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October 2006

NIEHS Spotlight

Science Notebook

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NIEHS Spotlight

Marc Hollander Is New Executive Officer

By Eddy Ball

On September 17, NIEHS welcomed Marc Hollander as the new Executive Officer, holding the official title of Associate Director for Management. Hollander is a veteran executive with a track record of successfully facilitating coordination between administrative and scientific personnel and managing scientific operations.

Executive Officer Marc Hollander. (Photo courtesy of Steve McCaw)

In his new role, Hollander will influence virtually all operational aspects of NIEHS as it deals with the challenges of its FY 2007 budget and refocuses its research strategies. In announcing Hollander's acceptance of the position in April, Director David Schwartz wrote, "His previous experience has provided him with a very diverse background which will serve as a great asset to the future of this Institute. Some of these areas include serving as a Chief Information Officer, Chief Financial Officer, and EEO Officer." Hollander's duties will include overseeing the management of financial, human resource, information technology and procurement activities. He will also oversee the coordination of the institute's ethics and equal employment opportunity and diversity programs.

Before coming to NIEHS, Hollander was the manager of the Management and Technical Support Office at the National Aeronautics and Space Administration (NASA) Engineering and Safety Center. The center was formed in response to the Columbia Accident Investigation Board's final report as an independently funded NASA program with a dedicated team of scientific and engineering experts to provide objective engineering and safety assessments of critical, high-risk projects for the Agency. Prior to joining NASA, Hollander served as the Deputy Assistant Secretary and Chief Financial Officer for the Science and Technology Directorate, Department of Homeland Security (DHS). Among his roles at DHS was his position as first center director of the Plum Island Animal Disease Center, formerly part of the US Department of Agriculture.

Hollander served in a series of progressively responsible positions after he joined the Department of Energy as a General Service budget officer in 1989. He spent his final years there in a Senior Executive Service position as the first chief information officer in the National Nuclear Security Administration (NNSA), a nuclear weapons and non-proliferation component of the department. Along with his many other accomplishments, he developed and issued the first NNSA Enterprise Information Architecture for the agency.

Hollander holds a bachelor's degree in Accounting from George Mason University and a master's degree in Management from the Florida Institute of Technology. He is a Certified Project Management Professional. In addition to his academic credentials, he is also a graduate of the Office of Personnel Management Federal Executive Institute and the Program Management Institute.

Hollander spoke of his new position with enthusiasm. "I already enjoy an excellent working relationship with Dr. Schwartz and a deep appreciation for the importance of the institute's mission," he said. "My strong desire

to join this professional and dedicated community of scientists and support personnel was fueled by my passion for scientific advancement coupled with my long-standing ability to enable scientific and technical breakthroughs which will be good matches for achieving the goals of NIEHS in the years to come."

Hollander added, "I am delighted that Mr. Rich Freed has accepted the position of Deputy Executive Officer providing his invaluable insight and vast operational knowledge into the NIH as well as NIEHS' inner workings. I see Rich and me as a solid team on behalf of NIEHS, and am looking forward to working together."

Anne Sassaman Set to Retire

By Eddy Ball

DERT Director Anne Sassaman. (Photo courtesy of Steve McCaw)

On November 3, after 32 years of federal service, DERT Director Anne Sassaman, Ph.D., will retire from her position at NIEHS. One of the top professionals in her field, she will leave with a long list of major accomplishments and awards to her credit and fond memories of her many friendships over the years.

Known and admired throughout NIH, Sassaman had an enduring influence on the institute and earned the respect of everyone who worked with her. Commenting on Sassaman in a recent announcement to NIEHS staff, Director David Schwartz wrote, "All of us will miss her enthusiasm and her ability to oversee a very complex operation.… [and] I will personally miss her loyalty and persistence."

Since joining NIEHS in 1986, Sassaman took her group from program status with 26 employees, including only three program administrators, and a small portfolio of individual research grants and centers, to a division with 20 program administrators and a large cadre of other extramural professionals. Today, DERT is responsible for overseeing more than 800 grants, more than 3,000 individual researchers and a network of core environmental health research centers and centers specializing in innovative research into children's health, breast cancer and the environmental health effects of the oceans.

In recognition of her leadership and the quality of her work, NIH presented Sassaman with a series of Director's Awards over the years, and the American Association for the Advancement of Science honored her with its prestigious fellowship in 2002. She received her first Director's Award while still at the National Heart, Lung and Blood Institute, where she was an administrator for ten years before coming to NIEHS and was instrumental in developing national and international programs in thrombosis and hemostasis.

Even more important than the growth of DERT reflected in sheer numbers during Sassaman's tenure is the evolution in the quality, focus and diversity of research supported by the division. Today's DERT is a proactive force in the field of environmental health research with a mission shaped by the visions of Sassaman and the three NIEHS directors she worked for throughout her tenure. "We probably have the most diverse portfolio of any institute at NIH, particularly an institute of our size," Sassaman observed.

As DERT director, Sassaman helped NIEHS grow beyond its initial role as an agency concerned primarily with toxicology testing and assessment of environmental hazards. By 2006, NIEHS had become a scientific powerhouse spearheading interdisciplinary research into the use of environmental science to study disease on the cellular and genetic levels as well as the effects of the environment on public health.

With characteristic modesty, Sassaman describes her greatest accomplishment as "being able to recruit great people and work with them to create new programs." Thanks to her management style and personal charisma, DERT has enjoyed a high level of success in recruiting and retaining exceptional staff, including some current staff who joined DERT through Stay in School appointments and have moved ahead in their careers. The division has also benefited from her visibility in Bethesda, helping to maintain a high profile for NIEHS among sister institutes.

As a young woman entering a career in science, Sassaman often found herself in the distinct minority where she worked and studied, and she experienced institutional barriers to her dual role as a professional woman and mother. In her undergraduate chemistry program at Auburn, she was the only woman enrolled. During her doctoral program in Microbiology-Immunity and post-doctoral work in the Departments of Biochemistry and Medicine (Cardiology Division) at Duke, she pursued her career in an environment still dominated by males.

In her career at NIH, she flourished in a more nurturing environment, and she did her part to raise awareness of gender and family issues in the workplace. When the NIEHS Diversity Council inaugurated the Spirit Lecture Series in 2002 to honor outstanding women during Women's History Month, few were surprised with the choice of the first lecturer, Anne Sassaman speaking on "Life! In Science."

William Stokes Honored

By Eddy Ball

During its 2006 Annual Convention in Honolulu, the American Veterinary Medical Association (AVMA) paid one of its highest tributes to Dr. William Stokes of the National Toxicology Program (NTP), headquartered at NIEHS. Stokes received the organization's prestigious Charles River Prize for distinguished contributions to the field of laboratory animal medicine and science. Stokes is a doctor of veterinary medicine and currently serves as director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). A Captain in the Commissioned Corps of the U.S. Public Health Service, he is a 20-year veteran of NIH and Chief Veterinary Officer for the U.S. Public Health Service.

Award Winner William Stokes. (Photo courtesy of Steve McCaw)

An international authority on the care and use of laboratory animals for biomedical research and testing, Stokes was recognized for establishing procedures to validate and gain regulatory acceptance of new safety testing methods to reduce, refine and replace animal use. As co-chair of the U.S. Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) from 1994 to 2001, he led the review and adoption of new methods that significantly reduced the numbers of animals and the pain and distress involved in testing.

In his current position as a NTP Center Director, Stokes administers and provides scientific support for the ICCVAM, which is composed of scientists from 15 federal agencies, including the conduct of international validation studies on proposed new safety assessment methods. Stokes said upon receiving the award, "This award acknowledges the significant progress that has resulted from the sustained efforts and interagency teamwork of the many dedicated scientists on the ICCVAM and at NICEATM and the contributions of many scientists and stakeholders in industry, academia, animal protection groups and the international community."

His AVMA award is the latest in a series of honors Stokes has received for his work. He is a recipient of the NIH Director's Award, the Society of Toxicology's Enhancement of Animal Welfare Award, the Russell and Burch Certificate of Recognition Award from the Humane Society of the United States, Army and Public Health Service Meritorious Service Medals, the Army Expert Field Medical Badge and the Outstanding Veterinarian of the Year Award from the Massachusetts Society for the Prevention of Cruelty to Animals.

Stokes' AVMA award is sponsored by the Charles River Laboratories Foundation, whose Humane Care Initiative drives its outreach activities and funding of educational programs on the humane care of laboratory animals. Stokes was one of 15 individuals, including 14 member veterinarians, honored at the Opening Ceremony and President's Installation Luncheon during the annual meeting. Established in 1863, AVMA is a not-for-profit association representing more than 74,000 veterinarians working in private and corporate practice, government, industry, academia and uniformed services.

Martin Matzuk Delivers First Distinguished Lecture

By Eddy Ball

On September 12, noted clinical pathologist and reproductive biologist Martin Matzuk opened the NIEHS 2006-07 Distinguished Lecture Series with a presentation on "Genetic Dissection of Fertility Pathways" in the Rodbell Conference Center. Matzuk, the Stuart A. Wallace Chair and Professor of Pathology, Molecular and Cellular Biology, and Molecular and Human Genetics at Baylor College of Medicine, spoke to a near-capacity audience of NIEHS and area scientists and scholars. His lecture surveyed his laboratory's recent research to understand the molecular mechanisms of mammalian reproduction.

Martin Matzuk flavored his lecture with a little laboratory humor. (Photo courtesy of Steve McCaw)

In the course of his research, Matzuk has been intrigued by the fact that 25 percent of human male infertility cases have no known cause. He speculated that these men may carry as-yet unidentified genetic anomalies in some testis-specific genes. By tracing the gene-specific fertility pathways, researchers may be able to discover clinically useful interventions. Research into mammalian reproduction may also lead to novel approaches for developing more effective means of contraception.

Matzuk's research parallels that of NIEHS researchers. The male testis is a unique organ, because it expresses genes that function in male reproduction, but are expressed nowhere else in the body. By use of genetically-engineered mouse lines Matzuk's laboratory has deleted certain of these genes and asked about their effects on different aspects of reproduction.

Matzuk's talk focused on the work he and his colleagues have performed on knockout mice using four testes-specific genes that affect male fertility. Mice deficient in one of the genes produced sperm that were less able to bind to eggs. Mice with anomalies in another gene produced sperm that were less able to traverse the female reproductive tract. These mice also showed a marked decline in fertility with age. Knockout mice with anomalies in another gene developed significantly smaller testicles than their wild type counterparts. Mice with only one copy of a normally two-copy gene showed a severe deficiency in the number of spermatozoa in their semen, leading to a high rate of male infertility.

At the end of the lecture, Matzuk turned to the direct applications of his experimental laboratory work to understanding human infertility. His clinical studies are extensive, involving collaborations with both basic scientists and physicians in a network at Baylor, universities around the country and in England. Following his talk, he joined NIEHS students and postdoctoral fellows for lunch and further discussions of fertility research.

Matzuk has contributed more than 200 scientific articles. His research focuses on the critical proteins involved in normal and abnormal reproductive development. Since 1995 he has been Co-director of Baylor's Medical Scientist Training Program, and he serves on many national and international advisory boards and review panels.

Following the lecture, Matzuk joined Host William Schrader. (Photo courtesy of Steve McCaw)

David Clayton Opens Special Seminars Series

By Eddy Ball

On September 25 at 10:00 AM in Rodbell Auditorium, Laboratory of Molecular Genetics (LMG) researchers welcomed guest lecturer David A. Clayton, Ph.D., as the first speaker in its 2006-07 Special Seminars Series. Clayton, who is the vice president and chief scientific officer at the Howard Hughes Medical Institute (HHMI), spoke on "Mammalian Mitochondrial DNA Replication: What We Know" to an audience of NIEHS investigators and local area scientists. Sponsor Sherine Chan of LMG introduced Clayton and invited interested scholars to join the speaker for a brown bag lunch following the talk.

Clayton opened his talk by emphasizing the wealth of information yet to be discovered about mitochondrial DNA (mtDNA) replication. "I hope no one takes from the title 'what we know about mtDNA replication' that the seminar will be about three minutes long and we'll all be able to take an early lunch," he said. "Of course, what we don't want to see in the title is 'what we don't know' because that lecture would take all week, and I'd be here talking to myself."

David Clayton described a comprehensive model of mtDNA replication. (Photo courtesy of Steve McCaw)

The rest of Clayton's lecture focused on his laboratory's work elucidating the modes of mammalian mtDNA replication and transcription. Initial studies characterized the physical forms of closed circular supercoiled mtDNA from several mammalian species. This, in turn, permitted the analysis of replicative intermediates of mtDNA, principally by high resolution ultracentrifugation and electron microscopy techniques. Taking advantage of emerging technologies in molecular cloning facilitated the sequencing of the entire mouse mtDNA genome in 1981 and, subsequently, the discovery and characterization of proteins involved in transcription and replication.

Clayton explained that the mtDNA system has provided many surprises, including an altered genetic code, unusual forms of transfer RNAs and the formation of a novel RNA-DNA hybrid region with unusual stability. The 13 proteins encoded by mtDNA are essential for cellular vitality, and there are now many examples of human disorders owing to mutations and other defects in mtDNA.

LMG Seminar Sponsor Sherine Chan and LMG Senior Investigator Bill Copeland listened with interest to the speaker's narrative of discoveries about mtDNA replication. (Photo courtesy of Steve McCaw)

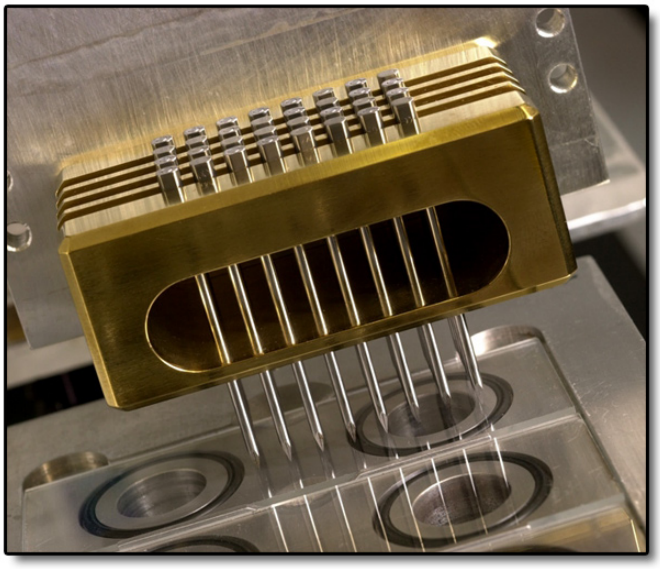
In the course of his talk, Clayton reminded his audience of the need to use several platforms in research and to survey the literature exhaustively. Clayton, for example, used Atomic Force Microscopy, a more sensitive methodology, to investigate evidence of a strand-coupled model of mtDNA replication proposed by another lab. The newer methodology helped Clayton and his associates resolve the apparent contradiction and develop a more comprehensive model. By resisting the tendency among researchers to ignore older research, he observed, investigators can mine more data to support their conclusions and utilize insights that may have a stronger bearing on today's work than when they were initially published.

Prior to joining HHMI, Clayton was a professor of both pathology and developmental biology at Stanford University. He has made several highly significant contributions to the understanding of mtDNA replication and is an elected member of the Institute of Medicine of the National Academies. Furthermore, Clayton has been instrumental in the planning of the HHMI Janelia Farm Research Campus, which is a new interdisciplinary research facility fostering highly collaborative research.

Science Notebook

CEBS Database Now Online

By Eddy Ball



Microarray printer (Photo courtesy of Steve McCaw)

NIEHS National Center for Toxicogenomics (NCT) has completed the first version of what many skeptics believed too daunting a task to ever be accomplished. On September 6, NCT launched version 2.07 of an integrated, dynamic database known as Chemical Effects in Biological Systems (CEBS), the first public repository of its kind for toxicogenomics data. CEBS developers, such as NCT Assistant Director Mike Waters, envision that the information gained through mining data in CEBS ultimately will enable health scientists and practitioners to understand and mitigate, or even prevent, diseases caused by adverse environmental exposures.

The database will prove to be an important tool for scientists researching in the field of toxicogenomics. Toxicogenomics is a scientific sub-discipline that combines the study of the nature and effects of poisons with the investigation of how our genetic make-up translates into biological functions. With improved access to more data, scientists will be able to study how and when the body's cells respond to stress, drug or toxicant, by altering the pattern of expression of genes within their chromosomes.

Even in its early stages, CEBS promises to aid researchers in identifying metabolite fingerprints and genetic signatures that may help to diagnose and define the ways in which specific chemicals, environmental exposures or stressors lead to disease. By linking damage in particular organs to alterations in serum and urine markers, researchers will strive to achieve more sensitive detection of exposure or risk factors. With CEBS, "We have an opportunity to see a landscape we've never seen before," explained Waters. "It's analogous to suddenly having the lights turned on in a room we've never seen in its entirety before, but only gotten glimpses of a small part of it, such as with a flashlight or under a street lamp."

The current version of CEBS allows researchers to access information by several analytical paths: select study workflow, study characteristics workflow, subject characteristics workflow, proteomics experiments workflow and microarray workflow. With these search capabilities researchers can view the "landscape" of data dynamically as a flow, rather than focusing exclusively on individual data gathered at single points in time.

One of the most important accomplishments of CEBS is the combination of data from microarray assessments of genetic transcriptions with traditional clinical chemistry and histopathology findings in the same database. The combination allows researchers to fully capture dose response over time, how an ongoing exposure to environmental stress modifies genetic expression and cumulatively sets the stage for disease development. The database is also multigenomic, including information for humans, rats, mice and the nematode *C. elegans*, a worm whose genetic makeup has been studied extensively.

Because CEBS merges different kinds of data from several sources, compiling the data presented the NCT with significant data evaluation challenges. Pulling in data from earlier research raised questions of accuracy,

and different sources for the same types of data sometimes used different ascension numbering. Database developers needed to establish standard nomenclature and numerical units for searches to be effective. The diversity of existing and pending array platforms, data acquisition methods and normalization procedures presented challenges in terms of data comparability and quality.

NCT has overcome a major barrier to developing a quality toxicogenomics database by obtaining the participation in CEBS of private sector researchers with potential proprietary interests in their information. Companies that have published data to date in CEBS include Iconix Biosciences, Johnson & Johnson, Pfizer and Sankyo. CEBS developers anticipate that more companies will agree to participate when they understand the advantages that expanded toxicogenomic research will have for them as well.

According to Waters, the job is far from over. CEBS is a powerful tool and its integration of data is impressive. However, developers admit that CEBS is hardly an intuitive research engine, and NTC will need to devote significant time and energy to user education. CEBS is a large database, with over 3,000 microarry hybridizations, 75 two-dimensional gel images, and traditional findings from over 600 animals, but it is still in its early stages. Frequent visitors to CEBS should be seeing new versions coming online in the future, as upgrades are developed to enhance loading capabilities, integrate CEBS with other data resources and expand the user base.

NTP Holds Biomarkers Workshop

By Robin Arnette

The National Toxicology Program (NTP) sponsored a workshop titled "Biomarkers for Toxicology Studies" on September 20-21 in Rodbell Auditorium. The meeting brought together experts in lipid/carbohydrate metabolism, lung disorders and cardiac function to identify and evaluate biomarkers for inclusion in rodent toxicology studies. Adding new tests to the current battery of evaluations will make toxicological testing more precise and give investigators a better understanding of how environmental toxicants affect rodents and humans.

(Image courtesy of EHP)

The workshop began with a welcome by NTP Interim Associate Director Allen Dearry, followed by a charge from the workshop chair, President of the Society of Toxicology James A. Popp of Stratoxon LLC. The morning session was dedicated to overview presentations about the NIEHS Exposure Biology Program, biomarker characterization and standard biomarkers currently in use in lipid/carbohydrate metabolism, lung and heart. During the afternoon session, the three groups participated in breakout sessions, with each group responsible for recommending new biomarkers that could provide valuable toxicological data. For background information the co-chairs, Gregory Travlos and June Dunnick of NIEHS, compiled lists of biomarkers for the three areas as a starting point for group discussions. Group findings were reported during the second day of the workshop.

Steven Kleeberger of NIEHS chaired the lung biomarker group and said that his group recommended that bronchoalveolar lavage analysis, enhanced histopathology and gene expression analysis should be added to the list of lung markers. When asked about the importance of his group's recommendations, Kleeberger stated that the suggestions would be good for NTP, NIEHS and the field in general. "From the perspective of lung biology and lung biomarkers, coming up with a series of markers that can be evaluated adds great value intramurally and extramurally," he said.

The next to report was the heart group, chaired by NIEHS's Bennett Van Houten. In addition to developing recommendations, the group proposed a decision tree to help investigators prioritize the tests they should do. Besides performing the standard histopathology on cardiac tissue, researchers should consider the following: serum troponin, rat α2-macroglobulin and serum β-type natriuretic protein, perhaps in conjunction with echocardiography. Although all of the chairs agreed that some recommendations would be expensive to implement, Van Houten said cost wouldn't be a problem when incorporating the top three recommendations. "A lot of the biomarkers that we discussed are extremely easy to implement because the costs aren't exorbitant, but if you go to some of the more difficult ones such as gene expression profiling, then the costs are very high," he added.

The final group to report was lipid/carbohydrate metabolism, chaired by Sheila Collins from the CIIT Centers for Health Research. The recommendations included tests for cholesterol/triglycerides, insulin and reduced glutathione. Collins commented on the importance of the meeting for her discipline. She said, "It's been very good as an idea generator for expanding the effort to look at not only the classic toxicology markers, but to begin to look at such things as heart disease and lipid irregularities."

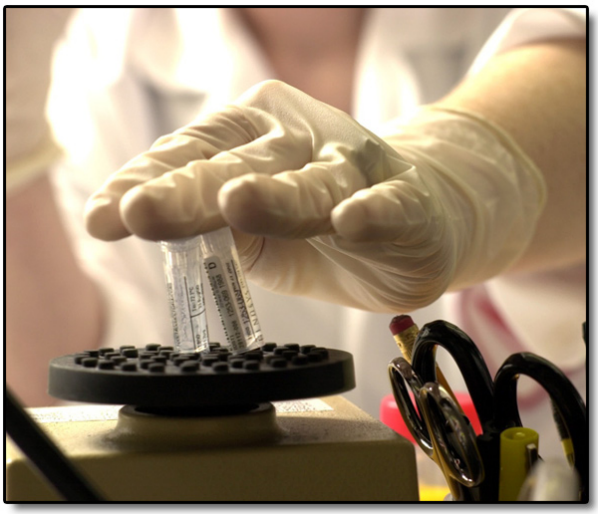
John Bucher of NIEHS said that all of the recommendations would be considered, but some would be implemented faster than others. "Tests such as the troponin assay are relatively simple," he said, "[but] others would require a little developmental work to make sure that they are technically feasible, sensitive enough and applicable in rodent studies."

Popp applauded the NIEHS staff for organizing the meeting and stated that this gathering may lead to a new era in toxicological testing. "NTP has made great contributions in the past in terms of study design and evaluation, in addition to the results that they've created," he said. "I predict that this [workshop] is going to be the beginning of setting a path forward, not only for NTP, but [for] toxicology programs across the nation."

Manganese Pathway Linked to Motor Deficits

By Eddy Ball

In an NIEHS-funded study published by the journal *Experimental Neurology*, an interdisciplinary team of researchers at the Johns Hopkins Bloomberg School of Public Health and Thomas Jefferson University presented a novel explanation for the neurological impact of chronic exposure to manganese. Medical science has known for decades that manganese exposure produces motor deficits that are similar to those found in early stages of Parkinson's Disease (PD) and are usually irreversible. The researchers used a combination of assessment methods to determine, for what they believe is the first time, the effects of manganese on dopamine (DA) release in the brains of non-human primates.



(Photo courtesy of Steve McCaw)

Study results may have implications in the ongoing debate about chronic exposures to ambient levels of manganese, including inhalant exposures of manganese from the combustion of gasoline containing the octane enhancer methylcyclopentadienyl manganese tricarbonyl (MMT). Identifying the mechanism of manganese on DA release may also help scientists develop effective interventions for the manganese-induced condition, also known as manganism, which does not damage neurons in the same way as PD and produces a distinct symptom cluster that differs in several ways from PD.

Researchers established baseline imaging values, behavior ratings, general activity patterns and fine motor skills assessments in a group of young adult male research macaques. The team then started a regimen of injecting the primates with small doses of manganese sulfate based on body weight once each week over a period of 39 to 40 weeks. Three additional animals that did not receive injections or experimental procedures served as a comparison group for post-mortem brain analysis. Researchers monitored behavior, activity and fine motor performance of injected animals regularly during exposures and used a modified rating assessment based on a Parkinson's symptom rating scale developed for non-human primates.

After initiation of manganese administration, the primates underwent the same imaging studies as at baseline. The team studied *in vivo* DA release in response to an amphetamine challenge, dopamine receptors and dopamine transporters to assess the effects of manganese on DA neuron function. Following euthanasia the researchers examined the animals' brains and measured blood and brain tissue levels of manganese, iron, copper and zinc. They performed post-mortem analysis of dopaminergic neuronal markers to confirm the *in vivo* findings.

According to the study, exposure to manganese produced a distinct increase in scores of motor deficits corresponding with a progressive decline of *in vivo* DA release measured in the brain's striatum. Concentrations of brain manganese and copper increased significantly, but researchers found no significant effects on iron or zinc concentrations. The manganese-induced decrease in DA release was present despite the fact that dopamine transporter levels were not changed, indicating an intact but dysfunctional nigrostriatal dopamine system.

In addition to discovering physical and behavioral evidence of the distinct set of symptoms of manganese exposure, the researchers also determined whole blood manganese concentrations. Results were found to be within the upper range of concentrations reported in children or adults in previous studies of environmental exposures. This finding raises new questions about the harmful effects of exposure to manganese such as those from the combustion of MMT-containing gasoline that is approved for use in such countries as Canada and South Africa. Largely because of this possibility, the U. S. Environmental Protection Agency continues to call for long-term animal testing to more accurately define the risk.

Manganism produces early symptoms of behavioral, psychiatric and memory disturbances. Patients then develop motor symptoms, including action tremor, abnormalities in walking and motion instability. The most effective early therapy for PD, L-dopa, has not been found to be effective. Understanding the response of the dopamine system to manganese may consequently help scientists develop an effective intervention.

Citation: Guilarte TR, Chen MK, McGlothan JL, Verina T, Wong DF, Zhou Y, Alexander M, Rohde CA, Syversen T, Decamp E, Koser AJ, Fritz S, Gonczi H, Anderson DW, Schneider JS. 2006. Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. Exp Neurol on-line early release doi:10.1016/j.expneurol.2006.06.015.

MRM Protocols Assist Brain Studies

By Eddy Ball

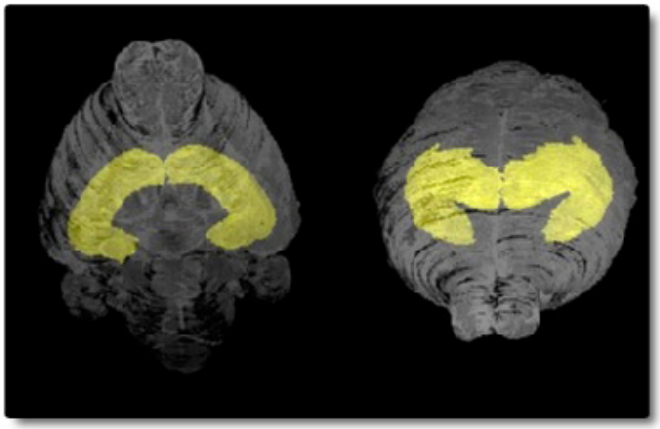
In a recent study published in the September issue of the journal *NeuroToxicology*, an interdisciplinary team of NIEHS scientists in the Laboratory of Experimental Pathology demonstrated new applications for laboratory protocols that can expand the potential of developmental neurotoxicity testing. According to the researchers, the use of magnetic resonance microscopy (MRM) in combination with the Cavalieri method of volumetric estimation shows good agreement with conventional methods, which utilize linear measurements on stained histologic sections. The protocol also can help investigators utilize time and personnel more efficiently and will provide a more thorough examination of the whole brain with the ability to obtain three-dimensional volumetric

measurements of important brain structures. These features will permit additional insights from studies on the effects of exposure to environmental agents on the developing rat brain.

Principal Investigator Kennita Johnson. (Photo courtesy of Steve McCaw)

Because it is non-invasive and examines the intact organ in place, MRM is more adaptable than conventional histological methods, giving it potential for use in longitudinal studies of live animals and ultimately in human studies. In addition, the sensitivity of three-dimensional MRM may allow scientists to identify exposures at lower doses than those which cause gross neuropathology and readily detect effects of exposure not easily determined by the limited tissue sampling of conventional histology. Researchers can also use MRM as an adjunct to conventional histology, since it does not destroy the organ and offers a unique dataset that is easily stored and accessed for further interpretation. "The data is entirely digital," explained lead researcher Kennita Johnson, a post-doctoral biomedical engineer at NIEHS. "We can share it by e-mail or put it on a server."

Along with Johnson, neuroscientist Jill Marcus and pathologist Robert Maronpot collaborated with specialists from two area labs, MRPath, Inc., and Integrated Laboratory Systems, Inc., in the study. The team studied first-time pregnant female Sprague-Dawley rats that were injected with either methylazoxymethanol acetate (MAM) or saline during their pregnancies. A compound found in seeds from the tropical plant Cycad, MAM is a known neurotoxin, DNA methylating agent and carcinogen with documented effects on rat brain.



With imaging, researchers could look at internal structures of the brain (hippocampus highlighted) from different angles. Shown are a ventral (left) and a dorsal view (right) of the same normal whole brain. (Image courtesy of NIEHS Laboratory of Experimental Pathology)

At 23 and 60 days following birth, investigators imaged rat brains to measure changes in form, volume and size. They used a small animal MR imaging system to scan intact brains and then performed conventional histologic examination of stained slices to identify histologic changes. To determine volume of the whole brains, the researchers initially used the gold-standard water displacement method before examining MRM data with the more efficient Cavalieri method, a mathematical model that can be easily used with computer software to make rapid estimations of volume.

Study findings were consistent with earlier research into the effects of MAM. The compound had no long-term effect on body weight of control and dose animals. The researchers did find a statistically significant difference in fixed brain weight, whole brain weight and morphology, and whole brain volume between control and dose animals. Examining the MRM whole-brain scans, researchers were able to detect a trend toward reduction in size of the hippocampus and cerebrum in the high dose animals.

The researchers concluded that their protocol offered several additional benefits over conventional methods. Three-dimensional MR images made possible a more complete morphological assessment using both linear and volumetric measurements by revealing microscopic changes that impact brain function before cell death or lesions become apparent. MRM overcame problems with precise orientation inherent in histologic sectioning that can confound measurements of brain structures. MRM enabled researchers to obtain three dimensional images

throughout the brain in contrast to time-consuming discrete histological slices. Using the Cavalieri method with MRM, scientists can obtain an unbiased estimation of substructure volumes of any size or shape, eliminating the process of exhaustively tracing brain substructures.

Citation: Johnson K, Ryan L, Davis J, Elmore A, Guenther B, Marcus J, Maronpot RR. 2006. Application of magnetic resonance imaging in developmental neurotoxicity testing: A pilot study. Neurotoxicology 27(5): 846-851.

DERT Papers of the Month

By Jerry Phelps

Second Hand Smoke Injures Infants' Lungs

A new study by University of California Davis researchers details how the lungs of infants are damaged by secondhand cigarette smoke. NIEHS grantee Kent Pinkerton and colleagues exposed pregnant rhesus macaque monkeys to the same amount of smoke a woman would be exposed to if someone in her home or workplace smoked. Likewise, newborn monkeys were exposed to secondhand smoke levels equivalent to what a human baby would be exposed to if one of its parents or caregivers were a moderate to heavy smoker.

The research discovered that during pregnancy and the early postnatal period, critical times for lung development, secondhand smoke exposure caused premature death of alveolar cells due to apoptosis. Exposure to tobacco smoke was shown to suppress Nuclear Factor kappa Beta (NF-κB) activity and down-regulate NF-κB-dependent anti-apoptotic genes resulting in the increase of apoptotic death of alveolar cells in lung tissue.

Exposure in children to second hand smoke is a hazard and a widespread public health problem even though smoking continues to decline in the U.S. Exposure during the perinatal period causes adverse effects on lung development and reduces lung function. The current research conducted in this laboratory sheds light on the precise cellular mechanisms disrupted by environmental tobacco smoke and may elucidate new pathways for treating lung function decrements.

Presumably, killing cells at a higher rate during a critical developmental period when alveoli are supposed to be proliferating may have permanent effects on lung function. Pinkerton concludes that "smoke exposure causes significant damage and lasting consequences in newborns. The lungs may never be able to recover."

Citation: Zhong CY, Zhou YM, Joad JP, Pinkerton KE. 2006. Environmental tobacco smoke suppresses Nuclear Factor-{kappa}B signaling to increase apoptosis in infant monkey lungs. Am J Respir Crit Care Med 174(4):428-436.

Glutamate-Cysteine-Ligase Gene Polymorphisms Are Associated with Cystic Fibrosis Lung Disease

NIEHS-supported scientists report that a polymorphism in a gene that regulates glutathione synthesis influences the severity of cystic fibrosis lung disease. The research team examined the genetic makeup of 440 subjects with cystic fibrosis. They found that polymorphisms in the glutamate-cysteine ligase catalytic subunit gene were associated with lung function in subjects with a milder form of the defective gene that causes cystic fibrosis.

Cystic fibrosis is a genetic disease affecting approximately 30,000 children and adults in the United States. A defective gene, known as the cystic fibrosis trans-membrane conductance regulator causes the body to produce abnormally thick, sticky mucus that clogs the lungs and can lead to life-threatening lung infections. Every year about 1000 people are diagnosed with the disease in the U.S. Life expectancy is generally shorter for people with the disease although medical advancements have prolonged life for many.

This finding demonstrates that lung disease severity in people with cystic fibrosis is mediated by factors that regulate levels of glutathione in the lung. The authors conclude that treatments to increase lung levels of glutathione may reduce the decline in lung function seen in patients with cystic fibrosis, especially those with the milder form of the mutation.

Citation: McKone EF, Shao J, Frangolias DD, Keener CL, Shephard CA, Farin FM, Tonelli MR, Pare PD, Sandford AJ, Aitken ML, Kavanagh TJ. 2006. Variants in the glutamate-cysteine-ligase gene are associated with cystic fibrosis lung disease. Am J Respir Crit Care Med 174(4):415-419.

α-Synuclein Gene Promoter Variability and Parkinson's Disease

Variability in the α-synuclein (*SNCA*) gene promoter is linked with a greater susceptibility for Parkinson's disease, according to a study in the August 9 issue of the *Journal of the American Medical Association*. Previous research has shown that the origins of Parkinson's can be both genetic and environmental. One of the most promising leads in the genetics of Parkinson's disease is the potential role of the *SNCA* gene. Some evidence suggests that *SNCA* may be associated with risk of Parkinson's disease, but studies from different populations have yielded conflicting results. Large-scale studies have been lacking.

NIEHS grantees Demetrius M. Maraganore and Harvey Checkoway and colleagues with the Genetic Epidemiology of Parkinson's Disease Consortium, conducted a study to examine several issues, including whether allele-length variability in the dinucleotide repeat sequence (REP1) of the *SNCA* gene is associated with Parkinson's disease susceptibility. The researchers performed a collaborative analysis of individual-level data on *SNCA* REP1 and markers in patients with Parkinson's disease and controls. Eleven participating sites in the genetics consortium provided clinical data for 2,692 cases and 2,652 controls. The researchers found that genotypes defined by the 263 base-pair gene were associated with Parkinson's disease.

"Our study demonstrates that the *SNCA* gene is not only a rare cause of autosomal dominant Parkinson disease in some families, but also a susceptibility gene for Parkinson disease at the population level. Based on our results, we estimate that REP1 locus variability may explain approximately 3 percent of the risk in the general population. This is in the same range as the population effect of other common variants implicated in Parkinson disease. The additive effects of these and other common gene variants may ultimately account for a substantial fraction of the susceptibility to Parkinson disease," the authors write.

Citation: Maraganore DM, de Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, Kruger R et al. 2006. Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease. JAMA 296(6):661-670.

Inflammatory Enzyme Affects Motor Neuron Damage in Amyotrophic Lateral Sclerosis

Serge Przedborski of Columbia University reported in the August 8 edition of the *Proceedings of the National Academy of Sciences* new insights into the death of motor neurons resulting from amyotrophic lateral sclerosis (ALS). Przedborski has been a pioneer in the investigation of the molecular mechanisms leading to the death of neurons that occurs in ALS and Parkinson's disease.

Also called Lou Gehrig's disease for the legendary New York Yankee first baseman who died of the disease in 1941, ALS is a progressive neuromuscular disease that weakens and eventually destroys motor neurons connecting the brain with the skeletal muscles. Patients gradually lose the ability to speak, swallow and move voluntarily. Sensory function and intellectual ability are unaffected, and death usually results from loss of respiratory function. Approximately 30,000 patients in the United States currently have ALS. The disease has no racial, socioeconomic or ethnic boundaries. The life expectancy of ALS patients is usually three to five years after diagnosis. ALS is most commonly diagnosed in middle age and affects men more often than women.

The researchers discovered that an enzyme known as reduced-form nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an important component in the generation of destructive reactive oxygen species during inflammation, is active in the spinal cords of ALS patients and also in a mouse model of the disease. When the researchers inactivated the enzyme in the mice, neurodegeneration was significantly delayed and the mice lived longer. Additional studies also showed that NADPH-oxidase-derived oxidative products also damaged proteins including insulin-like growth factor 1 (IGF1) receptors located on motor neurons. IGF1 has been demonstrated to have therapeutic potential in ALS patients. These results suggest that co-administration of an anti-inflammatory agent may improve the therapeutic response of IGF1 in ALS patients.

Citation: Wu DC, Re DB, Nagai M, Ischiropoulos H, Przedborski S. 2006. The inflammatory NADPH oxidase enzyme modulates motor neuron degeneration in amyotrophic lateral sclerosis mice. Proc Natl Acad Sci U S 103(32):12132-12137.

DIR Papers of the Month

By Robin Arnette

p38 MAPK May Offer Treatment for Viral Hemorrhagic Fevers

Viral-induced hemorrhagic fevers such as Lassa Fever, Dengue, Marburg and Ebola cause high morbidity and mortality in humans and have the potential to be used as biological weapons. Currently, there are no FDA-approved treatments for these illnesses, except for yellow fever, which has a viable vaccine. But researchers from NIEHS and the University of Chicago Pritzker School of Medicine may have found a possible treatment for these illnesses.

The results of the study appeared in the July 2006 issue of the *Journal of Clinical Immunology* and demonstrated how endothelial cells (ECs) were activated and eventually impaired after infection by a virus. Previous work done by this group had established that viral-induced inflammation was mediated by activation of p38 Mitogen-Activated Protein Kinase (MAPK)—a protein kinase that performs a crucial step in relaying signals from the

plasma membrane to the nucleus—and others in the field had reported that ECs were involved in viral hemorrhagic fevers. Nevertheless, the exact mechanism of viral-induced hemorrhagic fever remained unknown, particularly what caused vascular permeability and barrier dysfunction in ECs.

The researchers grew human lung ECs in culture and infected them with either bluetongue virus (BTV), the agent that causes hemorrhagic fever in ruminants, or double-strand RNA (dsRNA), a common viral structure that is present in some viruses or may form during the lifetime of the virus. Infected cells were tested using trans-endothelial electrical resistance (TER), which determines vascular permeability. In both instances, BTV or dsRNA-treated cells exhibited decreased TER, which is an indication of increased vascular permeability. To determine whether p38 MAPK was involved in this vascular permeability, ECs were pretreated with a p38 MAPK inhibitor, exposed to BTV or dsRNA, and continuously measured using TER. The results indicated that inhibiting p38 MAPK blocks the reduction in TER, therefore suggesting that the p38 MAPK pathway is involved with vascular permeability.

The results of this study have far-reaching implications with regard to therapeutic approaches to treating viral-induced hemorrhagic fevers.

Citation: Chiang ET, Persaud-Sawin D, Kulkarni D, Garcia JGN, Imani F. 2006. Bluetongue virus and double-stranded RNA increase human vascular permeability: role of p38 MAPK. J Clin Immunol 26(4):406-416.

Estrogen Receptor-α Suppresses Development of Testis-Specific Cells in Mouse Ovaries

The tendency of ovaries to produce estrogens and testes to produce androgens is determined by the types of specialized cells and enzymes that arise during development of the fetus. In the August issue of *Endocrinology*, researchers from NIEHS and the Centre Hospitalier Universitaire de Quebec have determined that one of the estrogens, estradiol, may be an important factor in ensuring that Leydig cells do not inappropriately develop in the ovaries of females. Leydig cells are specific to the testes of males and responsible for testosterone production.

The team studied three groups of female mice: a line of mice developed by this research group that lacked the estrogen receptor (αER), a transgenic line with elevated levels of luteinizing hormone and wild-type mice with normal ovaries. Using Northern blotting, radioimmunoassay and in-situ hybridization, the investigators determined that the ovaries of female mice lacking αER produced enormous amounts of the male androgen testosterone. These mice also showed masculine-like characteristics. Further study indicated that ovaries from the αER null females possessed an enzyme, hydroxysteroid (17b)-dehydrogenase 3 (HSD3), that is normally found only in testes and is necessary for the final step in the production of testosterone. Using transmission electron microscopy, the researchers found that the ovaries of these mutant female mice had Leydig cells similar to those that produce testosterone in the testes of males. Therefore, the investigators discovered a form of hormonal and cellular "sex-reversal" in females that occurs when the αER is removed.

These data are the first to demonstrate that αER may play an important role in the proper development of the ovaries in females. By repressing Leydig cells and the presence of the male-specific enzyme, HSD3, αER ensures that females are not exposed to excessive amounts of testosterone that could lead to a loss of feminine characteristics. The researchers suggested that αER is integral to the proper development and maintenance of the female phenotype.

Citation: Couse JF, Yates MM, Rodriguez KF, Johnson JA, Poirier D, Korach KS. 2006. The intraovarian actions of estrogen receptor-α are necessary to repress the formation of morphological and functional Leydig-like cells in the female gonad. Endocrinology 147(8):3666-3678.

Identifying Changes in the Rat Serum Proteome During Acetaminophen-Induced Liver Injury

Exposure to xenobiotic compounds produces a myriad of pathologies in living organisms, and may lead to damage in vital organs and tissues. Of all of the bodily fluids, one offers the best source for scientists to monitor organ or tissue injury: blood. Currently, many researchers are mapping the soluble human blood elements—serum or plasma proteome—in an attempt to better understand various diseases, but little of the technology in serum proteome mapping has been applied to studying damage in the liver. To this end, researchers from NIEHS and the Large Scale Biology Corporation, Germantown, Md., measured changes in the serum proteome during acute liver injury and recovery in rats. Lab rats were exposed to a high dose of the analgesic acetaminophen, which causes a liver pathology in rats similar to that seen in humans after accidental overdose.

The investigators performed proteomic analysis of rat serum at various times over a five-day period after acetaminophen exposure using gel electrophoresis, mass spectrometry and antibody arrays. They typically monitored over 800 serum proteins and identified over 50 serum proteins as significantly altered during liver damage. Changes in the serum proteome reflected the animal's reaction to liver injury by evoking changes in acute phase response, coagulation, protein degradation, intermediary metabolism and scavenger proteins in the general blood circulation. These changes in serum proteins accompanied an inflammatory response that helped recruit reparative immune cells from blood into the liver. In addition, an increase in serum catalase activity acted as an antioxidant that could provide a critical defense to the body's blood vessels during liver repair.

NIEHS researchers believe that tracking serum proteome changes in experimental animals provides a means to gain insight into how the body mounts a collective tissue response for recovery from acute liver injury that represents processes with relevance for other human hepatic diseases.

Citation: Merrick BA, Bruno ME, Madenspacher JH, Wetmore BA, Foley J, Pieper R, Zhao M, Makusky AJ, McGrath AM, Zhou JX, Taylor J, Tomer KB. 2006. Alterations in the rat serum proteome during liver injury from acetaminophen exposure. J Pharmacol Exp Ther 318(2):792-802.

Drug-Induced NAG-1 Inhibits Tumor Growth

In an article published in the August 2006 issue of The *Journal of Pharmacology and Experimental Therapeutics*, researchers from NIEHS, NCI, EPA, University of Tennessee-Knoxville and the University of Occupational and Environmental Health, Kitakyushu, Japan, studied the interaction of a potential anticancer drug and a gene with anti-tumor properties. The team confirmed that nonsteroidal anti-inflammatory drug-activated gene (NAG-1) suppresses tumor growth in mice, and that the expression of NAG-1 can be controlled with anticancer drugs. These findings are important in the fight against cancer because drugs that target NAG-1 may lead to the development of new cancer treatments.

The investigators used 2-(4-amino-3-methylphenyl)-5-fluorobenzothaizole (5F203) to determine whether it induced NAG-1 expression in human breast cancer cells. The compound is the active moiety of Phortress, an experimental anticancer drug currently undergoing phase I clinical trials in cancer patients in the UK. Western analysis using NAG-1 antibodies indicated that treatment with 5F203 induced NAG-1 expression, and this expression was dependent on time of incubation and drug concentration.

Since most of the information about NAG-1 is based on *in vitro* experiments, the team wanted to confirm that the up-regulation of NAG-1 is associated with inhibition of tumor development *in vivo*. They injected MCF-7

(breast cancer cell line) cells into controls and treated nude mice by injecting 15 mg/kg or 10 mg/kg of 5F203. The investigators then measured the size of the mammary tumors produced and used polymerase chain reaction to measure NAG-1 levels in the tumors. The median tumor weight in treated mice decreased by up to 75%, and needle biopsies of the tumors taken 6 and 24 hours after 5F203 injection indicated a dose-dependent increase of NAG-1 expression compared to controls. Taking all of the data into account, treating mice with 5F203 increased NAG-1 expression and inhibited tumor growth *in vivo*. This outcome indicates that NAG-1 is an important mediator for the activity of 5F203 and provides a possible treatment for cancer.

Citation: Martinez JM, Sali T, Okazaki R, Anna C, Hollingshead M, Hose C, Monks A, Walker NJ, Baek SJ, Eling TE. 2006. Drug-induced expression of nonsteroidal anti-inflammatory drug-activated gene/macrophage inhibitory cytokine-1/prostate-derived factor, a putative tumor suppressor, inhibits tumor growth. J Pharmacol Exp Ther 319(2):899-906.

Did You Know?

OCPL Welcomes New Staff

By Eddy Ball

OCPL recently welcomed three new employees. On September 17, Cheryl Thompson started her new position as NIEHS Web Manager and over the next few months will assume responsibility for overseeing the institute's new web site. The same day Robin Arnette began work as scientific editor for the web site and newsletters. In August, Eddy Ball joined the staff as editor of the *eFactor*, the institute's web-based employee newsletter. Commenting on the new hires, OCPL Director Christine Flowers said, "The new employees reflect the broadening of our efforts to communicate with the scientific community and make our science resources available on our new web site."

Web Manager Cheryl Thompson. (Photo courtesy of Steve McCaw)

Thompson comes to NIEHS from Irving, Texas, where she was internet architect, web software manager and web master for seven years with the City of Irving, a community of approximately 185,000 in the center of the Dallas-Fort Worth Metroplex. Her content management system roll-out for the site earned the 2005 Technology Excellence Award from the Texas Association of Government Information Technology Managers. She served until recently as the founding Gulf Region director of the National Association of Government Webmasters, where she spoke at the 2005 conference on web re-design project management.

A graduate of Yale University, Thompson holds a Master of Business Administration in Information Technology from the University of Dallas, where she was a finalist for the Texas Business Hall of Fame Scholarship. She also completed two years of coursework in the Graduate Program in Epidemiology at Texas A&M University, where she was a Regent Scholar.

Science Editor Robin Arnette.
(Photo courtesy of Steve McCaw)

Prior to joining NIEHS, Arnette spent three years as editor of the *Minority Scientists Network* and a contributing writer for *Science's Next Wave*, two online journals published by the American Association for the Advancement of Science (AAAS). While at AAAS, she edited more than 300 articles and wrote 39 of her own feature stories. She also worked with Education and Training Systems of Chapel Hill as medical science editor. She contributed articles for the UNC Chapel Hill magazine *Endeavors* and for the Postdoctoral Association web site at UNC.

Arnette earned her doctorate in Biology with special emphasis in Biochemical and Molecular Parasitology in 1999 from the University of Toledo and was awarded a Lineberger Comprehensive Cancer Center Fellowship as a postdoc at the UNC School of Medicine, where she served for two years. She has contributed research studies to *Molecular Biochemistry and Parasitology* and the *Journal of Biological Chemistry*.

Ball was a writing instructor at Wake Technical Community College for two years before joining the OCPL staff. He also worked for Great Smokies Diagnostic Laboratory in Asheville, NC as an editor of publications for physicians. He taught English as a Visiting Assistant Professor at the University of North Carolina at Asheville and held adjunct positions and graduate teaching assistantships at other universities.

Ball has undergraduate and graduate degrees in English language and literature. He received his doctorate in literature and composition from the University of South Carolina, where he was recognized for his academic performance. He was the first scholar ever awarded a National Defense Education Act Fellowship in the English Department at Georgia State University.

Working out of Nottingham, the new employees will join veterans on the OCPL team under the direction of Flowers. News Director Robin Mackar collaborates with DIR and NTP to enhance presentation of new research to journalists. Public Affairs Specialist John Peterson works with program administrators in DERT and a core of 100 major grantees to highlight news-worthy research initiatives funded by NIEHS throughout the country. Responding to inquiries from professional organizations, health groups and the general public, Public Information Officer Lou Rozier searches for the answers, information and resources requested by people who are outside NIEHS, but not members of the press.

eFactor Editor Eddy Ball.
(Photo courtesy of Steve McCaw)

"Biggest Losers" Are Lifestyle Winners

By Eddy Ball

Biggest Loser Elliott Gilmer has a good reason to smile. (Photo courtesy of Steve McCaw)

If NIEHS employees reflect the national trend toward bigger and heavier, then as many as two-thirds, or more than 800 of the people who work for the institute could stand to shed some weight. Thanks to a recent NIEHS Wellness and Fitness Program, many of the 84 participants of "The Biggest Loser Challenge" are now looking for new clothes to fit their new bodies and striving to keep up the good habits the program encouraged. The program was created by NIEHS Program Manager Diane Crawford, Health and Fitness Program Manager Stephanie Bullock-Allen, and Health and Fitness Specialist Jennifer Cordani.

The group lost a total of 309.6 pounds during the eight-week regimen of exercise, diet modification, team spirit and education. Third place team winner Elliott Gilmer, the challenge's top individual loser, deserves special kudos for his dedication. Named after the television show of the same name, "The Biggest Loser" program helped Gilmer, a contract employee with Raven, bid farewell to 16.3 pounds.

At the beginning of the program, competitors were assigned to groups of six to 14 teams for the competition and took weight and girth measurements. Teams chose their own catchy names for the teams, such as "Soul Man and Serious Sistahs" and "Fatty Acids," to build team spirit and kept records of their activities, along with a requested weekly weigh-in. Fitness Room staff helped the competitors achieve manageable goals each week. Tasks included walks around the lake, set times using exercise machinery, walking as fast as possible from the cafeteria to F Module and back, placing daily calorie limits on snack consumption and bringing healthier lunches from home once a week.

According to Bullock-Allen, the response to "The Biggest Loser Challenge" was much greater than initially expected. "We were hoping for four or five teams, and we ended up with 14," she said. Not everyone came just to lose weight. Average team member weight averaged between 157 and 226 pounds, but several people participated more as a preventive measure than because of concern about their current weight.

Bullock-Allen is planning already for an encore program in January or February – "Just about the time people realize they are not keeping those New Year's resolutions," she explained. In the meantime, she encourages NIEHS employees to take advantage of the Fitness Room and the professional staff there. Living proof of the benefits of exercise and healthy eating, Bullock-Allen is a professional fitness expert, adjunct professor at North Carolina Central University and personal trainer with a Master's in Recreational Administration.

The challenge winning team To Conquer and Destroy chalked up 100.5 points in the competition, topping second place No Weigh Out, which garnered 78. Pictured are team members (left to right) Bill Fitzgerald, Stephanie Bullock-Allen, Versal Mason, Elena Braithwaite, Undi Hoffler and Jennifer Cordani. (Photo courtesy of Steve McCaw)

The Fitness Room is open from 7:00 AM to 7:00 PM and staffed by Bullock-Allen and Health and Fitness Specialist Jennifer Cordani. NIEHS offers several incentive programs to help employees improve health and fitness. In addition to the on-site fitness equipment and programs, the institute sponsors discounted memberships at two area gyms and spas with locations throughout the Triangle.

For more information about NIEHS Health Fitness Programs, contact Diane Crawford, Stephanie Bullock-Allen or Jennifer Cordani by e-mail or call Crawford (541-0124) or the Fitness Room (541-3291). For information online, visit the Health and Fitness page.

Tallying 40 challenge points, Biggest Loser Second Place Winners, The Flab Busters, dropped a team total of 42.1 pounds. Proudly displaying their trophies for the camera are (left to right) Katina Johnson, Chris Hunt, Vee Vee Shropshire, Keith Holloway, Lindia Engram and Sarah O'Donnell. (Photo courtesy of Steve McCaw)

The number one team with a total loss of 47.2 pounds, team Fatty Acids also racked up 45 challenge points. Shown (left to right) are Maria Sifre, Rhonda Wilson, Wanda Holliday, Tonia Hermon and Lysandra Castro (not pictured: the team's biggest loser, Kevin Trotter, who shed 13.4 pounds). (Photo courtesy of Steve McCaw)

L.O.W.S (Lots of Weight Shed) placed third with a total weight loss of 20 pounds. Pictured are team members Ruby Wiggins, Keisha Register, Michelle Shields (on the bike), Elliott Gilmer and Annette Rice (Chris Lee not pictured). (Photo courtesy of Steve McCaw)

Fiesta Highlights Hispanic Heritage

By Eddy Ball

Members of the Hispanic Heritage Committee join NIEHS Cafeteria Chef Luz Bazan in preparing Hispanic dishes. Shown (left to right) are Georgie Pagan, Lysandra Castro, Luz Bazan, Maria Sifre (front row), Juanita Roman, Lisa Banks-Padilla, Gerard Roman (second row) and Rodrigo Franco in the back. (Photo courtesy of Steve McCaw)

NIEHS celebrated Hispanic Heritage Awareness Month on September 28 with its annual Fiesta, a combination of music, food, arts and crafts. The Diversity Council-sponsored event began at 2:30PM in the cafeteria and featured music by the master guitarist Julius Carrasco. Carrasco has studied in Spain under renowned flamenco jazz artist Gerardo Nuñez and performed in venues all over the world.

Julius Carrasco presented a diverse repertoire, all beautifully played. This versatility on the guitar shows in his performances of flamenco and "nuevo flamenco," a mixture of jazz and flamenco. Although he played none of his classical work at the Fiesta, Carrasco is also accomplished in that genre, and his love of Bach and the Baroque period shines through in his CD "Baroque is Bach." Reviewers of his five CDs have commented on his striking dexterity and technical precision, both amply evident in his NIEHS performance.

To commemorate Hispanic Heritage Awareness Month, the cafeteria, under the direction of Diane Crawford, featured Hispanic dishes each Tuesday from September 20 to October 10. Upcoming specials include the Celebrity Chef Day Lunch Combo on October 3, which features roasted Spanish Pork, Arroz con Grandules, Flan and Sassy Gria Punch, and hot pressed Cuban sandwich on October 10.

In addition to the Fiesta activities, the Hispanic Heritage Awareness committee is collecting Hispanic dessert recipes that it plans to publish in special cookbook.

Featured master guitarist Julius Carrasco (right) enjoys the vocals of accompanist Hugo Quintero. The two are part of the group Sonidos Latinos. (Photo courtesy of Steve McCaw)

Education Leader Speaks at NIEHS

By Eddy Ball

On August 29 in Rodbell Auditorium, the 2006 NIEHS Labor Day Presentation featured an address by Eddie Davis, a prominent social activist, tireless lobbyist and head of the North Carolina Association of Educators (NCAE). Sponsored by the NIEHS Diversity Council and the American Federation of Government Employees (AFGE) Local 2923, Davis focused on pressing issues of equality in education for the state's children and young people and encouraged his audience to become involved at the community level in improving education in North Carolina.

Eddie Davis urges his audience to get involved in improving education. (Photo courtesy of Steve McCaw)

During his talk, the Weeksville, N.C. native reflected on his childhood in the segregated South and described his community's experience with the Extension Service Home Demonstration Projects as an example of ways communities respond to effective grassroots organization. He commended the popular Extension Service initiative, which sponsored educational gatherings of farmers and homemakers in their homes and on their farms, for the pride and empowerment it fostered in rural communities. Davis presented it as a model for community outreach to help parents, especially in impoverished areas, access their schools and support the best education possible for the children in their communities.

Midway into his presentation, Davis took the audience even farther back in Southern history to an icon of the plantation days. For Davis, the Magnolia tree, both because of and despite of its negative associations with slavery and exploitation, could serve as an evocative symbol for education. The Magnolia is sturdy, tall and broad, with limbs reaching low to embrace the area around its base. "Education," he explained, "should be like the Magnolia, aspiring to reach as high as possible, yet ready to nurture the smallest and weakest down below."

Davis helps Bill Jirles (left) and EEO Specialist Ginny Ivanoff (center) display the poster for the event. (Photo courtesy of Steve McCaw)

Davis presented more challenges than answers in the course of his talk, but he left his audience more aware of the continuing difficulties in educational equality. He reminded his audience of the striking differences between the "privileged" Research Triangle Park and other parts of the state. "You folks are a world away from many parts of North Carolina," he said. Davis said many neighborhoods in the state fail to offer children the support and resources they need to succeed in today's economy.

Introducing Davis, AFGE local Vice-President Bill Jirles, a program analyst at NIEHS, highlighted Davis' rise from a young English teacher in Weldon, N.C., to the top position in the NCAE, formed in 1970 as the successor of two segregated teacher organizations dating from the 1800s. Davis is the recipient of numerous honors for accomplishments as a teacher and a labor leader.

Davis served on the National Test Panel, which formulated the original specifications for former President Bill Clinton's proposed national tests for fourth-grade reading and eighth-grade math. In 1989, Davis helped a group of Hillside High School students convince the North Carolina General Assembly to retroactively ratify the 24th Amendment, which outlawed the poll tax. When the legislature convenes again in January 2007 for the new Biennial Session, Davis is sure to be lobbying again, raising the awareness of legislators and the public about the needs of the state's teachers, support personnel and students.

Softball Team Finishes in Second Place

By Steve McCaw

Members of the NIEHS softball team, the BioHazards, have good reason to be smiling about their very respectable season. This year the "B" League softball team came-in second place out of seven teams with a final record of nine wins and five loses. The BioHazards had a very good year considering it was a "rebuilding year" for the team, with many of the players being on the roster for the first time. The young team lost its first games at the very start of the season, but then won five in a row to power the team on to a winning year. The NIEHS players ultimately lost in the play-offs to the Trimeris team, who went on to win the "B" League title.

The BioHazards gather for an end-of-the-season photo opportunity. Pictured are (left to right) Andrea Moon, Matt DellaVecchia, Krystal Finney, Greg Travlos, Tina Searcy (knelling), Zac Pursell, Steve McCaw (Captain), Matt Rushing, Danny Sanders, Nolan Wright, Russ Campbell, Yvette Cobb and Keith Merritt (standing). Dave Malarkey, Jason Williams, Mary Watson, Michael Wyde, Reid Lerner and Vee Vee Shropshire were not present for the photo. (Photo courtesy of Steve McCaw)

Upcoming Events

Coming Soon...Distinguished Lecture with Entomologist and Cancer Researcher

By Eddy Ball

On October 10, Bruce Hammock, Ph.D., will deliver the second lecture in the 2006-2007 NIEHS Distinguished Lecture Series at 11:00 AM in Rodbell Conference Center. He is the Distinguished Professor of Entomology and Cancer Research Center at the University of California–Davis. Hosted by Dr. William Suk, Hammock's talk is titled "Herbicides to Hypertension: The Soluble Epoxide Hydrolase as a Therapeutic Target for Hypertension, Inflammation and Analgesia."

Photo courtesy the University of California-Davis

With interests in the biochemistry of insects and humans, Hammock has researched hydrolytic enzymes, which are key defenses of the body against a variety of toxic and mutagenic compounds. His laboratory cloned the

first soluble epoxide hydrolases from several species including man, and his lecture will address his continuing research into the therapeutic potential of inhibiting this enzyme. Hammock and his colleagues are also involved in developing immunoassays for agricultural chemicals and have expanded the technology in terms of hapten design, production of antibodies by classical and recombinant means, integration of the technology with other analytical tools and improved detector systems.

In a 2002 Superfund Basic Research Program Distinguished Lecture, Hammock traced the link between his work with insects and its application to human health. "Since the soluble epoxide hydrolase can be induced by a variety of pharmaceuticals, agricultural chemicals and industrial products, and inhibited by some agricultural chemicals, it represents a target of action of environmental chemicals," he explained. "Interestingly, this research in environmental chemistry has led to a new class of compounds that could be useful in inhibition of high blood pressure, vascular inflammation and atherosclerosis."

Professor Hammock was recognized for his original approaches by election to the National Academy of Sciences in 1999 and has received numerous other awards and recognitions. These include the Frasch and Spencer Awards of the American Chemical Society and the Alexander von Humboldt Award in recognition of the most significant advances in U.S. agriculture during the previous five-year period. He has also received numerous international fellowships for research in France, Australia and England.

LMG Will Host Peter Burgers

By Stephanie Nick McElhinny

At 10:00 AM on October 30 in Rodbell Auditorium, Peter M. J. Burgers, Ph.D., will deliver the second talk in the LMG Special Seminars Series, titled "When Good DNA Turns Bad: Clamps Slide to the Rescue." Burgers, a professor of Biochemistry and Molecular Biophysics at the Washington University School of Medicine, has contributed more than 90 research studies over the past 30 years.

Photo courtesy of Washington University School of Medicine

Burgers' research efforts are focused on the study of nuclear DNA replication and DNA repair in the yeast *Saccharomyces cerevisiae*. The current biochemical and genetic efforts of his laboratory focus on the mechanisms which ensure genome fidelity and integrity during DNA replication and the DNA damage response.

Specifically, Burgers' research group aims to understand the functions of the replicative DNA polymerases at the replication fork, the mechanisms by which accessory factors associate with these DNA polymerases to form replication-competent complexes, and how the different replication complexes at the leading strand and at the lagging strand physically interact into a replisome to ensure coordinated DNA replication of the chromosome.

Burgers' group also is interested in determining how the replication machinery responds to DNA damage. Specific research questions include how the replication machinery mediates signals to cell cycle checkpoint factors when it encounters DNA damage, how the replication fork is remodeled in response to DNA damage to either a mutagenic or non-mutagenic fork which can replicate across the damaged site, and how alternative DNA clamps and clamp loaders may be involved in processing damage to generate a signal for the cell cycle response machinery.

October Events Focus on Work/Life Balance

By Dona McNeill

As part of its efforts to help NIEHS staff "Balance Your Work, Balance Your Life," OM's Office of Employee Services is sponsoring several lectures, workshops and information sessions in October to commemorate Work/Life Month. Manager Dona McNeill, Cynthia Radford and staff have scheduled convenient lunchtime events and longer sessions to ensure that there will be something to benefit just about everyone at NIEHS. Some events require registration, and several are designated as brown bag events.

Play to Learn with Tanya Dennis
Workshop for Parents and Grandparents
Oct. 2, 11:30-1:30
101 Rodbell C (sign-up, bring lunch)
Participants will learn about "play-learning" and child development.

Outreach Table
Visitors can talk with Work/Life Staff and pick up information and giveaways.
Oct. 10, 11:00-12:30
101 Cafeteria

Life Styles Inventory with Nancy Russell-Forsythe and Greg Forsythe
Oct. 13, 11:30-2:30
101 E-450 (sign-up, bring lunch)
Participants will take a self assessment (LSI 1 by Human Synergistics) online and bring the results to the workshop where they will review and work with the results to develop strategies for life and career balance.

Art work courtesy of Dona McNeill

Outreach Table
Visitors can talk with Work/Life staff, pick up information and giveaways.
Oct. 17, 11:00-12:30
East Campus Lobby

Goals to Reality for Scientists with Sherry Essig
Oct. 19, 9:00-12:00
Nottingham 204AB (sign-up)
The *Goals to Reality for Scientists* workshop will enable individuals to utilize proven techniques to advance their careers, improve results and accelerate personal progress.

Emotional Intelligence for Managers with Merlin Walberg
Oct. 27, 2:00-4:00
101 Executive Dining Room (sign-up)
Attendees will learn about recognizing, utilizing and improving their EI competence.

Parenting School Age Children-Lunch & Learn
Oct. 23, 12:00-1:00
101 Executive Dining Room (sign-up)
A discussion with Durham County Outreach Educator, Peggy Kernodle. Peggy will focus on the joys and the challenges of raising older school age children.

Outreach Table
Visitors can talk with Work/Life Staff and pick up information and giveaways.
Oct. 24, 11:00-12:30
Nottingham Lobby

Myers-Briggs & Your Communication Style with Mary Charles Blakebrough
Oct. 25, 1:00-3:00
Executive Dining Room (sign-up)
Participants will take the Myers-Briggs Type Indicator online and bring the results for discussions focusing on communication styles.

To sign-up contact A'tondra Carree at 541-7883 or Cynthia Radford at 541-1806.

October Is Disability Awareness Month

The NIEHS Diversity Council's Disability Advocacy Committee has planned a series of events in October to commemorate Disability Awareness Month. The month is designated each year as a time to focus on the abilities of individuals and to separate individuals from the physical challenges which almost every person will face some time in his or her lifetime. It is also a time to raise awareness of environmental and technological barriers and safety risks that exist for disabled people - whether they experience temporary physical challenges or must live with physical challenges throughout their lives.

Seminar: Reasonable Accommodations in the Workplace
Wednesday, October 4
10:00 AM -11:00 AM
Building 101 Rodbell B

Guest Speaker: Mr. Carlton Coleman, Disability Program Manager, NIH OEODM

North Carolina Now: Asthma (Video followed by a Panel Discussion)
Thursday, October 5
2:00 PM-3:00 PM
Building 101 Rodbell B

Panel Members:
Dr. Darryl Zeldin, Head, Molecular and Biology Section
Laboratory of Respiratory and Environmental Cardiopulmonary Diseases Section, Office of Clinical Research

Dr. Stephanie London, Senior Investigator
Genetic Epidemiology Branch with joint appointment in the Laboratory of Respiratory Biology

Hearing Dog Demonstration –
Meet Panther and See Him in Action
Wednesday, October 18
10:00 AM-11:00 AM
Building 101, Rodbell B

Assisted by Ms. Kelly Godfrey, Supply Technician, Administrative Services and Analysis Branch, NIEHS

Kelly Godfrey will take Panther through his motions as a part of Disability Awareness Month. (Photo courtesy of Steve McCaw)

Disability Resources (Information & Exhibits)
Tuesday, October 24
11:00 AM-2:00 PM
Building 101, Patio Adjacent to NIEHS Cafeteria

Seminar: Increasing Community Participation of People with Disabilities through Universal Design of the Built Environment
Tuesday, October 31
10:30 AM -11:30 AM
Building 101 Rodbell A

Guest Speaker: Ms. Laurie Ringaert,
Director Office of Research, School of Public Health University of North Carolina-Chapel Hill

Followed by a special musical presentation performed by *SeaBreeze Singers & Mr. James Benton (Spokesperson)*.

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