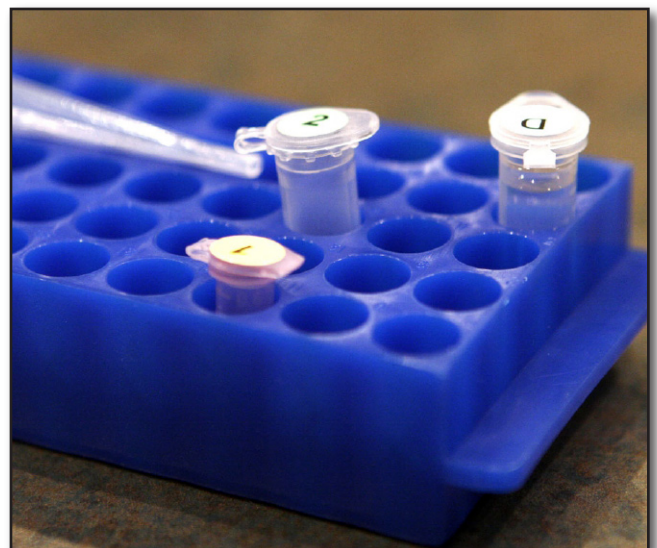
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## **N. C. Association for Biomedical Research Holds Teacher Workshop**

*By Robin Arnette*

The North Carolina Association for Biomedical Research (NCABR) held its “Rx for Science Literacy AgOdyssey” professional development workshop on February 28 in Rodbell Auditorium 101-A&B. The free, one-day workshop was open to K–12 science teachers and administrators from public, private and federal schools in North Carolina. The “Rx for Science Literacy” series is sponsored by Carolinas HealthCare System, Duke University Medical Center, East Carolina University, GlaxoSmithKline, University of North Carolina at Chapel Hill School of Medicine and NIEHS.

AgOdyssey—a curriculum developed by Bowling Green State University (BGSU) with a grant from NIEHS — is a problem-based learning adventure designed to let students investigate how the environmental health impact of factory farms compares to that of small, family farms. Jennifer Zoffel, Program Manager at BGSU’s Project EXCITE, provided an overview of the AgOdyssey curriculum.



*The equipment used in the hands-on “DNA Magic” demonstration was simple, but effective — a pipette, three tubes and a holder. With the right reagents, DNA in fish sperm became visible. (Photo courtesy of Steve McCaw)*

During the school year, NCABR holds approximately 12 workshops at member research facilities throughout the state. Participants get to tour laboratories, learn about the latest scientific research and take home a free curriculum and bioscience education materials for use in the classroom. North Carolina-certified teachers also receive one unit of certification renewal credit.

David A. Schwartz, M.D., director of NIEHS, and Liam O’Fallon, of the Community Outreach and Education Program at NIEHS, gave opening remarks. Schwartz thanked the teachers for the important role they play in the education of the state’s young people and said they had an extremely important role in training the next generation.

Derek Howles, Program Manager at NCABR, spoke on behalf of the organization in the absence of NCABR President Karen Hoffman and explained what the organization does. “We are a state-wide, non-profit, member-supported bioscience education organization. Our goal is to promote understanding of scientific research throughout the state,” Howles said. “We target the public, media, bioscience community and most importantly, K–12 teachers and students.” Marian Johnson-Thompson, Ph.D., director of Education and Biomedical Research Development at NIEHS and a former board member of NCABR, helped organize the AgOdyssey workshop.

After lunch Diane Forsyth, D.V.M., current NCABR board member and chief of the Comparative Medicine Branch (CMB) at NIEHS, and Mary Grant, D.V.M., also of CMB, took participants on a tour of the animal facility at the Institute. Leslie Brickhouse, a sixth grade science teacher at Leesville Road Middle School in Wake County, said the animal tour was her favorite part of the day. “I liked it because it was something that you don’t get to see everyday,” she said.

“Normally, when you go to a workshop you sit in a room and get information, but here, we were able to actually see what they were talking about.”

Participants also got to precipitate DNA during the DNA Magic demonstration, led by Lauranell Burch, Ph.D., of NIEHS and Molly Vallant of the Environmental Toxicology Program at NIEHS. Burch said that it was important for teachers to have a hands-on activity at the workshop. “I think everyone has an understanding of what DNA is and how important it is, but it’s really hard to relate to DNA because it is a microscopic substance,” she commented. “We are going to precipitate enough DNA, so that the workshop participants can actually see it.”



*Two area teachers try the DNA precipitation exercise for themselves. (Photo courtesy of Steve McCaw)*



*NIEHS Science Education Committee members, such as EEO Specialist Gerard Roman, also participated in the exercise — having fun with the task, but also keeping a look out for people who might need a little extra attention. (Photo courtesy of Steve McCaw)*

During the last hour of the workshop, Freya Kamel, Ph.D., of NIEHS discussed Parkinson’s disease and pesticide exposure, and NCABR’s Connie McElroy-Bacon conducted the workshop evaluation.

By the end of the day, the teachers had not only learned a lot, but felt it was a day well spent. Providing an enjoyable experience may be why the “Rx for Science Literacy” series is so successful. According to Howles, it is the largest and most popular workshop series that NCABR offers. Sangena Shirma, a high school biology teacher at Provisions Academy Charter School in Lee County, has attended six NCABR workshops and plans to attend others in the future. “The multiple resources I get are amazing, but my favorite today was the problem-solving strategy work,” she said. “It was a wonderful experience.”

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## Panel on Depression Wraps BIG Black History Month Observances

*By Robin Arnette*

In conjunction with the NIEHS Office of Clinical Research, the Research Triangle Park Chapter of Blacks in Government (BIG) presented “Addressing the Silent Crisis of Depression,” a panel discussion that provided information on the impact of depression on the African-American community. The event took place in Rodbell Auditorium on February 27 and was the last of RTP BIG’s Black History Month observances.

Marian Johnson-Thompson, Ph.D., director of Education and Biomedical Research Development at NIEHS, gave the welcoming address and focused on the importance of observing Black History Month. She also challenged the audience not to forget the many nameless African-Americans, both slaves and descendents of slaves, who fought and died for their freedom. Their efforts led to the enactment of laws that now protect not only the civil rights of African-Americans, but also the civil rights of all who had previously been marginalized.

The four panelists represented institutions or organizations from the Triangle area, and each gave a ten-minute presentation that dealt with a specific subtopic of depression. Panel moderator Alfiee Breland-Noble, Ph.D., assistant professor in the Department of Psychiatry and Behavioral Sciences at the Duke University Medical Center (DUMC), began with a brief overview of the illness. Clinical depression is defined as a state of intense sadness, melancholia or despair that has advanced to the point of being disruptive to an individual’s social functioning or activities of daily living. Breland-Noble



*Moderator Alfiee Breland-Noble discussed her AAKOMA Project. (Photo Courtesy of Steve McCaw)*



*Wei Jang made several important points about depression as a risk factor for cardiac disease. (Photo Courtesy of Steve McCaw)*

continued, “There are three major types of clinical depression: major depressive disorder, bipolar disorder—formerly known as manic depression—and dysthymia, which is a general persistent malaise.”

Breland-Noble went on to say that the mental health community needs more research on African-Americans and depression because there are very little data. However, Breland-Noble said there is an uneasiness in the African-American community about volunteering for such studies because of lingering mistrust of the medical community after the [Tuskegee Syphilis Experiment](#). Her current project may help change this way of thinking while helping African-Americans get the treatment they need. Her African-American Knowledge Optimized for Mental-Health Awareness (AAKOMA) Project intends to 1) identify factors associated with participation in research and treatment and 2) develop an intervention to increase participation in research and treatment.

Wei Jiang, M.D., associate professor of Medicine and associate professor of Psychiatry and Behavioral Sciences at DUMC, talked about the importance of understanding the impact of depression on cardiac diseases. Currently, clinical depression is the leading cause of disability in North America and in other countries, but Jiang stressed the role the two diseases will play in the future. “By 2020, the top two causes of disability worldwide will be cardiac disease and depression,” she said.

Elwood Robinson, Ph.D., professor of Psychology and interim dean of the College of Behavioral and Social Sciences at North Carolina Central University, presented data dealing with African-American women and depression. “African-American women, compared to African-American men and Caucasian men and women, were least likely to commit suicide, although they are probably just as depressed as everyone else,” he asserted. Robinson petitioned the audience to theorize why this is the case. Many in the audience smiled and offered several responses, all with a common theme: African-American women have too many things to do. They don’t have time to kill themselves.

Although this retort was offered as a humorous interpretation of the data, Robinson brought up another study during the question and answer session that appeared to back up this idea. “Similar studies with single African-American fathers suggest that they also have a low rate of suicide,” he declared. “Just like African-American women, they are responsible for so many people that they have to stay strong and keep the family together.”

Nayo Watkins, founder and director of The Mekye Center, a Durham-based program for children who are “different learners” and their parents, provided a first-hand account of the pain and loss that depression can cause. Her 16-year old son, Mekye, committed suicide in 1998, and since then, she has dedicated her life to helping people recognize the symptoms of depression and encouraging them to seek treatment. “African-Americans have the attitude that we [as a people] don’t commit suicide,” Watkins stated, “and that depression is a sign of



*Elwood Robinson presented data on the impact of depression on African-American women. (Photo Courtesy of Steve McCaw)*



*Nayo Watkins recounted her experience dealing with the loss of her son to suicide. (Photo Courtesy of Steve McCaw)*

weakness. It isn't." She encouraged audience members to look for signs of depression in their loved ones — disturbed sleep patterns, fatigue, loss of appetite, irritability and trouble concentrating, to name a few.

All of the panelists reiterated that depression is a disease of the brain and that there is no shame in seeking help. Family doctors, mental health specialists and other health professionals may provide a variety of treatments, including medications and short-term psychotherapies. More than 80 percent of people who receive treatment improve.

For more information about depression and other mental health issues, please see the [National Institute of Mental Health](#) Web site.

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## Spirit Lecturer Urges Women to Keep Striving

*By Eddy Ball*

The NIEHS Diversity Council welcomed to the podium the sixth speaker in its series of annual Spirit Lectures on March 20 in Rodbell Auditorium. The 2007 Spirit Lecture was delivered by Alice Huang, Ph.D., a noted scientist, educator and activist. In the course of a talk titled "Beyond the Numbers: Where Are We Going?" Huang challenged her audience to continue to be vigilant about the rights of women and minorities and to strive for true equality.

NIEHS Deputy Director Sam Wilson, M.D., welcomed the audience to this year's Spirit Lecture. Education and Biomedical Research Development Director Marian Johnson-Thompson, Ph.D., introduced her long-time friend and associate. Following the lecture, Spirit Lecture Committee Chairperson Molly Vallant, Ph.D., presented Huang with the 2007 Spirit Lecture Award.

Huang is currently senior councilor for External Relations and faculty associate in Biology at the California Institute of Technology. The Johns Hopkins-educated virologist has received a long list of honors for her scientific and educational contributions. She holds several chairs and sits on the boards of major organizations, including the Foundation for Microbiology and the Food and Drug Administration Advisory Committee on Vaccines and Related Biological Products.

Huang opened her talk with an account of her personal experiences. Born and reared during her early years in China, after she came to America, Huang experienced



*2007 Spirit Lecturer Alice Huang. (Photo courtesy of Steve McCaw)*



*In his opening remarks, Wilson emphasized the Institute's commitment to workplace parity for women. (Photo courtesy of Steve McCaw)*

not only the challenge of being a woman in the male-dominated world of science during the 1960s and 1970s, but also the sense of being an outsider in a strange new place who “wanted very much to blend in.”

Those experiences affected how Huang tackled the professional roles she has played — as a scientist, educator and leader. She credits one of her many roles, as a dog owner and lover, with affecting how she has fulfilled these roles. “What they [my dogs] have taught me is something important as well,” she said. “In my interactions with people, with friends and with colleagues, in addition to being professional, loyalty, love and respect for the other individual are important.”

Huang turned to statistics to show how far women have come and how much there is still to do. Although the situation is improving for women and minorities, the numbers make it clear that many obstacles remain. Disparity in income has decreased, and a greater percentage of women are now getting doctorates in science and making careers in the health sciences and the world of academia

However, women remain at a distinct disadvantage when it comes to representation at the higher levels of business, government and education. Women make up only 9.3 percent of full professors at Harvard Medical School and other prestigious institutions. In the world of business, they constitute a mere 3.3 percent of top earners, and only two Fortune 500 corporations employ a woman as chief executive officer.

“There are still too few women and minorities in the pipeline,” she explained, “... [and] woman are stalled at the bottom of many professions.” Women and minorities still face myths in the workplace, myths that they are not as capable or competitive or ambitious. Many employers still assume that women are limited by family responsibilities and that efforts to increase diversity will lower the standards of performance.

Women and minorities too often internalize the myths and begin to fulfill the misconceived expectations of others. They also tire of the struggle for parity. “What will often cause complacency,” Huang said, “is the feeling that there’s no problem any longer. Yes, it’s better than 30 years ago, but there are still problems left.”

Rather than accepting casual remarks that reinforce the myths, women should be intolerant of the attitudes that marginalize their contributions. For its part, society should make sure that the bar for women and minorities is not set higher to exclude these groups. Businesses, universities and other organizations should also promote



*When she introduced her friend of almost twenty years, Johnson-Thompson praised Huang for her work as a mentor and role model for young women. (Photo courtesy of Steve McCaw)*



*Darlene Dixon, D.V.M., and Charle League enjoyed one of the speaker’s lighter anecdotes. (Photo courtesy of Steve McCaw)*

diversity in the workplace. Like the natural world she has studied so carefully, according to Huang, society and the workplace can benefit from diversity.

Each year since 2002, the NIEHS Spirit Lecture Series has recognized outstanding women who have achieved a balance between the competing aspects of work and family in their lives, thereby becoming better scientists and better members of their families and communities. The series is sponsored by the NIEHS Diversity Council.

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*Vallant posed with Huang and the 2007 Spirit Lecture Award. (Photo courtesy of Steve McCaw)*



## Science Notebook

### USC Specialist Discusses Epigenetic Therapy

*By Eddy Ball*

The latest talk in the NIEHS 2006-2007 Distinguished Lecture series on March 13 featured University of Southern California (USC) Distinguished Professor of Urology Peter Jones, Ph.D. Jones is director of the USC/ Norris Comprehensive Cancer Center in the Kirk School of Medicine and holds the H. Leslie Hoffman and Elaine S. Hoffman Chair in Cancer Research. The topic of his lecture was “How the Epigenome Changes in Cancer.”

Lecture host and Laboratory of Molecular Carcinogenesis Chief Trevor Archer, Ph.D., opened the event by reviewing some of the highlights in Jones’ distinguished career. “Early in his career, Peter made a very seminal set of discoveries, hailed in *Nature* as ‘one of the milestones in cancer research,’” he observed. “Peter and his group demonstrated for the first time the causative relationship between methylation and gene expression and differentiation changes.”

In the years that followed, Jones and his group translated their findings into development of therapeutics and treatments now in various stages of pre-clinical and clinical trials. His work has been inspired by the conviction that epigenetic aberrations involved in cancer development are potentially reversible.



*Distinguished Lecturer Peter Jones. (Photo courtesy of Steve McCaw)*



Jones believes that epigenetic therapy has the potential to return the malignant cell population to what he described as “a quasi-normal state.”

During his talk, Jones focused on two major inter-related cancer-promoting processes that are the targets of his drug development efforts, DNA methylation and histone modification. By altering nucleosome occupation patterns, these processes work together to silence expression of tumor-suppressor genes and other genes that are critical to normal cell function.

Using an aerial photo of the earth at night, Jones invoked the image of light as an analogy for gene transcription. “So what goes on in cancer?” he asked. “The lights go out... [and] several genes can be actually inactivated and switched off.”

According to Jones, DNA methylation patterns, once established, can be copied and serve as a very powerful way of silencing genes. “Physiologically this [methylation] is essential for life,” Jones explained, “and pathologically if it goes wrong it gives rise to cancer.”

The enzyme DNA methyltransferase (DNMT) is responsible for triggering DNA methylation. When methylation occurs near the transcription start site, it silences genes that suppress tumor development. Drugs that target DNMTs are thus potentially useful in treatment.

The other important enzymatic process that Jones discussed is histone modification. Histones are basic proteins in nucleosomes that are wrapped in DNA. Their tails are subject to post-transcriptional alterations. Although there are several ways that histones may be modified, Jones focused on the deacetylation of lysine residues on histone tails, which results in chromatin compaction and inactivation of genes.

The enzyme involved in this process is histone deacetylase (HDAC). Loss of lysine acetylation through activation of HDAC has been identified as the first step in gene silencing. Loss of acetylation also leads to a decrease in DNA repair, further promoting cancer development and proliferation.

Jones and his group have studied more than twenty compounds shown to inhibit DNMTs and HDACs. As promising as many of these drugs are by themselves, especially for inhibiting these enzymes before lesions have actually occurred, they are not as effective as a stand-alone therapy after tumors have developed. Some of the drugs already approved or in trial are very short acting, and their effects can be transitory.

Jones suggested that the future of epigenetic therapy for cancer will probably involve chronic therapy with a combination of primary



*Among the audience for Jones' lecture on epigenetic therapies were EPA Genetic Toxicologist David M. DeMarini, Ph.D., left, and Laboratory of Signal Transduction Supervisory Biologist John Cidlowski, Ph.D. (Photo courtesy of Steve McCaw)*



*Host Trevor Archer will also host next month's lecture by C. David Allis of The Rockefeller University. (Photo courtesy of Steve McCaw)*

and secondary treatments. Such an approach would utilize a standard cancer tool, such as chemotherapy, immunotherapy or radiotherapy, in conjunction with enzyme inhibitors. Epigenetic drugs could set the stage for more effective treatment by reactivating tumor-suppressor genes and restoring DNA repair to improve the patient's response to other drugs and to make cells more chemo-sensitive to standard therapies.

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## Biologist Explores Reasons for Sexual Reproduction

By Eddy Ball

Biologist Matthew Meselson, Ph.D., addressed the question “Why Does Sexual Reproduction Exist?” during a March 9 talk in Rodbell Auditorium. Meselson is the Thomas Dudley Cabot Professor of the Natural Sciences at Harvard University, an adjunct scientist at the Marine Biological Laboratory in Woods Hole, Cape Cod, Mass., and winner of the prestigious Lasker Award.

“This question of why is it that it takes two individuals to produce one,” Meselson explained as he began his talk, “...is a fairly old question.” Although Darwin offered no explanations and, in fact, wrote that the reasons are “still hidden in darkness,” his theory of evolution sparked interest in the question among scientists. Today, the question of why such an involved process is necessary continues to be intriguing.

There are many costs associated with sexual reproduction, Meselson noted. These include the cost of finding a mate, or failing to find a mate, sexually transmitted diseases and parasites, and the inefficiency of a process that demands twice as many individuals to produce offspring.

Meselson noted that there are more than 20 different hypotheses as to why sexual reproduction predominates among organisms with a high taxonomic rank. One of the earliest was the proposal by the 19th century German evolutionary theorist August Weismann that sex exists because it generates the variation upon which natural selection can act. More recent theories have pointed to the proliferation of beneficial mutations — or the avoidance of harmful ones — as advantageous to sexually reproducing organisms as a way of “mixing things up.”

In contrast to the mixing theories, Meselson's own current hypothesis focuses on an organism's ability to keep the proliferation of parasitic retrotransposons from overwhelming it. Retrotransposons are mobile genetic elements that insert themselves into chromosomes and are present in virtually all eukaryotes. This kind of mutation, according to Meselson, “is particularly obnoxious... [because it] can replicate itself.”

Although such elements reproduce autonomously, their increase is constrained by processes dependent on sexual reproduction. In most cases, abandonment of sexual reproduction results in the number of such elements increasing indefinitely, eventually driving the asexual lineage to extinction.



*Meselson's lecture drew a large audience of postdoctoral fellows and investigators. (Photo courtesy of Steve McCaw)*

Interestingly enough, Meselson found support for his ideas in an exception to this pattern of extinction — the lack of retrotransposons in bdelloid rotifers. Bdelloids are an ancient class of invertebrate animals that are characteristically found in the water films of mosses and lichens, in rain gutters and in other ephemerally aquatic habitats. Even though scientists have studied these animals for hundreds of years, they have never observed any indication of sexual reproduction in this ancient life form.

According to Meselson, the key to their survival seems to lie in the remarkable ability of bdelloids to survive desiccation, or dying up, at any stage of their life cycle by entering a metabolically quiescent state and rapidly recovering as water becomes available. It is likely the adaptation of bdelloids to desiccating habitats and the associated DNA damage and repair that have depleted their genomes of retrotransposons and made it possible for them to “cross over” to avoid extinction.

At the end of his talk, Meselson conceded that “since this is the field of theoretical population genetics, it’s very difficult to really prove something [definitively]... The situation is so complex.” However, the bdelloids, “these marvelous creatures,” may offer the best example yet of “nature’s experiment” demonstrating why sexual reproduction exists.

The Laboratory of Molecular Genetics (LMG) trainees sponsored Meselson’s talk. Postdoctoral Fellow Libertad Garcia-Villada was the host of the lecture.

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## The Many Aspects of Matthew Meselson’s Life in Science

In the course of his long career as a scientist, Meselson has made several important contributions to molecular biology. These contributions include the development of equilibrium sedimentation of macromolecules in density gradients, the experimental proof of the semi-conservative nature of DNA replication, the demonstration of a break-reunion mechanism of genetic recombination in phage lambda, the discovery of the methylation-based mechanism that protects DNA against restriction enzymes, and the phenomenon of DNA mismatch repair. He is also well known for his expertise in chemical and biological warfare, which led him to ascertain the source of the putative poison “yellow rain” in Vietnam and the hidden story behind a lethal outbreak of pulmonary anthrax in Sverdlovsk.

While still a graduate student under Nobel Prize winner Linus Pauling at the California Institute of Technology, he became interested in DNA replication and repair. In 1957, he and colleague Frank Stahl performed the landmark experiment confirming that DNA replicates as predicted by the double helix structure Watson and Crick had recently proposed. This work is the subject of the book by Frederick Lawrence Holmes, *Meselson, Stahl, and the Replication of DNA: A History of “The Most Beautiful Experiment in Biology,”* published in 2001 by Yale University Press.

Meselson also has been politically influential as a vocal opponent of biological warfare. He worked at the Arms Control and Disarmament Agency and became a friend of Henry Kissinger in the 1960’s. He served as an advisor to the Biological Weapons Convention in 1972. Despite his influence during Nixon’s presidency, Meselson also ended up on one of the former president’s two enemies’ lists. In the years since, he has been active in the Harvard-Sussex Program on Chemical and Biological Weapons.

# Amphibian Specialist Challenges EPA and Pesticide Manufacturers

By Eddy Ball

On the afternoon of March 7, NIEHS scientists packed Rodbell C to hear a talk by biologist Tyrone Hayes, Ph.D. Hayes is a professor in the Department of Integrative Biology at the University of California – Berkeley. He is also a speaker who does not mince words when it comes to manufacturers of the herbicide atrazine and the federal agency responsible for regulating the compound.

Hayes' talk, "From Silent Spring to Silent Night: The Connection between Pesticides, Amphibian Declines, and Cancer," was an indictment of practices by companies that make the widely used herbicide. The biologist also had harsh words for the ruling by the Environmental Protection Agency re-approving atrazine, as well as the agency's conclusion that the herbicide is "not likely to be carcinogenic to humans."

Hayes' research has uncovered in frogs reproductive anomalies linked to endocrine disruption associated with exposure to small amounts of atrazine. Hayes contends that the chemical has similar effects in humans.

By up-regulating the enzyme aromatase, which converts the male hormone testosterone into estradiol and alters gene expression, atrazine exposure could trigger the development of hormone-stimulated cancers, such as breast cancer.

Ironically, it was Hayes' research during the 1990s for the industry-funded Atrazine Endocrine Disruption Panel that set the stage for his research. Working with African clawed frogs raised in his lab, Hayes began to see abnormalities in larynx growth in frogs exposed to doses of atrazine in concentrations as low as one part per billion (ppb).

Further research convinced Hayes that more than abnormalities of the larynx were involved when male frogs were exposed to the pesticide during their development. Hayes discovered that the up-regulation of aromatase and the subsequent conversion of male hormones to female hormones produced what he described as "chemical castration." Exposed frogs developed the reproductive organs of both sexes.

The results were disturbing, he explained, because under EPA guidelines, atrazine is considered safe in drinking water as long as it is found in levels no greater than three ppb, three times the level that causes endocrine disruption in amphibians. "I could take tap water that is regulated by the U.S. EPA," Hayes noted, "and I could chemically castrate frogs."



*"I give a talk at a meeting, and everybody remembers the black guy in the braids," Hayes remarked in a 2002 interview. While the message may have been disturbing, the messenger was charming, witty and engaging. (Photo courtesy of Steve McCaw)*



*Several times during the talk, Hayes refuted industry claims that what he found in frogs was the result of "normal variation." In field studies, he found that "100 percent of the time when we find hermaphrodites, we find atrazine, and vice versa." (Photo courtesy of Steve McCaw)*

Although Hayes has never performed studies with mammals, the connection between abnormalities in frogs and carcinogenesis in humans was a logical one for him. “Frog hormones are very similar, and in some cases identical, to human hormones,” he argued. “So what affects a frog, may also affect humans.”

If atrazine could cause endocrine disruption in frogs, he reasoned, it was likely to have similar effects in people, especially if they were exposed during development. His follow-up research at the bench with frogs and his extensive observations in the field soon convinced him that he was on to something important.

When Hayes’ began to talk and write about his results, industry-supported researchers attacked the accuracy of his data and tried to explain away the effects as “normal variation.” He continues to be a target of criticism by industry spokespersons, who, he believes, hope to discredit his research by claiming they cannot replicate his results.

To counter these attacks and EPA skepticism, Hayes pointed to results of over 40 studies that are in line with his hypothesis about atrazine’s effects on mammals. He also cited Sygenta-funded research that reported results similar to his own.

Research with frogs can cover several generations in the course of a year. However, it may take decades before investigators can reach definitive conclusions in studies of humans and persuade regulators and manufacturers that atrazine poses a significant health threat to humans.

Hayes’ talk was sponsored by the Laboratory of Experimental Pathology (LEP). LEP Veterinary Medical Officer Greg Travlos, D.V.M., was the host for the lecture.

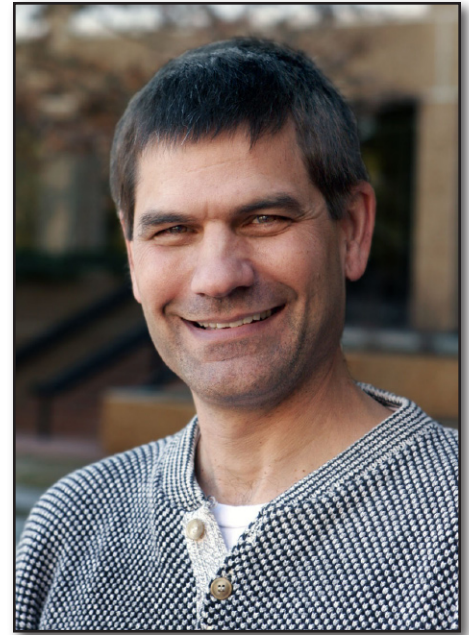
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## **NYU Environmental Scientist Outlines Nickel’s Epigenetic Effects**

*By Eddy Ball*

NIEHS scientists filled Rall F-193 on March 1 to hear a talk by guest lecturer Max Costa, Ph.D., on “Epigenetic Mechanisms of Nickel Carcinogenesis.” Costa is a professor and chairman of the Department of Environmental Medicine and professor of Pharmacology at New York University School of Medicine. He also serves as deputy director of the NYU Cancer Center and the director of the Nelson Institute of Environmental Medicine.

Because nickel is a well-established carcinogen that is not mutagenic or especially toxic, it offers researchers an especially useful medium for studying alternate mechanisms of carcinogenesis. Its potent



*Lecture host Greg Travlos  
(Photo courtesy of Steve McCaw)*



*Guest lecturer Max Costa spoke to a capacity audience. (Photo courtesy of Steve McCaw)*

carcinogenicity has been extensively documented in occupationally exposed nickel refinery workers, who have an increased incidence of lung, nasal and other cancers.

“It’s a very broad-acting carcinogen,” Costa observed. “Nickel compounds induce more different kinds of cancer than almost any other carcinogen.” Along with its carcinogenesis, nickel has been also implicated in contact dermatitis, lung dysfunction and cardiovascular disease, probably because of depletion of the amino acid taurine caused by exposure.

“The metal is actually not very toxic,” Costa explained, and it has known functions in plant enzymes. “This [lack of toxicity] may be important in why they [nickel ions] allow cancer cells to arise with epigenetic or genetic alterations.”

Using the soluble form of nickel, Costa and his colleagues have elucidated the mechanisms of the two cancer pathways used by nickel — hypoxia signaling and tumor suppressor gene silencing. The depletion of oxygen caused by hypoxia kills iron-containing enzymes in the cell and extends the stabilization of a transcription factor known as Hif-1 $\alpha$ , which normally has a half-life of minutes in the cell. Without the limits imposed by iron in the cell, Hif-1 $\alpha$  turns off and on a host of genes, especially cell proliferation factors and enzymes that regulate the energy production processes involved in cancer growth.

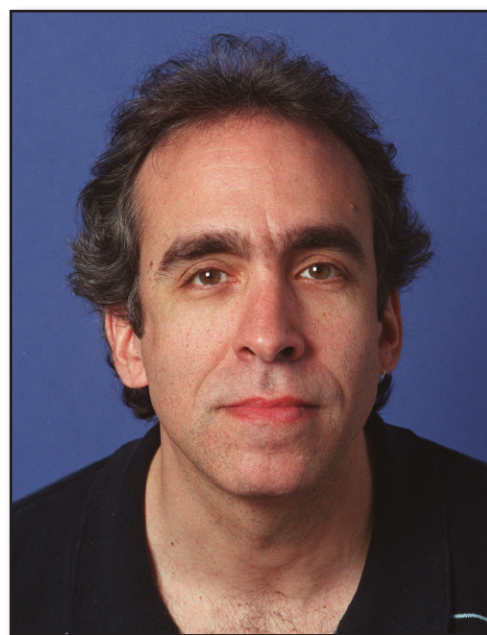
“Cancer is a disease where you lose genetic information,” Costa explained. Nickel’s epigenetic effects compound its hypoxic effects by promoting DNA hypermethylation and effecting changes in nucleosome condensation via histone modification. DNA hypermethylation silences tumor suppressor genes, allowing tumors to grow. Exposure alters transcription genes involved in activating receptors, invasion metastasis suppression, DNA repair, and inhibition of carcinogenesis and angiogenesis.

Research into the epigenetic mechanisms of nickel has identified an impressive list of cancer-related genes and helped researchers understand the metal’s differing effects on types of methylation. It has also pinpointed position-dependent variables involved in the effects of nickel on cell metabolism.

In terms of translational outcomes, this work has helped to identify potentially useful therapeutic compounds, such as valproic acid, which can reactivate tumor suppressor genes. Understanding the mechanisms also has allowed clinicians to monitor histone modification in breast cancer by observing changes in nucleosomes and to identify risk for atherosclerosis by measuring taurine levels.

In addition to his many academic distinctions, Costa is a member of several editorial boards of major journals in the fields of toxicology, pathology and trace element research. He is also a member of leading scientific organizations, including the American Society for Cell Biology, the American Society for Biochemistry and Molecular Biology, the Society of Toxicology and the American Association for Cancer Research.

Costa’s lecture was jointly sponsored by the NIEHS Laboratory of Pharmacology and Chemistry and the Laboratory of Molecular Toxicology (LMT). LMT Tenure-Track Investigator Jonathan Freedman, Ph.D., was the host for the lecture.



*Lecture host Jonathan Freedman  
(Photo courtesy of Jonathan Freedman)*

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## Upcoming Distinguished Lecturer

*By Eddy Ball*

C. David Allis, Ph.D. will deliver the next talk in the 2006-2007 NIEHS Distinguished Lecture Series at 2:00 p.m. on April 10 in Rodbell Auditorium. Allis is the Joy and Jack Fishman Professor and Head of the Laboratory of Chromatin Biology at The Rockefeller University in New York. His lecture is titled “Beyond the Double Helix: Reading and Writing the Histone Code.”

According to Allis’ online account of his research, his laboratory has postulated that “an epigenetic indexing system for the genome works as a fundamental regulatory mechanism in addition to the DNA and the genetic information itself.” This research is centered on the hypothesis that “distinct covalent histone modifications, acting alone, sequentially or in combination, form a ‘histone code’ that is then read by effector proteins to bring about distinct downstream events.” Allis’ goal is to understand better the dysfunctional processes leading to tumor formation.

Laboratory of Molecular Carcinogenesis Chief Trevor Archer, Ph.D., is host of the lecture.



*Distinguished Lecturer C. David Allis  
(Photo courtesy of The Rockefeller University)*

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## DETR Papers of the Month

*By Jerry Phelps*

### Prostate Cancer Linked to High Levels of a Mismatch Repair Protein

A Ph.D. candidate at the Wake Forest School of Medicine supported by NIEHS identified an increase in a DNA mismatch repair protein as a marker for prostate cancer. This finding represents the first documented evidence of an increase in a mismatch repair protein being associated with human cancer.

The purpose of the study was to identify new prognostic tools to identify prostate cancer patients at risk for particularly severe life-threatening forms of the disease compared to those who develop slower-growing, less severe forms. The research team analyzed tissue samples from prostatectomies and determined the presence or absence of the key mismatch repair proteins MSH2, MLH1 and PMS2. They found increases in PMS2 in the samples from prostate cancer tissue. Many previous studies have associated deficits in mismatch repair proteins with risks for tumor formation. The results also demonstrated that the PMS2 increase is associated with genetic instability.

The study results imply that the increase in PMS2 and the accompanying genetic instability are early events in the development of prostate cancer. The results also suggest that PMS2 may be used as a prognostic marker for the

early detection of aggressive forms of prostate cancer and could be used to direct individual treatment strategies for patients with the marker.

*Citation:* [Norris AM, Woodruff RD, D'Agostino RB Jr, Clodfelter JE, Scarpinato KD](#). 2007. Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate* 67(2):214-225.

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## **Air Pollution and Cardiovascular Disease in Women**

New research by NIEHS grantees at the University of Washington shows that the risk of harm from particulate air pollution to the respiratory and cardiovascular systems in post-menopausal women is about three times higher than previously estimated. The scientists found that the greater the level of the fine particulate pollution, the greater the risk of cardiovascular disease and death.

Investigators analyzed the medical records of more than 66,000 postmenopausal women participating in the Women's Health Initiative in 36 cities and followed them for six years. Particulate air pollution was measured by monitors placed near the subjects' homes. The size of the particles measured was smaller than 2.5 microns in diameter. During the study, 1,816 women had heart attacks or strokes or were diagnosed with arterial diseases, and 261 died.

The risk of dying from heart attack or stroke increased 76 percent for each ten microgram increase in particulate pollution. The annual average exposure was 13.5 micrograms per cubic meter of air, lower than the EPA standard of 15 micrograms.

Although the actual biological effects of particulate exposure are unknown, the scientists speculate that the particles cause inflammation in the lungs that spreads to the arteries, increasing arterial disease and the likelihood of heart attack and stroke.

*Citation:* [Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD](#). 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 356(5): 447-458.

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## **Exposure to Traffic and Lung Development**

University of Southern California researchers with support from NIEHS report that children living within 500 meters of a freeway in California had reduced lung-function compared to children living 1,500 meters or more from freeways. This finding is important because it shows that within certain communities, some children are at higher risk than others for adverse respiratory effects resulting from environmental pollution.

The study included 3,677 children aged 10-18 from twelve Southern California communities. Over an eight-year period, researchers gave the children early lung-function tests including forced expiratory volume and maximum midexpiratory flow rate. Results showed significant deficits in lung function for children living within 500 meters of the freeway.



The research team pointed to diesel exhaust as an important component of the impaired lung function. Diesel exhaust is known to contain a high fraction of particulate matter of a size that is readily inhaled deep into the respiratory system. Other human exposure studies show that breathing dilute diesel exhaust produces extensive inflammation in the bronchial walls and adverse effects associated with oxidative stress, activation of protein kinases and transcription factors, and perturbations in cell function by the chemical and physical properties of diesel exhaust particles.

*Citation:* [Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J.](#) 2007. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 369(9561):571-577.

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## ***In Utero* Bisphenol A Exposure Leads to Abnormal Egg Development in Mice**

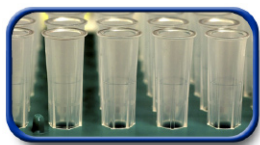
Recent experiments in pregnant mice exposed to the purported endocrine disrupting chemical bisphenol A (BPA) at doses comparable to the range of common human exposures resulted in chromosomal abnormalities in the eggs of the exposed fetuses.

The NIEHS-funded research found that exposure to BPA at early stages of development disturbs the growth and division of the eggs in the unborn female fetuses. When the fetuses reach adulthood, the perturbations lead to increases in chromosomally abnormal eggs and embryos. The results indicate that as many as 40 percent of the eggs and embryos from females exposed to the chemical may be affected compared to the background rate of less than one percent.

BPA is a component of polycarbonate plastics, resins that line food and beverage containers, and additives in a variety of consumer products. Humans are exposed to trace amounts of it by eating or drinking products stored in these plastics. Other human health effects that have been associated with BPA exposure include a variety of reproductive effects in males and females, increased susceptibility to prostate cancer, alterations in mammary gland organization, and deficits in neurological development. Emerging research is beginning to link exposure with the prevalence of obesity and other endocrine disorders.

*Citation:* [Susiarjo M, Hassold TJ, Freeman E, Hunt PA.](#) 2007. Bisphenol A exposure *in utero* disrupts early oogenesis in the mouse. *PLoS Genet* 3(1):e5.

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## DIR Papers of the Month

By Eddy Ball

### Exercise May Help Women Prevent Fibroids

An NIEHS-funded study of 1,189 white and African-American Women in Washington, D.C., could give women yet another reason to exercise regularly. In the study, published in the March issue of the *American Journal of Epidemiology*, investigators found an inverse association between physical activity and development of uterine leiomyomata (benign tumors known as fibroids). Fibroids significantly impact female reproductive health and are a leading cause of hysterectomy.

Investigators randomly selected women between the ages of 35 and 49 who were members of a prepaid health plan in Washington, D.C., and participants in the NIEHS Uterine Fibroid Study. In order to become a part of the study population, the women needed acceptable fibroid data, based on sonogram (76 percent), medical records (7 percent) or self-report of fibroid diagnosis (9 percent). Participants included 734 African-Americans and 455 Whites who self-reported their physical activity. The team collected data about potential confounders, such as reproductive history, smoking, alcohol intake and education.

Consistently reported risk factors for the condition are non-modifiable. The association found in this study between physical activity and fibroid status suggests that exercise may be protective against the development of fibroids in a dose response pattern, offering women the opportunity of making a lifestyle change that could benefit their reproductive health.

*Citation:* [Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM](#). 2007. Association of physical activity with development of uterine leiomyoma. *Am J Epidemiol* 165(2):157-163.

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### Obesity Impacts Ability to Conceive

Intramural researchers from the NIEHS Epidemiology and Biostatistics Branches have found that obesity was associated with reduced fecundity for all subgroups of women participating in their recent study of more than 7300 pregnant women. Their results, published in the February issue of *Human Reproduction*, suggests that weight loss could increase fertility for overweight and obese women, regardless of menstrual cycle regularity, parity, smoking habits or age.

The researchers selected the subjects from the more than 55,000 pregnant women enrolled in the Collaborative Perinatal Project at 12 study centers in the United States between 1959 and 1965. The team selected the 7,327 participants with complete physical and lifestyle data needed for statistical analysis. The study compared more fertile women, those who became pregnant in three months or less, with less fertile women. The team also compared women who planned their pregnancies with women had not, using BMI, age, smoking, parity and other demographic, gynecological and reproductive characteristics.

In their discussion, the authors of the study hypothesized that obesity-induced excess estrogen may be responsible for reduced fecundity. They suggest that “weight loss and improved knowledge of the fertile window should be encouraged as non-invasive first attempts for treating infertility for overweight and obese women.”

*Citation:* [Gesink Law DC, Maclehose RF, Longnecker MP](#). 2007. Obesity and time to pregnancy. *Hum Reprod* (2):414-420.

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## Involvement of Estrogen Receptor- $\alpha$ in Airway Hyperresponsiveness

An interdisciplinary research team has found a variety of lung function abnormalities and enhanced airway responsiveness to inhaled methacholine and serotonin in estrogen receptor- $\alpha$  knockout ( $\alpha$ ERKO) mice. Published in the *American Journal of Respiratory and Critical Care*, the NIEHS-funded study was a collaboration among researchers from NIEHS, the Environmental Protection Agency, the Medical College of Wisconsin and the National Jewish Medical and Research Center.

The team of investigators examined basal lung function and airway hyperresponsiveness in wild type,  $\alpha$ ERKO and  $\beta$ ERKO mice using a variety of approaches including non-invasive and invasive measurements of lung function *in vivo*, and *ex vivo* measurements of airway tension in isolated bronchial rings. They found that while ER $\beta$  had little influence on most aspects of lung function, disruption of ER $\alpha$  resulted in significant changes in a variety of respiratory parameters and played a critical role in regulating breathing and respiratory rhythmogenesis in mice. Moreover, lack of ER $\alpha$  led to spontaneous airway hyperresponsiveness via a mechanism that involved altered regulation of M2 muscarinic receptor expression and function. Importantly, absence of ER $\alpha$  in mice led to airway hyperresponsiveness *without* increased inflammation after allergen sensitization and challenge. Airway hyperresponsiveness is an important feature of human asthma.

Together, the findings in this study provide further insight into the mechanisms which underlie gender differences in lung function and response to environmental agents.

*Citation:* [Carey MA, Card JW, Bradbury JA, Moorman MP, Haykal-Coates N, Gavett SH, Graves JP, Walker VR, Flake GP, Voltz JW, Zhu D, Jacobs ER, Dakhama A, Larsen GL, Loader JE, Gelfand EW, Germolec DR, Korach KS, Zeldin DC](#). 2007. Spontaneous airway hyperresponsiveness in estrogen receptor-alpha-deficient mice. *Am J Respir Crit Care Med* 175(2):126-135.

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## Breast Enlargement in Prepubertal Boys

In a study funded by NIEHS, Laboratory of Reproductive and Developmental Toxicology investigators collaborated with University of Colorado School of Medicine pediatricians to report on the cases of three young boys, aged four through ten, with prepubertal gynecomastia. Previously, clinicians rarely have been able to identify a specific cause for breast enlargement in boys who have not reached puberty. Gynecomastia in older boys occurs in more than 60% of males during puberty and is usually linked to endogenous hormone levels.

The study, which gained considerable publicity after its publication in the *New England Journal of Medicine*, linked resolution of breast enlargement in the children to discontinuation of soaps, lotions and shampoos containing lavender and tea tree oils. The researchers demonstrated *in vitro* the capacity of the oils to disrupt the endocrine system and lead to imbalance in estrogen and androgen pathway signaling. Using human breast cancer cells, they showed that the oils modulated the expression of estrogen-related endogenous genes and produced inhibitory effects on androgen receptor activity.

This study appears to establish a connection between endocrine disruption *in vitro* and prepubertal gynecomastia. Thus, it offers clinicians an additional option to pursue when confronted by idiopathic cases of this kind.

*Citation:* [Henley DV, Lipson N, Korach KS, Bloch CA.](#) 2007. Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 356(5):479-485.

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## Inside the Institute

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### Japanese Student Delegation Visits NIEHS

*By Eddy Ball*

As part of a cooperative effort by NIEHS and the North Carolina School of Science and Mathematics (NCSSM), on March 14 the Institute welcomed a group of high school students from Iwate, Japan.

The students spent an afternoon involved in science lectures and hands-on learning in the laboratory. This delegation was the most recent of several from the Iwate schools to have visited NIEHS in recent years.

Like the many activities coordinated each year by Education and Biomedical Research Development Director Marian Johnson-Thompson, Ph.D., the event was part of the Institute's mission to foster young scientists by enhancing the quality of science education in grades K through 12. This event, however, featured something a little different — instruction in Japanese.

As the students entered the B-200 executive conference room, they heard the familiar sounds of their native tongue spoken by NIEHS Research Chemist Masahiko Negishi, Ph.D., as he gathered them at the conference table and translated Johnson-Thompson's welcome.



*Johnson-Thompson discussed the schedule as Negishi set up his computer for the training. (Photo courtesy of Steve McCaw)*

The Japanese-born scientist then introduced the young people to the geography and traditions of North Carolina. He also explained the organization and mission of NIEHS and NIH and provided commentary for the NIEHS video “Your Environment Is Your Health.”

Negishi’s scientific presentation was an overview of gene-environment interaction theory. He reviewed experiments showing the way genetic susceptibility can be mimicked and manipulated in laboratory animals to demonstrate how environmental exposures can trigger disease in some animals but not in others.

The next part of the program was a survey of “Human SNPs and Xenobiotic Susceptibility,” presented by Pharmacologist Joyce Goldstein, Ph.D. Negishi translated for the students as Goldstein moved through her talk about the impact of genetic differences in drug detoxification/activation enzymes on the reactions of different individuals to toxic exposures and medications.

Johnson-Thompson had arranged for additional translators when the students broke into smaller groups for lab visits. The lab visits included presentations by Kenjiro Asagoshi, Ph.D., on “DNA Repair and Nucleic Acid Enzymology”; by Mary Grant, D.V.M., on “Care and Use of Animals in Research,” with interpreter Chika Koike, Ph.D.; and by Lars Pedersen, Ph.D., on “Understanding DNA Polymerase Function through X-rays,” with interpreter Inoue Kaoru, Ph.D.

Before heading back to Durham with Steve Warshaw, Ph.D., vice chancellor for Academic Affairs at NCSSM, the students rejoined Johnson-Thompson and Negishi for an open-session discussion of their visit.

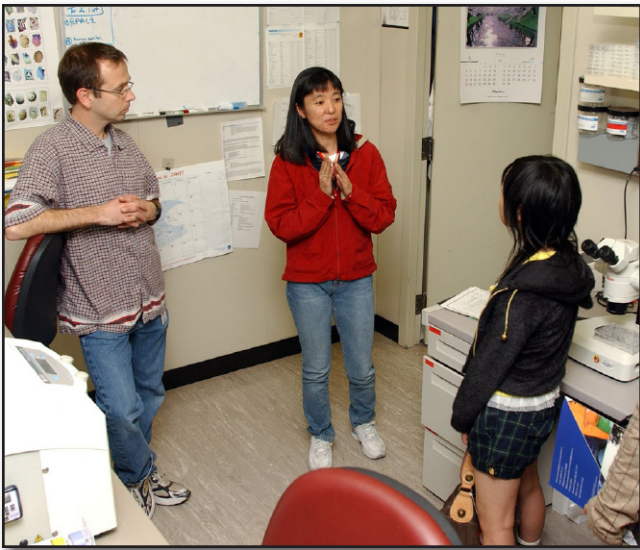
The visit was part of an ongoing exchange program started four years ago between NCSSM and schools in the Iwate Prefecture, or district, in Japan. The exchange program is one component of an initiative by schools in Iwate to encourage students to develop scientific skills and help expand the technology-base of the largely rural area. This year’s group came from the Mizusawa Super Science High School in Iwate. In addition to their visit to NIEHS, the students visited Duke University and the University of North Carolina at Chapel Hill and spent two days on the NCSSM campus in Durham.



*No introduction to North Carolina would be complete without an acknowledgement of the residents’ curious obsession with college sports. (Photo courtesy of Steve McCaw).*



*Negishi’s explanation of gene/environment interaction went right over the heads of most English speakers in the room, but the Japanese characters in his slides helped the students quickly grasp the concept. (Photo courtesy of Steve McCaw).*



*After Pederson's explanation in English, Kaoru interpreted for the students. (Photo courtesy of Steve McCaw).*



*Following the oral presentation on the work in Pederson's lab, the students and their chaperones had an opportunity for some hands-on experience. (Photo courtesy of Steve McCaw).*

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## **"Work, Learn, Discover" Wins Plain Language Award**

*By Eddy Ball*

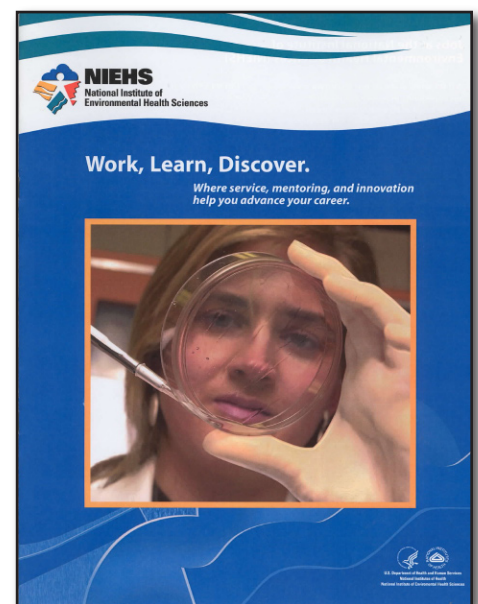
On April 17, six NIEHS employees will be recognized at the Seventh Annual Plain Language Award ceremony for their ability to write clearly and concisely.

NIEHS will receive Honorable Mention at the event for the booklet "Work, Learn, Discover," composed by a team that included Charle League, Deborah Swope, Ph.D., Marian Johnson-Thompson, Ph.D., Kathy Odenwald, Christine Bruske-Flowers and Robin Macker.

"Work, Learn, Discover" provides a general overview of NIEHS and its research initiatives, as well as information about scientific education, outreach, and employment and training opportunities at the Institute. Published in January 2006, the eight-page booklet is easy to read, colorful and filled with photographs and graphics. It has become a staple at conferences, meetings and other events where the Institute interacts with the scientific community and the public.

The annual NIH Plain Language competition is sponsored by the [Plain Language Action and Information Network \(PLAIN\)](#), a group of federal employees from many different agencies and specialties promoting plain language in government publications. The group's website offers resources for government writers. PLAIN reminds visitors that plain writing is not only a good practice, but also a goal mandated by President Clinton's 1998 executive memo and several statutes.

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# Ki Aikido Instructor Demonstrates Mind-Body Synergy

*By Eddy Ball*

As part of NIEHS Women’s History Month celebration, on March 21 in Rodbell Auditorium third-degree black belt Mayumi Case gave a demonstration and talk on “Self-Empowerment for Women Using Mind/Body Coordination.” A native of Japan, the diminutive Case has nearly a decade of experience in Shinshin Toitsu (mind-body coordination) Aikido, a school of martial arts that emphasizes the oneness of mind and body or “mind be the body,” and she is the head instructor at Raleigh Ki Aikido.

One of Case’s first objectives was to dispel the notion that martial arts necessarily involves the lethal kicks and flat-hand chops people see in the movies and on television. As Case teaches it, the discipline is a defensive tool when needed and a way of life, leading to harmony with others, positive thinking and self-empowerment — and away from negative introspection, conflict and collision.

“Women have a greater advantage when it comes to learning this concept and applying it in their lives,” Case began. “We pay more attention to our internal state, and we can’t resort to our physical strength, because we don’t have it.” The people who seem to learn Ki Aikido the most quickly are the most vulnerable, including children, women and older people.

After introducing the four principles of Ki Aikido (see sidebar), Case asked for volunteers. With the first, she explained how to find the “one point,” a center of gravity in the lower abdomen, and focus weight downward as a defensive mechanism. With her second volunteer, Case, who is petite at 5’1” and 120 pounds, demonstrated her power to resist the attack of a much taller, heavier and more muscular young man.

The “ki” in Ki Aikido, she explained, “can be translated roughly as ‘energy, life force or universal mind.’” It is the opposite of what she called “selfish mind” and gives the school its distinctive quality. In many ways, achieving oneness of mind and body is a return to an original state of integration. “Ki Aikido involves attention to the natural state,” she continued. “There’s nothing mystical about it. We all have that power.”



*Ki Aikido Instructor Mayumi Case proved that power can come in small packages. (Photo by Eddy Ball)*



*Case’s first volunteer, Biologist Wanda Holliday, quickly learned how to identify and “keep one point.” (Photo by Eddy Ball)*



*Maintenance Mechanic Versal Mason found his match in Case's ability to focus Ki to overcome his greater size and strength. "You felt like you had a steel plate in your body," the veteran body builder remarked afterwards. (Photo by Eddy Ball)*

## Four Major Principles to Unify Mind and Body

Keep one point: Allow your mind to dwell naturally at the one point in your lower abdomen.

- Relax completely: To relax completely is to completely release all stress from your total self -- mentally, physically, and emotionally.
- Keep weight underside: The weight of any object is naturally underside. Therefore, allow the weight of every part of your body to be naturally underside.
- Extend Ki: Our Ki is part of the Ki of the Universe. When we extend Ki out, new Ki naturally comes in to replace it. In this way, our Ki is always circulating with the Universe. This is our original and natural state. Everything in the Universe is born of the Ki of the Universe and returns to it.

*"If we unify our mind and body, become one with the Universe, and practice its principles, others will follow us gladly. Do not say that this is a world where we must struggle to live each day. The true way to success is exactly one and the same as the principle of non-dissension, and that is the way to peace."*

*Ki Aikido Master Tohei Sensei*

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# Sharon Finds New Fans

By Eddy Ball

Soon a new audience of children and parents will have a chance to be charmed by *Sharon Finds the Environment*. The NIEHS children's classic by Tom Hawkins will be the "Storytime" feature in the April issue of [Kidsville News](#). This latest version will feature new, distinctively *Kidsville* graphics, including the publication's mascot, Truman.

The story was first published in 2001 and won that year's NIH Plain Language Award for Hawkins. Since then, it has appeared many times in the United States and overseas. As a government publication, *Sharon* is not protected by copyright laws and may be published by anyone who is willing to acknowledge the authorship of Hawkins and NIEHS/NIH.

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# Remembering Colleagues

By Eddy Ball


Nutritionist and toxicologist Frank Kari died on March 13 from cancer after a period of declining health. He was an intramural scientist at NIEHS for 21 years and performed research in the National Toxicology Program and the DIR before moving into the Office of the Scientific Director. He will be missed by his colleagues and collaborators, as well as by the young scientists whose careers were influenced by his work.

Deborah Swope, of the Office of Fellows Career Development, passed away on March 26 after an extended struggle against cancer. Her many friends at the Institute will miss her as will the hundreds of postdoctoral fellows she helped in the course of her career. Swope began at NIEHS as a postdoctoral fellow and later became director of the Office of Postdoctoral Education, helping NIEHS achieve consistently high rankings as one of the "Best Places to Work for Postdocs."

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### Story Time

#### Sharon Finds the Environment



One morning Sharon woke up, and she wanted to find the environment. Miss Clark, her teacher, had told her that people need to keep the environment clean. But to keep it clean, Sharon had to find it first. Since it was Saturday, she had plenty of time to look.



When she got out of bed, she decided to look under the bed. It was dusty under there. But where was the environment?

Sharon went to the window. She looked out at the trees in the neighbors' yard. She smelled something a little smokey and funny in the air through the window screen. Maybe it was from the factory in town. It didn't smell good.

Then she went into the hall. Ugh, the smell of her dad's cigarette. But if she was going to find the environment, she'd better hurry up.

She washed her face and combed her hair. She brushed her teeth and watched the water rush from the faucet and swirl down the drain. Where did it all come from? Where did it go?

Then she went to the kitchen. Her mom was washing off strawberries for breakfast. Weren't they clean enough to eat? Mom was always telling her to wash her hands.



food you ate for breakfast."  
"That my mom washed!" Sharon said.  
"And the dust under the bed!"  
"The environment is just about everywhere you look," Herman said, as he reached for acorns under a nearby tree. "These are part of it, and I must say, they taste good. The environment is the air, the water, the soil, the plants, the animals, and the people. In fact, it's everything around us."  
Sharon thought about that. It wasn't part of the environment.  
"Oh, yes it is," Herman said. "You can get too much of it, even get sick from it. We squirrels build our nests, at least partly from it."  
For more information, download the Sunwise Activity Book, or all the other Sunwise School publications from the Environmental Protection Agency to promote safe sun.  
"So," Sharon said, standing up and looking around. "The environment is everywhere. In the water and under the bed."  
"And we can all help by remembering to wash our hands and the things we eat."

*Sharon's new friend, Truman, introduces the story of Sharon's quest to understand her environment. Some of the children who will read — or have read to them — this version of Sharon Finds the Environment weren't even born when Hawkins composed the popular tale. (Graphic courtesy of Kidsville News)*

# Calendar of Upcoming Events

- **April 2** in Rodbell, 10:00 – 11:30 — LMG Fellows Invited Guest Lecturer Christopher Mathews, Ph.D., Topic TBA.
- **April 4** in Rodbell, 8:00 – 5:00 — N. C. Travel and Vacation Fair
- **April 5** in Rodbell, 10:00 – 2:00 — NIEHS Vendor Show
- **April 5 -6 (off site event)** in Durham, 8:30 – 5:00 — CERHR Expert Panel Discussions
- **April 6** in Rodbell, 9:00 – 10:00 — Frontiers of Environmental Science Guest Lecturer William Kaufmann, Ph.D., Topic TBA.
- **April 10** in Rodbell, 2:00 – 3:30 — Distinguished Lecturer Series featuring C. David Allis, Ph.D., speaking on “Beyond the Double Helix: Reading and Writing the Histone Code”
- **April 12** (8:00 – 5:00) and **13** (10:30 – 5:00) in Rodbell — Soy Studies in Infants: Pilot Data and Future Plans
- **April 13** in Rodbell, 9:00 – 10:00 — Frontiers of Environmental Science Guest Lecturer David Armstrong , Ph.D., “Endocrine Disruption of Thyroid Hormone Signaling and Its Implications for Human Health”
- **April 16 (off site event)** at EPA, 11:00 – 5:30 — GEMS (Genetics and Environmental Mutagenesis Society) 2007 Spring Meeting “Integrative Bioinformatics: Systems Biology Approaches to Genetics, Metabolism and Disease”
- **April 20** in Rodbell, 9:00 – 10:00 — Frontiers of Environmental Science Guest Lecturer James Swenberg, D.V.M., Ph.D., Topic TBA
- **April 24** in Rodbell, 8:00 – 5:00 — Take Your Child to Work Day
- **April 27** in Rodbell, 9:00 – 10:00 — Frontiers of Environmental Science Guest Lecturer Richard Di Giulio, Ph.D., Duke, Topic TBA.
- **April 27 (off site event)** at EPA, 7:45 – 4:30 — 2007 NIEHS Biomedical Career Fair

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