Department Of Health And Human Services
National Institutes Of Health
National Institute Of Environmental Health Sciences

Minutes of The National Advisory Environmental Health Sciences Council
May 17, 2004

The National Advisory Environmental Health Sciences Council was convened for its one hundred twelfth regular meeting on May 17, at 8:30 a.m., at the Sheraton Imperial Hotel and Convention Center, Durham, North Carolina. The meeting was open to the public from 8:30 a.m. until 2:30 p.m. The meeting was closed for consideration of grant applications on May 17, 2:30 p.m. to 4:00 p.m. Dr. Kenneth Olden presided as Chair on May 17, 2004.

Members Present:

Douglas Benevento, J.D.
Teresa Bowers, Ph.D.
Deborah Brooks
Charlie Coon,J.D.
Joan Cranmer, Ph.D.
Elaine Faustman, Ph.D.
George Friedman-Jimenez, M.D.
Bernard Goldstein, M.D., Ph.D.
Frederick P. Guengerich, Ph.D.
David Losee, J.D.
Martin Philbert, Ph.D.
Peter Spencer, Ph.D.
Peter Thorne, Ph.D.
James G. Townsel, Ph.D.

Members Absent:

Dale Eastman
Michael Gallo, Ph.D.
George Gray, Ph.D.
Frank Talamantes, Ph.D.

Ex Officio Members Absent:

Eric L. Stephens

Liaison Members Present:

Marion Ehrich, SOT

Members of the Public Present:

George Lambert, Ph.D.
Bruce Lanphear, M.D.

NIEHS Staff:

Kathy Ahlmark
Janice B. Allen, Ph.D.
Beth Anderson
Lisa Archer
David Balshaw, Ph.D.
Martha Barnes
Linda Bass, Ph.D.
Sharon Beard
Lutz Birnbaumer, Ph.D.
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dorothy Duke
Sally Eckert-Tilotta, Ph.D.
Rich Freed
Janet Guthrie
Kimberly Gray, Ph. D.
Jerry Heindel, Ph.D.
Mike Humble, Ph.D.
Ethel Jackson, D.D.S.
Laurie Johnson
Annette Kirshner, Ph.D.
Dennis Lang, Ph.D.
Cindy Lawler, Ph.D.
Charle League
Elizabeth Maull
Carolyn Mason
Patrick Mastin, Ph.D
Liam O'Fallon
Michelle Owens
Ted Outwater
Joan Packenham, Ph.D.
Jerry Phelps
Chris Portier, Ph.D.
Les Reinlib, Ph.D.

Anne P. Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
William Suk, Ph.D., M.P.H.
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Charles Wells, Ph.D.
Brenda Weis, Ph.D.
Samuel Wilson, M.D.
Leroy Worth, Ph.D.

Other Federal Staff:

Ross Shayiq - CSR

I. CALL TO ORDER AND OPENING REMARKS

The one hundred twelfth regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Olden. Dr. Olden welcomed the members of the Council and introductions were made around the room.

II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST PROCEDURES - Dr. Kenneth Olden

Dr. Olden read the requirements of the Government in the Sunshine Act. All aspects of the meeting were open to the public except those concerned with review, discussion and evaluation of grant applications and related information. The Chairperson explained policies and procedures regarding confidentiality and avoidance of conflict of interest situations.

III. CONSIDERATION OF MINUTES OF February 23-24, 2003 MEETING

Council accepted the minutes without change.

FUTURE COUNCIL MEETING DATES

September 13-14, 2004 NIEHS
February 15-16, 2005 NIH - Bethesda
May 23-25, 2005 NIEHS (with Leadership Retreat)

IV. REPORT OF THE DIRECTOR, NIEHS - Dr. Kenneth Olden

Dr. Olden began his report by commenting on the Congressional Hearings and NIH's request for 28.8 billion dollars for FY 2005. There is a proposal to reduce the out-year cost-of-living increase to 1.9% so NIH could fund 10,393 new grants in 2005 (same number as in 2003). The

number was increased in 2004 by 258 grants. The doubling ended in FY 2003. In FY 2004 there was a Congressional recision that cost the NIH approximately $165 million dollars; the HHS taps cost the NIH approximately $570 million dollars; and extramural facilities construction was $119 million. These were all unanticipated reductions. Senator Spector is trying to increase the NIH's budget by $1.3 billion but there has not been a similar effort made by the House. There were questions at the hearing about the adequacy of the number of stem cell lines. Dr. Zerhouni's testimony to Congress was outstanding and when asked how NIH would spend this money he responded that the greatest need was translation and clinical research. Gene-environment interactions are an important aspect of many of the new NIH initiatives, so this bodes well for NIEHS.

Conflict of interest issues have been a major issue with Congress. An article in the Los Angeles Times pointed out problems, though no laws were broken. The appearance was the concern in terms of public trust. There are several questions that come out of the conflict of interest issues:

- Will changes hinder translation of biomedical research?
- Is it in the public interest for scientists to have consulting /collaborative relationships with drug and biotechnology companies? NIH scientists who do not participate in funding decisions are much like university scientists.
- Can scientists work in the public interest when they may at the same time have a financial interest in a company?
- Will the lure of profit corrupt biomedical research?
- Will fuller disclosure solve the problem? There is value in having interactions between basic research and the organization that are translating the research into practice.

The rules and regulations at NIH were relaxed in 1995 by Dr. Varmus to be in line with other agencies. Prior to the rules being relaxed, senior leadership could not accept any payments from outside sources. Other NIH employees could earn up to $25,000 year from a single source and $50,000 year total. The change in 1995 allowed senior leadership to consult with permission from NIH and financial disclosure. Dr. Zerhouni appointed a Blue Ribbon Committee which has made recommendations that tighter limits on outside income and conflict-of-interest rules. The panel was co-chaired by Dr. Bruce Alberts and Mr. Norman Augustine. The committee also made note that it is important that NIH scientists are able to interact with industry and academia. Congress is very concerned and may ban all consultation with pay. Implications are potentially harmful in that there is no inducement to collaborate and no attraction for recruitment. However, limits on how much one can earn will almost certainly be imposed. NIEHS does not have any problems in this area.

An editorial in The Scientist, "The Right and Wrong Way to Lead," was about the NIH and the Research and Development Office of the Department of Veterans Affairs. Dr. Zerhouni was cited for how he is dealing with the conflict-of-interest issues, stem cell research and sex research., whereas the Department of Veteran's Affairs is under scrutiny. Dr. Olden complimented Dr. Zerhouni on his open, forthright style.

Dr. Olden then commented on several new developments related to NIEHS that have received press attention or other visibility.

According to an article in the May issue of Pediatrics, breastfeeding appears to reduce significantly the chances that babies will die the first year of life. This study was led by Dr. Walter Rogan, an NIEHS epidemiologist.

Researchers at the Columbia Center on Children's Health, in an article published in Environmental Health Perspectives, showed for the first time a benefit to newborns in terms of increased birth weight from the Federal ban on home use of two insecticides, chlorpyrophos and diazinon.

Funding of four Centers for Oceans and Human Health (a total of $5 million annually for the next five years) by NIEHS and the National Science Foundation (NSF) has been favorably received, and Congressional briefings are scheduled with with The National Oceanic and Atmospheric Administration (NOAA) and NSF. NOAA has new authorization for similar centers and hopefully will be able to coordinate. NIEHS/NSF collaborations began several years ago.

The National Children's Study was also in the press with a nice write-up in the Washington Post. The study looks at the first weeks of pregnancy thru age 21. There will be a cohort of 100,000 pregnancies at 35 to 40 Centers around the nation. The estimated cost is about $3 billion. While some funds have been appropriated for planning, much more will be needed.

The Built Environment Conference was a big success. There were over 600 registrants and the conference generated lots of enthusiasm. Dr. Zerhouni and Secretary Thompson were there in addition to Dr. Satcher and Dr. Sullivan. This was an important conference and many agencies will have to be involved in solutions and high level interagency leadership will be requested.

V. Update on the NIEHS Director's Search - Dr. Frederick Guengerich

Dr. Guengerich reported on the activities of the search committee to date. Information was provided such as the member roster, the job announcement and the advertisements. Over 30 applications were received. The search committee had several meetings and conference calls. A short list has been sent to Dr. Zerhouni. Dr. Goldstein gave tribute to thank Dr. Olden for his leadership.

VI. Division of Research Coordination, Planning and Translation (DRCPT) - Dr. Allen Dearry

A new division was created approximately one year ago by Dr. Olden. This division works to ensure that NIEHS research is provided to and easily accessed by professionals and communities to improve public health. Americans want more information about public health. The majority of Americans support an increase in spending on biomedical research but greater than 50% have difficulty understanding and using the available health information. It is not real clear who the public trusts to provide that information.

There are many initiatives ongoing to enhance scientist-public interactions. The goal is to create two-way communication to be more proactively engaged with community at large. There are a number of benefits to this program but also a number of challenges. The major initiatives include

the establishment of Task Force 5, Obesity and the Built Environment, and NIEHS Spokespersons and internal coordination within NIEHS concerning communication. This division is also involved in coordination of the Roadmap, NIH Public Trust initiative, Trans-NIH Obesity Initiative and the NIH Prevention Research Committee.

Next steps include a communications audit; evaluation of the NIEHS external web; development of a NIEHS press kit; creation of an on-line press room; and offer of EHP news content thru Center Community Outreach and Education Programs. There are also Town Meetings scheduled through 2004 with the following subjects: Children and the Environment in Boston, Environmental Influences and Cancer in Chicago and Urban Sprawl in Atlanta. Translation will be addressed with a DRCPT and other collaborative efforts relating to environmental medicine and public health and integration of education, public input and research functions.

In the discussion that followed, a question was asked about how locations and communities for town meetings are chosen. Dr. Olden responded that NIEHS leadership will go anywhere it is invited and there is someone willing to organize the meeting. He continued by describing how NIEHS is proactive in identifying and responding to opportunities.

VII. Scientific Director's Report (See attachment B)

Dr. Birnbaumer gave an update of the Division of Intramural Research and the recruitments that are ongoing. The Laboratory of Neurobiology is a new lab and its creation involved the reshaping of the existing resources. Dr. Dale Sandler is now the permanent chief of the Epidemiology Branch. This branch has a number of different focus areas. Other new appointments were reported, and the selection of Dr. Marilyn Diaz for the Presidential Early Career Award in Science and Engineering was noted. This is a very prestigious award and it is an honor for both Dr. Diaz and NIEHS.

VIII. Centers for Children's Environmental Health Research and Prevention (See attachment C)

Dr. Collman opened with description and summary of the Children's Centers. The Centers conduct multidisciplinary basic and applied research in combination with community - based prevention research projects to support studies on the causes and mechanisms of children's disorders.

Dr. George Lambert directs the Center for Neurotoxicology and Exposure Assessment at University of Medicine and Dentistry of New Jersey, which is focused on autism. Dr. Lambert thanked Dr. Olden and named collaborators and partners for this center. He described autism and stated that it is a public health priority and that the cost of the health services is very large. Environment is important and we know that environmental exposure have a negative impact on normal children so the question is, "What is the impact on autistic children?" There is some evidence that chemicals can increase the incidence of expression of ASD (autism spectrum disorder). The Center consists of 3 basic science and 2 chemical projects and more information can be found at http://www.eohsi.rutgers.edu/childhood/index.shtml

Data are too limited at this point to compare children with autism with normal children in terms of exposures and outcomes. However, there will no doubt be new chemicals of concern based on the Centers for Disease Control analysis of population exposures, and there will be a need to look at the role of specific polymorphism and gene environment interaction.

Dr. Bruce Lanphear from the Cincinnati Children's Environmental Health Center described their program, which has a focus on residential exposures (http://www.cincinnatichildrens.org). A study of childhood blood lead levels and rates of arrest showed a significant does-response relationship. Other studies have shown that the greatest decrements in IQ in lead-exposed children is at levels below 10mg/dl. So there are important public health implications of their work, though the specific mechanism is not known.

The researchers in this Center are also studying prenatal tobacco smoke exposure and polymorphism in the DAT gene. These studies are showing a striking dose- response relative to negative behaviors such as ADD. Other tobacco exposure research is ongoing exploring impacts on asthma, and there are suggestions that cotinine may be more than a marker of tobacco exposure and itself a toxin. Other research in this center is described in the Web link.

Council members thanked the presenters and asked Dr. Lambert about his response to questions from parents regarding interventions in autistic children. He responded that scientists are comfortable with general information on reducing exposures. However, based on previous studies, he does not recommend chelation. He and other researchers are trying to get information from instances in which patients are using this anyway. Other comments related to the use of prevention/intervention studies as a way of helping to generate hypotheses to test.

IX. NIEHS Coordinating Center for Rodent Genetics - Dr. William Shrader (See attachment D)

Dr. Schrader discussed the Coordinating Center for Rodent Genetics and the concerted approach for the use of genetically defined experimental animals for projects unique to the mission of NIEHS and the National Toxicology Program. The goals of the center are to foster improved and more predictive genetic-based models, to serve as a national conduit for study of environmental agents, to review all mouse genetics initiatives at NIH and to look for opportunities for NIEHS and to represent NIEHS on related projects. The Strategic Plan (see attachment) outlines these objectives. Dr. Schrader's presentation emphasized the importance of phenotypic analyses and also the wide range of chemicals of interest. This makes NIEHS interests unique, and the National Toxicology Program has very valuable phenotypic database that will be an important element.

X. Report of the Director, DERT - Dr. Anne Sassaman (See attachment E)

Dr. Sassaman began her report by following up on items from the February meeting of the Council. She reviewed the status of NIH Roadmap initiatives and the process by which they would be reviewed by the councils/boards of the lead institutes over the summer. NIEHS is not a lead institute, and this council review would be required only if we decide to fund an application with NIEHS funds. In that case, the application(s) could be reviewed at the September meeting.

The second follow-up item involved questions regarding the Council-delegated authorities which were reviewed and approved in February. New members had asked for additional information about actions under these authorities, and Dr. Sassaman provided a document listing the authorities and examples of staff actions under each. One member of the Council stated later that he still had questions and wished to have a discussion of this topic at the September Council meeting.

Dr. Sassaman then reported on an interim assessment of the NIEHS Transition to Independent Positions (TIP) Award, covering the period 1999-2003. This award, first announced in 1998, provides a unique mechanism for attracting and supporting the transition to independent faculty positions of exceptionally talented new investigators who can impact the field of environmental health sciences. Over the five-year period through Fiscal Year 2003, 35 applications have been approved for funding and 27 have been activated. Since the goal of the program is to increase the probability of successfully competing for R01-type research grants, the assessment included a look at the number of applications submitted by and funded for the cohort, analyzing by intramural and extramural TIP applicants. The numbers are too small to draw any conclusions at this point, but the success rate for both groups is not impressive. NIEHS will continue to monitor the progress of the TIP recipients to be able to draw conclusions with more data regarding the overall success of our investment in this Program.

Council members expressed their interest in and general support for the TIP program. There was discussion regarding the requirement that the recipient obtain a tenure-track appointment at an academic institution in order to activate the award. It was pointed out that the tenure concept is undergoing significant changes in the academic community, and all agreed that the primary issue is an appropriate level of institutional commitment to the young investigator. Dr. Carol Shreffler, who administers the Program, responded that there is flexibility in it and that she works closely with the recipients as they look at positions and obtain employment.

The next item on the DERT Director's report was a brief presentation of a proposal to establish a partnership with the Avon Foundation though which a conditional gift of $250,000 would be used to support communication and outreach activities of the Breast Cancer and the Environment Centers Program. Council voted unanimously to accept this conditional gift. The specifics of the transfer will be developed with review and approval of appropriate legal staff of the NIH.

Dr. Sassaman concluded her presentation with a review of early council concurrence (ECC) and a proposal for its use by NIEHS. The primary advantage for this institute is that it will aid in the workload distribution for grants management staff, but it would also be useful as a means of reviewing RFAs or single applications that may not have been ready for Council at the time of the regular meeting. She presented a set of parameters that would determine the cohort of en bloc applications available for ECC as well as the proposed process. A panel of three members appointed in advance by the Council Chair would act on behalf of the Council; however, information on the list would be available to all members and any member could electronically remove an application from the en bloc list for review at the meeting itself. The proposal was unanimously accepted by the Council and will be used for the February Council round.

CLOSED PORTION OF THE MEETING

XI. Consideration of Grant Applications - Dr. Anne Sassaman and DERT Staff

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

XII. REVIEW OF APPLICATIONS

The May 2004 Council considered 388 applications requesting $90,591,116 in direct cost. The Council recommended 207 applications with a total direct cost of $53,376,956.

XIII. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 4:00 p.m. on May 17, 2004.

Attachments:

A. Council Roster
B. Report of the Director, DIR - Dr. Birnbaumer; *Adobe Acrobat* Format
C. Centers for Children's Environmental Health Research and Prevention - Abstracts
D. NIEHS Coordinating Center for Rodent Genetics - Dr. Schrader
E. Report of the Director, DERT - Dr. Sassaman

Division of Intramural Research

NAEHS Council Update

May 2004

Attachment B

DIR RECRUITMENTS

Senior Clinical Investigator The Office ofClinical Research is recruiting a tenured, senior investigator to conduct clinical research in the general area ofwomen's reproductive health. The person selected will be board certified or eligible in obstetrics and gynecology, and will conduct a clinical research program in some aspect of disorders ofwomen's reproductive health. There is particular interest in the influence of environmental factors on malignant and non-malignant disorders ofwomen's reproductive health; examples ofpossible topics for study include endometriosis, polycystic ovary syndrome, uterine fibroids, infertility of various types, premature ovarian failure, microchimerism, epigenetic disorders, cancer prevention and/or vaccines. Studies will be designed to help understand basic pathophysiology and aid in the development of new treatments for these conditions. The successful candidate will be expected to have an active clinical research program in his/her specific field of interest and to play an active role in the Gynecology Consult Service at the NIH Clinical Center in Bethesda. A search committee chaired by Dr. Darryl Zeldin, Laboratory ofRespiratory Biology, has been formed.

Tenure-track Immunologist The Laboratory of Respiratory Biology has conducted a national search for a cellular/molecular immunologist. The candidate will be expected to establish a high-quality independent research program in pulmonary immunology in a laboratory with diverse research interests and backgrounds. The successful candidate will have research strengths in, but not necessarily limited to, pulmonary biology (such as mechanisms of tolerance, allergy, adaptive and/or innate immune response to respiratory infections, etc). Dr. Farhad Imani, currently an Assistant Professor ofMedicine at the Johns Hopkins University School ofMedicine, has accepted this position.

Tenure-track Environmental Epidemiologist
The Epidemiology Branch has conducted a national search for an environmental epidemiologist. This person will be expected to develop an outstanding research program on the effects of environmental exposures and risks of chronic disease. Dr. Honglei Chen, currently an Instructor at the Harvard School of Public Health, has accepted this position.

Tenure-track or Tenured Biostatistician The Biostatistics Branch has conducted an international search for a tenure-track or tenured statistician to conduct independent research on methods development in statistical genetics. The successful candidate will be expected to develop statistical methods for family-based studies aimed at identifying and mapping genes that influence risk modifying quantitative traits or diseases or that interact with the environmental agents that cause human disease. An offer has been extended to a the leading candidate.

Tenure-traCk Investigator -Embryonic Stem Cell Biology The Laboratory ofMolecular Carcinogenesis is conducting a national search for a Tenure-Track Investigator in embryonic stem cell biology with research strengths in, but not necessarily limited

to, development and epigenetics. The search committee, chaired by Dr. Jean Harry, Laboratory of Neurobiology, has recommended candidates.

Tenure-track Investigator -Cancer Biology

The Laboratory of Molecular Carcinogenesis is conducting a national search to recruit a Tenure Track Investigator in cancer biologist with research strengths in, but not necessarily limited to, chromatin, transcription, and epigenetics. The search committee, chaired by Dr.Michael Resnick, Laboratory of Molecular Genetics, has recommended candidates.

Tenure-track Investigator-Endocrinology

The Laboratory of Reproductive and Developmental Toxicology is conducting a national search for a Tenure-Track Investigator in hypothalamic-pituitary-gonadal reproductive neuroendocrinology. The individual selected for this position will have a record of accomplishments in the field of mammalian reproductive neuroendocrinology, with a research emphasis on the regulation and function of the hypothalamic-pituitary-gonadal axis in reproduction. A search committee, chaired by Dr. Mariel Bimbaumer, Laboratory of Signal Transduction, has been formed.

Deputy Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The Environmental Toxicology Program is recruiting a staff scientist to serve as Deputy Director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods. The candidate will have responsibility for managing and overseeing external independent scientific peer review of new, revised, and alternative test methods submitted for evaluation by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The incumbent will also work with the Director to manage and oversee all aspects of scientific and administrative activities within the Center, including validation studies, workshops and coordinate test method reviews and other relevant activities with the ICCVAM, appropriate ICCVAM Interagency Working Groups, and other national and international regulatory and research organizations. Priority will be given to applicants with demonstrated ability to foster effective scientific review and results, and who possess a level of managerial and executive ability to create an atmosphere for maximum creativity, productivity, and cooperation. The candidate should hold a veterinary or medical degree, or a doctoral degree in toxicology or a related field, and have demonstrated credentials in scientific review, the validation of standardized toxicological test methods, and an understanding of the principles of chemical safety evaluations necessary to support public health. A search committee, chaired by Dr. Michael Shelby, National Toxicology Program, is evaluating candidates.

Staff Scientist--Toxicologic Pathologist The Laboratory of Experimental Pathology has conducted a national search for a toxicologic pathologist to provide support and peer review for the National Toxicology Program toxicity and carcinogencity studies and to provide support for NIEHS researchers. Dr. Gail Pearse, currently a Research Fellow in the Laboratory ofExperimental Pathology, has accepted this position.

Staff Scientist-Toxicogenomics

The National Center for Toxicogenomics (NCT) of the National Institute ofEnvironmental Health Sciences has conducted a national search for a Staff Scientist to lead a core facility to support a research program to direct the basic research applications of gene expression technologies within the NCT. The NCT is conducting an aggressive research program to apply genomic technology to

toxicology and to facilitate the identification ofbiomarkers of specific adverse effects of exposure to environmental agents including drugs, chemicals, and stressors. The activities ofthe Center will enable other investigators to probe the complexities of the mechanisms of normal genetic and metabolic pathways and to subsequently learn how diseases occur when these pathways malfunction. The search committee is chaired by Dr. Elizabeth Murphy, Laboratory of Signal Transduction. An offer has been extended to a leading candidate.

Staff Scientist-Epidemiology

The Epidemiology Branch of the NIEHS is seeking a staff scientist with interests in breast cancer, genetic susceptibility and biomarkers of exposure to be the project director for the Sisters Study, a large cohort study of genetic and environmental risk factors of breast cancer. Primary duties will include maintenance of a large specimen bank, oversight of data collection and fieldwork, data analysis and publication. The incumbent will serve as the interface among Branch, laboratory and contract support staff, will serve on the Steering Committee for the study, participate in priority setting for use of study data as well as collection ofnew data, and will conduct research using the cohort data. While the primary focus ofthe study is breast cancer, it will be possible to carry out research on other outcomes within the cohort. A search committee chaired by Dr. Barbara Davis, Acting Chief, Laboratory ofWomen's Health, is interviewing candidates.

Staff Scientist-Bioethics

The Office of Clinical Research has conducted a national search for a bioethicist to be involved with health policy research on the effectiveness offederal and Institutional Review Board regulations in addressing clinical studies,and The search committee:is chaired by Dr. Ronald Mason, Laboratory of Pharmacology Chemistry. An offer has been extended to a leading candidate.

Staff Scientist-Mass Spectrometry

The Laboratory of Structural Biology, Environmental Biology Program is seeking a Staff Scientist to serve as Head of the Protein Microcharacterization Facility and who will be responsible for the MALDIIMS, MALDIIMSIMS and capillary HPLC/ESIIMSIMS identification of proteins isolated by I-D and/or 2-D gel electrophoresis, in-gel digestion, determination ofsites ofpost-translational protein modifications, identification of sites of interactions in protein complexes by limited proteolysis, protein purification by LC, and use of affinity techniques combined with MS. Additional duties will include close interaction with Institute scientists serving as a mass spectrometry expert during the planning and execution of experiments, supervision of laboratory technicians, and providing training to Institute personnel in the interpretation of mass spectral data. A search committee chaired by Dr. Trevor Archer, Chief, Laboratory of Molecular Carcinogenesis, has been formed.

Dr. Leping Li
Biostatistics Branch

Dr. Leping Li joined the Biostatistics Branch in December, 2003, as a tenure-track principal investigator. Dr. Li was trained in medicinal chemistry (Ph.D. 1994, University of North Carolina at Chapel Hill). After graduation, Dr. Li worked with Drs. Thomas Darden (Laboratory of Structural Biology, NIEHS) and Lee Pedersen (UNC and Laboratory of Structural Biology, NIEHS) on molecular modeling. Three years ago, Dr. Li made the transition from molecular modeling to bioinformatics.

Dr. Li is pursuing two interrelated areas in bioinformatics, gene expression data analysis and promoter sequence data mining. Although, gene expression profiling study has provided valuable information about the expression changes of individual genes in response to environmental toxicants/stressors, investigators often face the challenges of making sense of the changes in a global prospective as the tools for integrating individual genes into functional pathways and networks remain undeveloped. Statistical/data mining approaches are urgently needed to make optimal use ofthese high-dimensional data. This need becomes greater as the size and complexity ofgenomics data are generated and biological questions to be addressed become more sophisticated. In collaboration with colleagues in the Biostatistics Branch, Dr. Li is developing computational methods for analysis of microarray data. In addition, Dr. Li is developing computational methods that combine the Gibbs sampling with phylogenetic footprinting,techniques to searchfor cis-regulatorymotifs thepromoterregipn genes.Thegoalisto combinegene expression data and genomic sequence data to find meaningful relationship between sequence and function.

Selected Publications

Liu D, Umbach D, Peddada S, Li L, Crockett PW, Weinberg CR. A random-peroids model for expression of cell cycle genes. Proc. Nat!. Acad. Sci. USA, in press.

Li L, Umbach DM, Terry P, Taylor *lA.* Application of the GA/KNN method to SELDI proteomics data. Bioinformatics, 2004.

Peddada SD, Lobenhofer EK, Li L, Afshari CA, Weinberg CR, Umbach D. Selecting and clustering genes using order restricted inference methodology with applications to time-course microarray data. Bioinformatics, 2003, 19, 834.

Li L, Weinberg CR, Darden TA, Pedersen LG. Gene selection for sample classification based on gene expression data: study of sensitivity to choice ofparameters of the GA/KNN method. Bioinformatics, 2001, 17, 1131-1142.

Dr. Angela King-Herbert
Laboratory of Experimental Pathology Branch

Dr. Angela King-Herbert joined the Laboratory of Experimental Pathology Branch (LEP) ofthe Environmental Toxicology Program (ETP) at the NIEHS as the head of Laboratory Animal Management/Staff Scientist for the National Toxicology Program (NTP) in January 2004. Dr. King-Herbert received her DVM degree from Tuskegee University in 1984. After several years of practicing as a small animal clinician, she returned to North Carolina State University, where she completed a residency program in Laboratory Animal Medicine. Dr. King-Herbert served as Director of a centralized animal facility, the Biological Resources Facility, for the College of Agriculture and Life Sciences at NCSU, in addition to serving as an adjunct professor in the Department of Zoology. Upon leaving NCSU, she became the Attending Veterinarian and Manager of Animal Biology in the Inhalation Toxicology & Animal Biology Division ofRJ Reynolds Tobacco Company.

At the NIEHS, Dr. King-Herbert is responsible for developing and managing a program to supply quality laboratory animals and experimental services to ETP. Dr. King-Herbert assists in the development and investigation of new animal models such as transgenic mice and establishes the supply of such animal models for evaluation of toxic and carcinogenic potential of chemicals. She also assists ETP researchers in experimental designs, selection of animal models and final data evaluation in support of ETP studies. Dr. King-Herbert will serve as Project Officer contracts for rodent production, rodent disease monitoring, and rodent genetic monitoring.

Selected Publications

Hamm, T. E., AP. King-Herbert, M. A. Vasbinder. Toxicology in "The Laboratory Rat", American College of Laboratory Animal Medicine Series, Academic Press (submitted).

TRAINING AND MENTORING

NIEHS Ranks as Third-Best Institution for Postdoctoral Training In a survey conduced by the journal *The Scientist,* the Division ofIntramural Research (DIR) at NIEHS was ranked as the third best Institution in the United States for postdoctoral training. Results ofthesurveywerepublishedintheFebruary 16,2004issueofthejournal.Thesurveywasbasedon over 3,500 usable responses from more than 48,000 invitations. Postdoctoral researchers were asked to assess their working conditions and environments by indicating their level ofagreement with 45 criteria in 11 different areas and to indicate which factors were most important to them. The most important factors were: comprehensive collections ofjournals and books, scientific career preparation, high-quality research tools, smooth communication in the lab, quality research, supportive colleagues, well-maintained buildings, scientific mentoring from PIs and laboratory technical support.

Transition to Independent Position (TIP) Awards

The NIEHS TIP Award Program is designed for exceptionally talented new environmental health scientists in basic, clinical or population-based (epidemiology) research who have demonstrated outstanding scientific abilities during their training. The objective of the program is to provide a commitment of support for the most promising new investigators early in their career while they establish their independent research program in a research-intensive environment relevant to environmental health sciences. The TIP investigators are expected to design and pursue their non mentored research projects independently in their areas ofinterest. It is anticipated that the successful applicant will use the award to establish an independent research programand obtain preliminary data that will be the basis for a future research application. Specifically, the TIP investigator is expected to use the preliminary data in the environmental health sciences as a basis foraninvestigatorinitiatedresearchgrant (RO1)orequivalentto theNationalInstitutes ofHealth (NIH) in an area of a science directly relevant to the mission ofthe NIEHS within the first 24 months after initiation of the award.

Dr. Daniel 1. Tomso, from the Laboratory of Computational Biology and Risk Analysis, received a TIP Award in March 2004, based on his grant application "Detection of Polymorphic Xenobiotic Response Elements." His mentor is Dr. Douglas Bell, Laboratory ofComputational Biology and Risk Analysis.

Kupper Dissertation Award Brian Neelon, a predoctoral student in the Biostatistics Branch, won the "Kupper Dissertation Award" for the best paper published by a student in the University ofNorth Carolina, Chapel Hill, Department ofBiostatistics. The paper was: Dunson, D.B. and Neelon, B. (2003). Bayesian inference on order-constrained parameters in generalized linear models. Biometrics 59, 286-295. His mentor was Dr. David Dunson. Dr. Dunson also received a mentoring award from the UNC Department ofBiostatistics.

2004 NIEHSINTA Career Fair The Seventh Annual NIEHS/NTA Career Fair was held on April 30, 2004 at the Sigma Xi Center, Research Triangle Park, NC. A career development workshop entitled "Advancing Your Career" was chaired by Dr. Beth Fisher, University of Pittsburgh, which was followed by panel discussions. Areas covered included large and small biotech, academia, science policy, science writing and grant

administration. Panel participants included Dr. William Schrader, Deputy Scientific Director, NIEHS; Dr. Ester Carballo-Jane, Research Fellow, Merck; Dr. Greg Falls, Manager, Investigative Toxicology and Pathology, Glaxo Smith Kline; Dr. Laura Healy, Veterinary Pathologist, Amgen; Dr. Ed Lobenhofer, Research Scientist, Paradigm Genetics; Dr. Vicki Burnette: Senior Informatics Scientist, OmniViz, Inc.; Dr. Gwen Spizz, Group Leader, Experimental Cancer Biology, Gene Network Sciences; Dr. Geraldine Hamilton, Director, Cell Products, Cellzdirect; Dr. George Stancel: Professor and Dean, Graduate School, University of Texas, Houston; Dr. Delores Grant, Assistant Professor, North Carolina Central University; Dr. Deborah Lycan, Associate Professor, Lewis and Clark College; Dr. Roni Kingsley, Associate Professor, University of Richmond; Dr. Conrad Mallia, Program Officer, NIAID, NIH; Dr. Dennis Lang, Deputy Director, Division of Extramural Research and Training, NIEHS; Dr. Julie Wilberding, Grants/Program Manager, Department of Defense; Dr. Nancy Sung, Senior Program Officer, Burroughs Wellcome Fund; Dr. Sheila Newton, Director, Office of Policy, Planning, and Evaluation, NIEHS; Dr. Albert Teich, Director, Science and Policy Programs, AAAS; Dr. Sharon Hrynkow, Acting Director, Fogerty International Center, NIH; Dr. Angela Eggleston, Editor, Nature; Mr. Allan Coukell; Dr. Evelyn Strauss.

There were more than 230 registered attendees from universities and research institutions in the Triangle Area and the rest ofNorth Carolina. The NIEHS, Sigma Xi, the Burroughs Wellcome Fund, Biolink Life Sciences, and Kelly Scientific, cosponsored this event.

LABORATORY OF NEUROBIOLOGY

In March 2004 a new Laboratory ofNeurobiology (LN) was formed at NIEHS in the Environmental Biology Program of the Division ofIntramural Research around five existing investigators (Dr. David Armstrong, Dr. Perry Blackshear, Dr. Serena Dudek, Dr. Jean Harry, and Dr. Jerry Yakel) from the Laboratories ofMolecular Toxicology and Signal Transduction who have expertise in neuronal and glial signaling at all levels of mammalian brain organization: from cells in vitro to behaving animals, particularly as it relates to cortical synaptic plasticity and inflammation. In addition two new tenure-track investigators are expected to be recruited in FY04-05.

The Laboratory mission is to investigate the cellular and molecular mechanisms that allow the nervous system to adapt to the environment. These mechanisms are examined within the framework of both normal and disrupted development and aging. Initial studies will focus on the molecular mechanisms regulating neuronal and glial cell development and function, and the cellular consequences of disrupting those processes. Neurobiology is an integral part of environmental health sciences. Disruption of neuronal development and function produces life-long effects on human cognitive potential. Consequently both early learning disabilities and later neurodegenerative diseases associated with aging have become major public health concerns. Because many of those neurological disorders show low concordance between monozygotic twins, such as attention-deficit hyperactivity disorder, Parkinson's and Alzheimer's diseases, environmental factors are implicated in their pathogenesis.

Dr. Mariel Birnbaumer (Laboratory of Signal Transduction) was an invited Speaker at the Keystone Meeting on G Protein Coupled Receptors, Taos NM, February 17-21 2004; and was named Associate Editor of *Molecular Endocrinology.*

Dr. Colin Chignell (Laboratory of Pharmacology and Chemistry) was named to the editorial board of *Photochemistry and Photobiology.*

Dr. Michael Cunningham (Laboratory of Pharmacology and Chemistry) was invited to present the Plenary Lecture, "Gene Expression Changes in F344 Rats Following Exposure to a Pharmacological Dose of Acetaminophen" at the International Symposium on Molecular Toxicology and Environmental Health, November 5-8,2003, Lucknow, India

Dr. Marilyn Diaz (Laboratory of Molecular Genetics) received the Presidential Early Career Award for Scientists and Engineers, from the Office of Science and Technology Policy at the White House, April 2004.

Dr. Thomas Eling (Laboratory of Molecular Carcinogenesis) received the 2003 Japanese Society for the Promotion of Science Travel Award.

Dr. Dori Germolec (Laboratory of Molecular Toxicology) received the Outstanding Young Investigator Award for the Immunotoxicology Specialty Section, from the Society of Toxicology, March 2004; and was named to the editorial board of *Toxicological Sciences.*

Dr. Joyce Goldstein (Laboratory of Pharmacology and Chemistry) was named Associate editor: *Journal ofBiochemical and Molecular Toxicology;* and was named to the editorial board of *Drug Metabolism and Disposition.*

Dr. Michelle Hooth (Toxicology Operations Branch) was elected to the Education Committee ofthe Society of Toxicology, February, 2004; and became a Diplomat ofthe American Board of Toxicology, November 2003.

Dr. Kenneth Korach (Chief, Laboratory of Reproductive and Developmental Toxicology) was awarded the Transatlantic Medal from the British Endocrine Society; was Keynote speaker at the Yale Center for Musculoskeletal Disorders Research Day, Yale University Medical School, New Haven, Connecticut; and was Keynote speaker at the 5th Japan Conference on Hormones and Cancer, Osaka.

Dr. Stephanie London (Epidemiology Branch and Laboratory of Respiratory Biology) was elected to the Executive Committee, Environmental and Occupational Health Section, American Thoracic Society.

Dr. Jeanelle Martinez (Laboratory of Computational Biology and Risk Analysis) won the North Carolina SOT President's Award for Research Competition at the Fall NCSOT meeting.

Dr. David S. Miller (Laboratory of Pharmacology and Chemistry) was named Associate editor of the *Journal ofPharmacology and Experimental Therapeutics* and the *Journal of Experimental Zoology.*

Dr. Yuji Mishina (Laboratory of Reproductive and Developmental Toxicology) was invited as a keynote speaker at the 5th international conference on Bone Morphogenetic Proteins, September, 2004.

Dr. Jingbo Pi (National Toxicology Program and NCI at the NIEHS) received the SOT Carcinogenesis Specialty Section Postgraduate Fellowship Award for 2004.

Dr. James W. Putney (Laboratory of Signal Transduction) will give the annual Newton-Abraham Lecture in Medical and Chemical Sciences at Oxford, England, Spring 2004.

Dr. Melissa Rhodes (Toxicology Operations Branch) has been selected by the American Association for Cancer Research to attend the Edward A. Smuckler Memorial *Pathology of Cancer* Workshop in Aspen. This workshop provides an intense, one-week course on the

molecular and morphologic aspects of human cancer for scientists working basic cancer research. Dr. Nigel Walker (Laboratory ofComputational Biology and Risk Analysis) is President-elect of the North Carolina SOT (NCSOT) for 2004.

Dr. Allen Wilcox (Epidemiology Branch) has been invited to give the keynote address at the 19th International Symposium on Epidemiology in Occupational Health, to take place in Norway in September 2005.

Dr. Kamel Abdo (Toxicology Operations Branch) has a collaboration with scientists at the Center for Environmental and Occupational Health Sciences, Birzeit University, Ramallah, Palestine to determine indices of nutritional status of children; and with scientists at the Department of Community, and Occupational Medicine, Ain Shams University, Cairo, Egypt, to investigate the association between pesticide use in Egypt and occurrence ofdifferent cancers among Egyptians.

Dr. Trevor Archer (Chief, Laboratory ofMolecular Carcinogenesis) has collaborative research projects with scientists at the Child Health Research Institute, University of Western Ontario, London, Ontario, Canada to perform a functional analysis of CpG methylation in the BRCAI promoter region.

Dr. David Armstrong (Acting Chief, Laboratory ofNeurobiology) has a collaboration with scientists in the Department of Physiology at the University of Edinburgh to study the structural basis for potassium channel regulation by the cAMP-dependent protein kinase.

Dr. Donna Baird (Epidemiology Branch) in collaboration with researchers at the Finish Institute of Occupational Health, Helsinki, Finland, to study changes in fecundability over time and fertility affects of solvent exposure and pesticide exposure among men and women in the Agricultural Health Study.

Dr. Douglas Bell (Laboratory of Computational Biology and Risk Analysis) was an invited symposium speaker, at the 4th International Conference on Environmental Mutagens in Human Populations, Florianopolis, Brazil, May 2003.

Dr. Perry Blackshear (Director, Office of Clinical Research and Laboratory of Neurobiology) has collaborations with scientists at McGill University, Montreal, Canada to study genetic modifiers of insulin action with PHAS-I knockout mice (which were developed at the NIEHS); with scientists at the Institute ofImmunology, Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece to study interactions between TTP knockout mice and TNF and TNF receptor knockout and knock-in mouse lines; with scientists at the Institute of Clinical Biochemistry and Pathobiochemistry, Medical University Clinic, Wiirzburg, Germany to study P38 kinase -TTP interactions using TTP knockout mice (which were developed at the NIEHS); with scientists at the University ofManchester, UK to resequence the promoter and exons ofthe ZFP36 gene, encoding TTP, in University ofManchester population ofpatients with well-characterized forms ofjuvenile rheumatoid arthritis; at the University of Udine, Italy to resequence the promoter and exons of the ZFP36 from patients with rheumatoid arthritis who either responded or didn't respond to anti-TNF therapy; with scientists at the University of Zurich, Switzerland to study interstitial cell MARCKS and MLP expression in the normal kidney and in kidneys ofmice with fibroproliferative diseases; with scientists in the Department ofApplied Biochemistry and Biology, Faculty of Agronomy, Gembloux, Belgium to study interactions between bovine leukemia virus, HTLV, and TTP in the pathogenesis ofbovine leukemia; with scientists in the Division for Immunology, Zurich University, Switzerland to evaluate TTP and TNF mRNA kinetics and responses in farm children exposed to low or high endotoxin levels; with scientists in the Department ofMolecular Genetics, The Weizmann Institute of Science, Rehovot, Israel to work on MARCKS and MLP in animal models oflissencephaly syndromes; with scientists in the Department ofVeterinary Microbiology,

University of Saskatachewan, Saskatoon, Canada to work on *Trypanosoma congolense* infections in TTP deficient mice; with scientists at the University of British Columbia, Canada to evaluate telomere length in mice deficient in a RECQL helicase, which may have a cancer-susceptible phenotype; with scientists at the Zentrum Molekulare Neurobiologie, Universitat Hamburg, Germany to study MARCKS interacting proteins and peripheral nerve migration; and with scientists in the Department of Pathology, Yonsei University, College ofMedicine, Seoul, Korea to work on mononucleotide repeats in MARCKS sequences in colon cancer. Dr. Blackshear also has a Cooperative Research and Development Agreement with Oxford Glycosciences, Abingdon, UK to look at proteomics modifications in diabetes as indicators of disease status and status of complications.

Dr. Colin Chignell (Laboratory of Pharmacology and Chemistry) has a collaboration with scientists at the Department of Pharmacy, University of Sydney, Sydney, Australia, to study the mechanism of phototoxicity of Lamotrigine (3 ,5-diamino-6-(2,3-dichlorophenyl)-1 ,2,4-triazine), a new anticonvulsant and antidepressant drug.

Dr. Glinda Cooper (Epidemiology Branch) is currently serving on the World Health Organization International Program on Chemical Safety (IPCS) Task Group to compose the Environmental Health Criteria "Scientific Principles and Methods for Assessing Autoimmunity Associated with Exposure to Chemicals." Dr. Cooper is collaborating with scientists in the University Health Network, Toronto, Canada, to study genetic and environmental factors involved in the development of systemic lupus erythematosus (SLE).

Dr. William Copleand (Laboratory of Molecular Genetics) is collaborating with scientists at the Unit ofMolecular Neurogenetics, National Neurological Institute "Carlo Besta," Milan, Italy, to study the consequences of mutations in the gene for the human mitochondrial DNA polymerase that cause progressive external ophthalmoplegia.

Theodora Devereux (Laboratory of Molecular Carcinogenesis) has a collaboration with scientists from Queens University, Kingston, Ontario, Canada to study global expression changes in sets of mouse lung tumor cell lines with different invasiveness based on movement through Matrigel.

Dr. Richard DiAugustine (Laboratory of Molecular Carcinogenesis) was an invited speaker at the Fourth International Symposium on Hormonal Carcinogenesis,
Valencia, Spain, June 21-25, 2003.

Dr. John Drake (Chief, Laboratory of Molecular Genetics) is serving as the DHHS mentor and a collaborator with scientists in Tbilisi, Georgia at the G. Eliava Institute of Bacteriophages, Microbiology and Virology. This is a Biotechnology Engagement Program (BTEP) project entitled "Study of Phage-Specific "Killer" Proteins" to understand just how bacteriophages used as antibiotics kill at the molecular level. He also has a collaborative research program with scientists at the Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw investigating the structural basis of DNA polymerase fidelity and serves on the Executive Board ofthe International Genetics Federation, an umbrella organization of numerous national genetics societies.

Dr. David Dunson (Biostatistics Branch) has a collaboration with scientists in the Department of Statistics, University of Padua, Italy; Department of Applied Statistics and Economics, University

ofPavia, Pavia, Italy; Service de Biostatistiques, Centre Hospitalo-Universitaire, Lyon, France; and Department of Gynecological Endocrinology and Reproductive Medicine, Staedtische, Kliniken Duesseldorf, Germany; to study the role of cervical mucus associated with decline in fertility during aging in humans.

Dr. E. Mitch Eddy (Laboratory ofReproductive and Developmental Toxicology) served as an external examiner for grant applications to the National Health and Medical Research Council, Australia; andwastheco-organizer ofthe16th CongressoftheInternationalFederation of Associations ofAnatomists, Kyoto, Japan. Dr. Eddy has collaborations with researchers in the Department ofLife Sciences, Kwangju Institute of Science and Technology (K-JIST), Kwangju, Korea to produce a conditional mutant for protamine 2; with scientists in the Department of Embryology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel to express and localize calpain-l, -2, and -11 in spermatogenic cells; with scientists at the Instituto de Biologia y Medicina Experimental, Buenos Aires, Argentina to produce a targeted mutation ofthe gene encoding epididymal protein DE; with scientists at the Monash Institute of Reproduction and Development, Monash University, Clayton, Victoria, Australia to study genetics ofhuman male infertility; with scientists in the Laboratory ofExperimental Animals, Department ofMolecular Biology and Immunology, National Institute ofAgrobiological Sciences, Tsukuba, Japan to study regulation ofexpression ofgenes essential for male fertility.

Dr. John French (Laboratory ofMolecular Toxicology) has a collaborations with scientists in the Laboratory of Carcinogenesis and Mutagenesis, The Netherlands National Institute ofthe Environment and Public Health, Bilthoeven, The Netherlands to study the Mechanisms ofDNA Damage and Repair in XPA and XPC deficientmice haploinsufficient in the p53 tumor suppressor gene. Dr. French also organized and chaired an international symposium entitled Alternatives to Carcinogenicity Testing using Genetically Altered Rodent Models for Carcinogen Identification and Mechanism of Action held in Washington, DC, on November 3, 2003.

Dr. Dori Germolec (Laboratory ofMolecular Toxicology) is currently serving on the World Health Organization International Program on Chemical Safety (IPCS) Task Group to compose the Environmental Health Criteria "Scientific Principles and Methods for Assessing Autoimmunity Associated with Exposure to Chemicals."

Dr. Beth Gladen (Biostatistics Branch) has collaborations with investigators at the Institute of Pediatrics, Obstetrics, and Gynecology, Kyiv, Ukraine; the National Medical University, Kyiv, Ukraine; Kyiv Medical Academy of Post-Diploma Education, Kyiv, Ukraine, and the University of Bristol, Bristol, UK to examine pollution and reproductive outcomes in two cities in Ukraine; with scientists at Health Canada, Ottawa, Canada to examine patterns of exposure to different polychlorinated biphenyl congeners in milk samples collected from women across Canada in 1992 in order to determine whether health effects of different congeners could be examined separately; with scientists at the Institut National de Sante Publique de Quebec in Sainte-Foy, Canada; and the Instituto Nacional de Salud Publica, Cuernavaca, Mexico to study effects ofDDT on anogenital distance in newborn boys and early menopause in women.

Dr. Traci MT. Hall (Laboratory of Structural Biology) has a collaboration with scientists at the Agricultural Biotechnology Center, Plant Biology Institute in Godollo, Hungary to determine the three-dimensional structures ofplant viral proteins that suppress post-transcriptional gene silencing.

Dr. Jean Harry (Laboratory of Neurobiology) was a member of the WHO working group, Principles and Methods for the Risk Assessment of Chemicals in Food, Joint Food and Additatives Organization, to update the document of the Food Additive Organization (FAO)/WHO: Principles and Methods for the Risk Assessment of Chemicals In Food, December, 2002; and a member of the External Steering Committee on Aluminum and Animal Neurotoxicity, Health Canada, Ottawa, Canada, to help with the development of a study design to assess the potential for dietary consumption of aluminum in the drinking water and in food to produce deficits in cognitive dysfunction in an aged population, April 2003.

Dr. William Jameson (National Toxicology Program) was the National Toxicology Program representative at the International Agency for Research on Cancer (IARC) Working Group meeting in Lyon, France in February to review nominations to the
IARC and provided guidance on prioritizing these nominations for future IARC Monograph evaluations. The reviews and evaluations ofthis Advisory Group resulted in the publication ofthe IARC Monograph *Reportofan Ad-Hoc Monographs Advisory Group on Priorities for Future Evaluations.*

Dr. Anton Jetten (Laboratory of Respiratory Biology) had collaborations with scientists from the Department of Molecular Medicine, University of Osaka, Osaka, Japan to study the function of the nuclear orphan receptor RORgamma; with scientists at the Department ofMucosal Immunology, University of Tokyo, Tokyo, Japan to study the role of the nuclear orphan receptor in the immune system; with scientists at the Department ofMolecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel to study the function of p63 in the differentiation of esphageal and tracheal epithelium; with scientists at the Department of Structural Biology and Structural Genomics, Institut de Genetique et de Biologie Moleculaire et Cellulaire, Illkirch, France to study the structure of the RORgamma protein; with scientists at the Department of Biochemistry, University of Western Ontario, London, Canada, to study the role of the transcriptional factor Glis3 in muscle differentiation and its connection to wnt signaling; and with scientists at Organon, Oss, The Netherlands, to analyze agonists and antagonists for the nuclear receptor RTR/GCNF.

Dr. Maria Kadiiska (Laboratory of Pharmacology and Chemistry) has a collaboration with scientists at the Faculty of Medicine, Uppsala University, Uppsala, Sweden; the Heart Research Institute, Sydney, Australia; the Unilever Health Institute, Vlaadrdingen, The Netherland; University of ESSEX, Colchester, UK; and Otto-Von-Guericke University, Magdeburg, Germany, to study biomarkers of oxidative stress.

Dr. Steven Kleeberger (Chief, Laboratory of Respiratory Biology) has a collaboration with researchers at the National Institute of Health and Medical Research, INSERM, Paris to investigate the genetic basis for susceptibility to the effects of coal dust in miners; and with scientists at Johns Hopkins University to study the role of toll-like receptors in respiratory syncytial virus (RSV) infection and disease progression in infants and children. The clinical portion of this study is currently being conducted in Buenos Aires, Argentina.

Dr. Thomas Kunkel (Chief, Laboratory of Structural Biology) has collaborations with scientists at the Graduate School of Engineering Science and Graduate School of Frontier Biosciences at Osaka University, Osaka, Japan; Dept ofMedical Biochemistry and Biophysics, Umea University, Umea, Sweeden; and the Centro de Biologia Molecular Severo Ochoa, Universidad Aut6noma, Madrid, Spain, to investigate the functions

and fidelity of human DNA polymerase eta, epsilon and lambda, respectively.

Dr. Larry Lazarus (Laboratory of Computational Biology and Risk Analysis) has collaborations with scientists at the Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan and the Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy on the synthesis and functional bioactivity ofunique opioid mimetic substances with specificity for the d-and mopioid receptors; and with scientists at the CNRS/INSERMIULP, Illkirch Cedex, France, to study the inverse agonist properties ofd-opioid receptor antagonists.

Dr. Stephanie London (Epidemiology Branch and Laboratory ofRespiratory Biology) has collaborations with scientists at the National Institute of Public Health, Cuernavaca, Mexico to study the genetics of childhood asthma in Mexico City; with investigators at the National University in Singapore and the University of Southern California to investigate the relation between diet and the incidence of asthma and chronic bronchitis in a cohort of 63,000 adult Singaporeans of Chinese ethnicity; and with scientists at the Wuhan Public Health and Anti-Epidemic Station and the University of Southern California to study indoor air pollutants in relation to childhood respiratory symptoms.

Dr. Matthew Longnecker (Epidemiology Branch) has collaborations with scientists at the Erasmus University, Rotterdam, The Netherlands to study the effects of exposure to phthalates, bisphenol A, and organophosphate pesticides; andresearchers at the National Institute ofPublic Health in Cuernavaca, Mexico to examine the relation between maternal serum levels of the androgenic DDT metabolite DDE in relation to anthropometric measures in 200 male newborns in Tapachula, Mexico, where there has been recent, high-level exposure to DDT.

Dr. Heinrich MaIling (Laboratory of Molecular Toxicology) has a collaboration with scientists in the Department of Psychology, Section ofNeuroscience, University La Sapienza of Rome, Rome, Italy, to study the role of PhiX in neuronal function. Dr. MaIling was on the program committee for the 5th International Environmental Mutagen Societies meeting in San Francisco in Sept 2005 and chairman ofthe Symposium on Mutagenic effects ofNano Particles.

Dr. James Mason (Laboratory ofMolecular Genetics) has collaborations with scientists at the Institute of Science History and Technology, Russian Academy of Sciences, St. Petersburg, Russia, to characterize telomere-telomere interactions in *Drosophila;with* scientists at the Institute ofGene Biology, Russian Academy of Sciences, Moscow, Russia, to identify and clone a second mutation that increases telomere length in *Drosophila;* and with scientists in the Laboratory ofMolecular Cytogenetics, Institute of Cytology and Genetics, Russian Academy ofSciences, Novosibirsk, Russia, to study chromatin structure of*Drosophila* telomeres as it relates to the transcriptional activity oftransgenes inserted into telomeric regions.

Dr. Scott Masten (National Toxicology Program) has a collaboration with scientists at the University ofMilan, Milan, Italy, to study gene expression in people environmentally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a result ofan industrial accident in Seveso, Italy.

Dr. Ronald Melnick (National Toxicology Program) has a collaboration with scientists at the Information Technologies in Society, Zurich, Switzerland to study dosimetry modeling ofrats and mice exposed to radiofrequency radiation in reverberation chambers. Dr. Melnick also participated in meetings of the International Advisory Committee and the Research Coordination Committee of

WHO's International Electromagnetic Fields Project. These were held in Geneva, Switzerland in June 2003.

Dr. B. Alex Merrick (National Center for Toxicogeniomics) was an invited speaker at the IPCS Workshop on Toxicogenomics and the Risk Assessment ofChemicals For the Protection of Human Health, Berlin, Germany, November 17-19,2003; and at International Meetings ofthe Human Proteome Organization, June 17-19,2003 and April 21-22, 2004, Bethesda, MD.

Dr. David Miller (Laboratory of Pharmacology and Chemistry) has collaborations with scientists at the Department of Pharmacology & Toxicology, Nijmegen Center for Molecular Life Sciences, Nijmegen, The Netherlands to characterize the regulation ofxenobiotic export pumps in renal proximal tubule; and with scientists at the Institute for Pharmacy and Biotechnology, University of Heidelberg, Heidelberg, Germany to characterize the role ofdrug export pumps in blood-brain barrier function.

Dr. Fred Miller (Office ofClinical Research) co-chaired with Dr. Lisa Rider (Office of Clinical Research) the International Workshop on Myositis Outcome Measures and Clinical Trial Design Issues. Dr. Miller is also a member of The International Myositis Collaborative Study Group with scientists from Montreal, Canada; Santiago, Chile; Guatemala City, Guatemala; Mexico City, Mexico; Guadalajara, Mexico; Aachen, Germany; Nijmegen, The Netherlands; Warsaw, Poland; Glasgow, Scotland; Barcelona, Spain; Stockholm, Sweden; New Delhi, India; Tokyo, Japan; and Seoul, South Korea which has been organized to collect standardized data and specimens on myositis patients.

Dr. Yuji Mishina (Laboratory of Reproductive and Developmental Toxicology) has a collaboration with scientists at the Brain Science Institute, RIKEN, Saitama, Japan
Group to uncover the function ofbone morphogenic protein signaling in brain development.

Dr. Masahiko Negishi (Laboratory of Reproductive and Developmental Toxicology) organized a Symposium for the Nagano Society for the Regulation of Gene Expression
Nagano, Japan, November 2003.

Retha Newbold (Laboratory of Molecular Toxicology) worked with DES Action International providing scientific information on DES exposure and animal models and with the World Wildlife Fund reviewing proposals and providing scientific information on endocrine disrupting chemicals. Ms. Newbold also has collaborations with scientists at the University of Rome "La Sapienza," Italy to study effects of environmental estrogens on development ofbone tissue; with scientists at the University of Karlsruhe, Germany to study effects of genistein and daidzein on the developing reproductive tract; with scientists at the University Hospital of Copenhagen, Denmark to study effects of genistein on the developing ovary; with scientists at Bar-ilan University, Ramat-Gan, Israel to test a natural antioxidant found in spinach for hormonal activity; and with scientists at the Okazaki National Research Institute, Japan to study effects of endocrine disrupting chemicals on the developing reproductive tract using fetal or neonatal mouse models.

Dr. John O'Bryan (Laboratory of Signal Transduction) has a collaboration with scientists at the Max-Planck Institute ofNeurobiology, Munich-Martinsried, Germany; to study the involvement of the intersectin scaffold in the endocytosis ofEph receptor tyrosine kinases and their membrane ligands the ephrins.

Dr. Richard Paules (National Center for Toxicogeniomics) was an invited speaker at the EU-US Workshop on Molecular Signatures of DNA Damage Induced Stress Responses, Cortona, Italy, September 24-0ctober 4, 2003; and met with scientists at Gifu University, Gifu-shi, Japan, January 27-31, 2004, to discuss the most recent advances in technologies and applications ofgenomics to toxicological problems as well as strategic planning for predictive toxicogenomics and translation to benefits for human health.

Dr. John Pritchard (Chief, Laboratory of Pharmacology and Chemistry) has collaborations with scientists at the Universitaet Goettingen in Goettingen, Germany to study the evolution of xenobiotic transporter gene structure and function; and with scientists at Mahidol University, Bangkok, Thailand to study the roles of two human transporters (hOATI and hOAT3) in the elimination ofstevioside, a natural non-caloric sweetener, and its metabolites.

Dr. James W. Putney (Laboratory of Signal Transduction) is currently the Newton-Abraham Visiting Professor in Medical, Biology and Chemical Sciences in the Department of Physiology, Oxford University, Oxford, England, were he is studying the electrophysiology of capacitative calcium entry in cells. Dr. Putney will give the annual Newton-Abraham Lecture in Medical and Chemical Sciences at Oxford, England, Spring 2004.

Dr. Michael Resnick (Laboratory of Molecular Genetics) organized an international meeting "Functional consequences ofTP53 mutations" to be held at IARC, in Lyon, France, from June 30 to July 3, 2003 to explore the importance ofvarious p53 functional mutations and their relevance to cancer as well as to develop further the existing p53 database as IARC.

Dr. John Roberts (Laboratory of Molecular Carcinogenesis) has a collaboration with scientists at the First Department of Surgery, Osaka City University, Osaka, Japan to study the role of the PI3K1Akt pathway in the adhesion and spreading of a human cell gastric carcinoma.

Dr. Dale Sandler (Chief, Epidemiology Branch) has a collaboration with researchers at the Prague Institute of Advanced Studies, Prague, Czech Republic and the Center for Epidemiological Studies, Pribram, Czech Republic to study cancer risk among underground uranium miners in the Czech Republic.

Dr. Roel M. Schaaper (Laboratory of Molecular Genetics) has collaborations with scientists at the Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland to study mechanisms of DNA replication fidelity; and with scientists in the Department of Genetics, St. Petersburg State University, St. Petersburg, Russia to study base analog detoxification by molybdenum-dependent activities, research that is supported by a Collaborative Linkage Grant awarded by NATO.

Dr. William Stokes, (National Toxicology Program and Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods) in collaboration with the European Centre for the Validation of Alternative Methods designed and initiated a multi-laboratory international study to evaluate the usefulness of cytotoxicity data from the BALB/c 3T3 Neutral Red Uptake (NRU) and the Normal Human Keratinocyte (NHK) NRU assays for estimating the acute oral toxicity potential oftest substances; the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), ECVAM; and NICEATM are collaborating to conduct a

validation study on three in vitro test methods for assessing dermal irritation; in March 2003, ICCVAM and ECVAM made joint presentations to a subcommittee of the OECD Good Laboratory Practice (GLP) Working Group on the need for further international guidance on the application of GLPs to in vitro toxicological testing. International Conference on Validation and Regulatory Acceptance was held in Stockholm, Sweden, from March 6-8, 2002 released at document entitled, "The Development, Validation and Regulatory Acceptance ofNew and Updated Test Methods in Hazard Assessment" in October of2003. Dr. Stokes also participated in the ECVAM Workshops on Strategies to Replace In Vivo Acute Systemic Toxicity Testing, held September 15-18,2003 and on Validation Principles and Approaches for Toxicogenomics-Based Test Systems, held December 1112,2003.

Dr. Kenneth Tomer (Laboratory of Structural Biology) served as an expert in separations for the International Human Proteome Organization Consortium, coordinating development of microfluidic/mass spectrometry approaches to proteomics.

Dr. Bennett Van Houten (Laboratory of Molecular Genetics) has collaborations with scientists in the Department of Molecular Genetics, Cancer Research Institute, Slovak Academy of Sciences, Vlarska Bratislava, Slovakia, to study the bacterial UvrABC DNA repair system; and with scientists at the Novosibirsk Institute of Bioorganic Chemistry, Siberian Branch of Russian Academy of Sciences, to study DNA contact sites ofnucleotide excision repair proteins. Dr. Van Houten was an invited speaker at the Genetic Toxicology Gordon Research Conference, Oxford, UK.

Dr. Clarice Weinberg (Chief, Biostatistics Branch) is involved in a collaboration with a reproductive genetic epidemiologist at McGill University, Montreal, Canada, who is studying genetic effects on intra-uterine growth retardation, on gestational survival, and on childhood cancers; and is a co-investigator ofa multinational research project on a birth defect, oral clefting (cleft lip and cleft palate) with scientists at the University of Bergen, Bergen, Norway and with scientists in Denmark.

Dr. Michael Waters (National Center for Toxicogeniomics) has a collaboration with scientists at the European Bioinformatics Institute (EBI), Hinxton, United Kingdom, to develop international toxicogenomic database standards and has addressed the technical problems involved in microarray and toxicology data upload, the demand for standardizing data storage and exchange formats, the requirement for identifying minimal descriptors to represent toxxicogenomics experiments, the definition ofparameters that assess and record data quality and the creation of standardized nomenclature and ontologies to describe biological data.

Dr. Samuel H. Wilson (Laboratory of Structural Biology and Deputy Director) was an organizer and keynote speaker at the EU-US Workshop on Molecular Signatures of Stress-Induced DNA Damage Responses held at Centro Convegni S. Agostino, Cortona Sviluppo, Cortona, Italy, September 26-30,2003; organized and chaired a session at the First US-EU DNA Repair Meeting: Endogenous Stress, held at National Conference Center, Leesburg, VA, October 14-18, 2003; and organized the 2nd Japan-U.S. DNA Repair Meeting, held at the Marriott Ihilani Resort, Ko Olina, Hawaii, June 4-8, 2004.

Dr. Jerry Yakel (Laboratory ofNeurobiology) had a collaboration with scientists at Biophysics Sector and INFM Unit, International School for Advanced Studies (SISSA), Trieste, Italy to study Ca^{2+} regulation of nicotinic acetylcholine receptor channels in rat hippocampal neurons.

Dr. Darryl Zeldin (Laboratory ofRespiratory Biology) had a collaboration with scientists at the University of Bochum and St. Josef Hospital, Bochum, Germany to study variants in the human *CYP2J2* gene and with scientists at the Tongji Medical Center, Tongji, Peoples Republic of China to study the regulation ofendothelial nitric oxide synthase (eNOS) by endothelium-derived hyperpolarizing factors (EDHF) and the relevant signaling pathways involved. Dr. Zeldin was the organizer ofa Symposium on Eicosanoids in the Cardiovascular System, International Winter Eicosanoid Meeting (March 2004).

NATIONAL TOXICOLOGY PROGRAM
UPDATE
MAY 2004

NTP Contributions Receive Society of Toxicology Awards

Dr. Kenneth Olden, Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) was presented the Public Communications Award at the 43rd Annual Meeting ofthe Society ofToxicology (SOT) on March 21,2004, in Baltimore, Maryland. The citation read: "His exemplary leadership of the NIEHS has fostered a strong human disease outcome focus to guide environmental health research and has served as a model for effective integration and focusing ofbasic research on human and environmental health issues ... His ability to reach all audiences and tireless commitment to bettering the health ofthe public-at-Iarge makes him one of our discipline's most effective advocates and communicators." Dr. Olden is a Fellow of the Academy ofToxicological Sciences and has championed a strong relationship between the NIEHS and SOT through many initiatives, including teacher training workshop, underrepresented minority education programs and NIEHS-sponsored symposia at SOT annual meetings.

Toxicological Sciences Best Paper Award

Dr. Abraham Nyska of the Laboratory ofExperimental Pathology, NIEHS, is a co-author on the paper entitled *Inhaled Environmental Combustion Particles Cause Myocardial Injury in the Wistar Kyoto Rat (ToxSci* 71:237-245,2003) that was selected by the Board of Publications to receive the SOT Award for Best Paper in Toxicological Sciences published during the past year. The paper presents comprehensive work showing cardiac effects due to particulate matter (PM) in rats under experimental conditions relevant to human exposure. The authors comprise a team of scientists from the NIEHS, the Environmental Protection Agency (Drs. Urmila P. Kodavanti, Allen D. Ledbetter, Mette C. Schladweiler and Daniel L. Costa), the Harvard University School of Public Health (Drs. Russ Hauser and David C. Christiani) and Pathology Associates (Dr. Carolyn F. Moyer). With expertise in inhalation toxicology, cardiac pathology and occupational health, the scientists worked collaboratively on characterization of the particles' composition and extent of myocardial injury and on identifying the potential causative agent(s). Zinc was the predominant metal in the particles and the findings suggest that particle-associated zinc may playa role in myocardial damage. The paper provides the first clear evidence of the effect of PM on the heart, and provides supportive evidence for previous epidemiological associations between exposure to ambient PM and cardiovascular morbidity.

NTP Vision Activities

The NTP sponsored a public meeting to receive comment on the vision and elements for a roadmap at the National Library of Medicine's Lister Hill Auditorium on January 29, 2004. A panel conposed of members of the three working groups for the vision (see below) received the comments and provide remarks to the NTP. The NTP Board of Scientific Counselors Working Group for the Vision met with invited constituents and experts to discuss input and strategies for implementing the road map for the NTP Vision in Baltimore on March 25, 2004 at the time ofthe SOT. The Board Working Group is one of three work groups that includes an internal NIEHS Working Group and the NTP Executive Committee Working Group. The work groups have been charged independently to make reports on the input for the roadmap. The NTP will provide opportunity for public input on the vision and elements for the roadmap at the upcoming NTP Board of Scientific Counselors meeting in June (see below) and will hold a retreat this summer to complete the roadmap. The roadmap rollout for the vision is expected to be in the fall.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Federal Agency Responses to ICCVAM Test Recommendations

The Interagency Coordinating Committee on the Validation of Alternative Methods (lCCVAM) under NICEATM, coordinates the development, validation, acceptance and harmonization ofnew, alternative and revised toxicological test methods. The NTP published a notice in the *Federal Register* (Vol. 69, No. 47, pages 11448 -11449) on March 10,2004, announcing the availability of Federal agency responses to ICCVAM test recommendations for the revised Up-and-Down Procedure for determining acute oral toxicity and *in vitro* methods for assessing acute systemic toxicity

Center for the Evaluation of Risks to Human Reproduction (CERHR)

CERHR Expert Panel to Evaluate Acrylamide

The CERHR will hold an expert panel evaluation of the potential reproductive and developmental hazards associated with exposure to acrylamide on May 17-19,2004, at the Holiday Inn Old Town Select in Alexandria, Virginia. This meeting is open to the public with opportunity for public comment. Sections 1-4 ofthe draft expert panel report on acrylamide are now available electronically on the CERHR web site (http://cerhr.niehs.nih.gov) along with details about the meeting.

CERHR Expert Panel Report on Fluoxetine Available

The Fluoxetine Expert Panel Report is available on the CERHR web site. Public comments on the report are requested *[Federal Register* April 29, 2004 [Vol. 69, No. 83] and will be used by the NTP in preparing the NTP brief -the program's opinion on the potential reproductive and/or developmental hazard to humans associated with exposure to fluoxetine. A 12-member expert panel composed of scientists from the federal government, universities, and private companies conducted the evaluation of the reproductive and developmental toxicities of fluoxetine hydrochloride on March 3-5, 2004 in Alexandria, Virginia.

NTP Board of Scientific Counselors

The NTP Board is set to meet on June 29, 2004, at the NIEHS. Tentatively on the agenda for discussion are the NTP Vision for the 21 sl Century, including a report on recommendations forthe roadmap from the three external groups for the NTP vision (working groups ofthe NTP Board, NTP Executive Committee, and the NIEHS), recommendations for nominations to the **11** th Report on Carcinogens by the NTP Board Report on Carcinogens Subcommittee, actions on draft NTP Technical Reports by the Technical Reports Review Subcommittee, and a report by a working group of the NTP Board on statistical methods for evaluation offindings in phototoxicology studies. Additional items may be added as the agenda is finalized.

NTP Satellite Symposium on Hepatic Pathology

The NTP will sponsor a satellite symposium on Saturday, June 12,2004, before the start ofthe Society of Toxicologic Pathology Annual Meeting. The annual meeting is scheduled for June 13 17, 2004, at the Grand America Hotel in Salt Lake City, Utah. The format for the satellite symposium, which includes audience participation, will be the same as the one used at the 2004 meeting in Savannah. Audience response units (for audience voting and instant display ofthe results) will be provided during the satellite symposium. The emphasis for the cases will be hepatic lesions although non-hepatic lesions will also be included.

The Center for Neurotoxicology and Exposure Assessment
University of Medicine and Dentistry of New Jersey and Rutgers, the State Univeristy of New Jersey

The Center for Childhood Neurotoxicology and Exposure Assessment initially had 5 inter-related clinical and basic science studies. The overall aim of the Center is to address the effects of environmental chemicals on neurodevelopment and especially in regards to the expression of autism. Children with autism have several features that suggest that their autism may be altered by environmental factors including chemicals. These factors include altered brain growth during prenatal and postnatal development, regression or loss of function in almost a third of the children at the time the children begin to explore their environment, chemicals such as thalidomide that appear to increase the incidence of autism, and the possibility that the incidence of autism is increasing in the population. The original 3 basic science studies will be briefly presented which study the effects of environmental chemicals on neurogenesis and regional brain growth; adhesion and repulsion molecules; and a developmental animal model of chemical induced regression and retardation. In addition, 3 other exciting studies that have been added to the Center's scope of work will be discussed including gene environmental studies and computational toxicology. Lastly the Center's two clinical studies will be presented that address the two main hypothesis that children with autism may be at higher risk of exposure to environmental chemicals as compared to controls and the expression of regression and altered brain growth in children with autism may be related to exposure to environmental chemicals and a potential gene-environment interaction. The interaction between all of the clinical and basic studies will be highlighted as well as the Center's activities reaching out to other NIH and CDC autism and none autism Centers to conduct collaborative work as well as the autism community and other communities.

ADVERSE NEUROBEHAVIORAL CONSEQUENCES OF LOW-LEVEL EXPOSURE TO ENVIRONMENTAL TOXINS: THE CINCINNATI CHILDREN'S ENVIRONMENTAL HEALTH CENTER

Bruce P. Lanphear, M.D., Kim N. Dietrich, Ph.D., Cynthia F. Bearer, M.D., Ph.D., Robert Kahn, M.D., Kimberly Yolton, Ph.D., Richard Hornung, Dr.P.H., Douglas Ris, Ph.D., John Wright, Ph.D., Kim Cecil, Ph.D., and Dana Barr, Ph.D., with the Cincinnati Children's Environmental Health Center, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio, Case Western Reserve University, Cleveland, Ohio, and the Centers for Disease Control and Prevention, Atlanta, GA.

Background: There is increasing evidence that environmental exposures during fetal development and early childhood are major contributors to disease and disability in childhood and adulthood.

Introduction: The adverse neurobehavioral effects of fetal and early childhood exposures to numerous environmental toxins, including lead, mercury, PCB's and environmental tobacco smoke (ETS), are reasonably well established. Still, many studies linking environmental toxins with neurobehavioral and reproductive effects typically involved children who had relatively high exposures or relied almost entirely on observational studies. The relationship of exposures to other environmental toxins, such as pesticides, and the interaction of various toxins are unclear. Moreover, the best biomarkers to measure fetal exposure to toxins are uncertain.

Methods: Our Center is undertaking numerous studies to identify and validate biomarkers of fetal and early childhood exposure to prevalent toxins, including maternal hair, maternal blood and urine, cord blood and meconium. We are also conducting randomized controlled trials to examine the effect of reducing exposures to environmental hazards, such as lead, ETS and physical hazards. In two existing longitudinal cohorts, we are examining the long-term consequences of exposure to prevalent toxins, including the relationship of childhood lead and ETS exposure with dental caries, criminality and ADHD. Finally, we are exploring gene-environment interactions to enhance our understanding of mechanisms of disease and identify susceptible populations.

Implications: These longitudinal studies will test whether low-level exposure to prevalent toxins is associated with prevalent diseases and disorders in children. Moreover, while observational studies are important, we will test the safety and efficacy of interventions to lower exposures to prevalent and persistent toxins using randomized trials. The Children's Environmental Health Centers offer a tremendous opportunity to conduct translational, community-oriented research to explicate underlying mechanisms of disease and prevent disease and disability.

The National Institute of Environmental Health Sciences Coordinating Center for Rodent Genetics

("CRG")

Prepared by William T

Schrader, Ph.D.[1] Deputy

Scientific Director NIEHS

April 28, 2004

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Introduction

Recent advances in molecular genetics and genomics, including the completion of The Human Genome Project, have changed the landscape of biological research and brought focus to the importance of human genetics in human biology. The role of genetic mutation in human heritable disease has been firmly established for many years. However, it is now apparent that genetic components influence susceptibility to and progression of many acute and chronic human diseases as well as normal human development, reproduction, aging and behavior. Some human diseases have both inherited and sporadic forms, indicating that a phenotype can correlate to multiple genotypes; this observation also reflects the fact that both germ line and somatic mutation play roles in human disease pathology. In addition, numerous biological characteristics and pathological states result from the coincident influence of several genetic factors, further increasing the complexity of the genetic component of biological characteristics. It has also recently been recognized that epigenetic factors play a significant role in many human diseases including cancer, adding still another layer of complexity to the genetic component of human biology.

In parallel with the revolution in molecular genetics and genomics, there is increasing awareness of the interconnectedness of human health and environmental health and of the fragility of the environment in which humans live. Human industrialized civilization is having a large impact on the health of the local and global biological and physical environment, and the reciprocal effect of the environment on human health is equally significant. Historically, the effort to understand the interplay between the environment and human health has been considered primarily the domain of toxicology. Toxicologists have relied heavily on relatively well-established approaches, especially long-term rodent bioassays that detect biological endpoints of late disease (Le., tumor development) or acute clinical signs of toxicity. However, the field of toxicology has recently begun the process of reinventing itself, in light of the rapid state of technological and conceptual change in molecular biology and genomics. It is impossible to ignore the value and potential of targeted analysis of the genetic components of toxic responses. Such targeted research is possible, because of dramatic advances in the ability to analyze and manipulate the genomes of animal model systems, including rodent model systems, and to correlate results in these animal models to humans. Thus, the new fields of toxicogenomics and pharmacogenomics have recently emerged to exploit these new research opportunities. As a result, significant advances are being made in understanding the genetic basis of disease susceptibility and drug efficacy.

Rodent models (and cell lines derived from them) are essential tools in biomedical research because they allow researchers to systematically ask and answer questions about a defined biological system. Rodent-derived studies are especially useful and informative in toxicology and pharmacology research, because one can readily manipulate the timing and magnitude of exposure to a specific agent and measure the dose-response relationship using quantitative methods. This approach lies at the heart of both traditional toxicology testing to identify human health hazards and compound evaluation for discovery of pharmaceuticals. In addition, animals at various stages of an exposure-disease continuum can be used in biomarker development. In this way, the

stages of response including early pathobiology, pre-clinical disease, and clinical disease states can be assessed individually for stage-specific molecular indicators. Such indicators can provide important leads for development of biomarkers for human disease.

Since the late 1980s when the first "designer mice" were developed for studying cancer susceptibility, researchers have been mouse strains for specific research purposes. Some strains, such as Oncomouse M strains, are considered general research tools. Many of these strains are commercially available and are now considered essential "reagents" in laboratories that use the mouse as an experimental model. Other strains are excellent models for specific human diseases including diabetes, obesity, Parkinson's disease, xeroderma pigmentosum, severe combine immunodeficiency disease and others, or are targeted disruptions of specific genes.

Purpose

The purpose of this document is to bring awareness to the importance of rodent models in fulfilling the promise of modern toxicogenetic and pharmacogenetic research in keeping with the NIEHS Mission. When this awareness is coupled with a desire to promote rapid progress in understanding, preventing and treating human disease and a recognition of the importance of efficient use of valuable research funding and other resources, the need for a mechanism to coordinate and promote leading edge research in rodent genetics and toxicogenetics seems imperative. Such an interdisciplinary program will have several essential components, an important one being the collection, maintenance and dissemination of engineered mouse models for disease susceptibility and modern toxicology research. This program will also create and maintain a database on rodent toxicogenetics, provide core services to the research community including essential genetic characterization, phenotyping and toxicology assays, and promote rodent toxicogenetics research and training through the NIEHS extramural program. Therefore, it is timely to establish a structure to coordinate these activities across all of the NIEHS enterprise. Because this endeavor will be relevant and valuable to scientists in many sectors of the biomedical community, the program is expected to evolve as an initiative tightly linked to other interested NIH Institutes or organizations. Because the program is envisioned primarily as an umbrella structure to facilitate productive use of resources, the name for the program is the Coordinating Center for Rodent Genetics (CRG).

Background

The mouse is a major research tool for the study of human disease and biologic mechanisms for several reasons. The genomes of mice, humans and other placental mammals are highly conserved, such that almost all human genes have counterparts in the mouse genome recognizable by cross-species hybridization. The haploid size of the mammalian genome billion base pairs) and its underlying genomic organization has remained relatively constant. Thus, the cloning of a human gene often leads directly to the cloning of a mouse homolog, or the reverse. The mouse is the most developed mammalian model system offering highly developed traditional genetic techniques, a rich pathology database, excellent animal husbandry techniques, molecular genetic techniques including the ability to construct specific gene-altered strains by gene

targeting and a complete reference genomic sequence. Other advantages of the mouse as a representative mammal include its small size, short generation time and high fertility rate under laboratory conditions.

Mouse and rat rodent models are used in virtually all the sciences upon which U.S. environmental regulatory policy is based. The National TOXicology Program (NTP), the Food and Drug Administration and the pharmaceutical industry are all heavily invested in rodent model systems in part because of the massive amount of historical toxicology and efficacy studies that have employed these model systems.

A highly developed infrastructure to support research using rodent models is needed to optimize progress in toxicology and other fields of biomedical research. Furthermore, such an infrastructure will conserve research resources and promote efficiency by 1) disseminating useful and novel research tools and information, 2) facilitating collaborative efforts and 3) reducing duplication of effort. It should be emphasized that it requires sizeable resources to generate mice strains and maintain large healthy rodent colonies. Because it is so costly to establish and maintain the infrastructure for state-ofthe-art rodent genetics research, even a modest increase in efficiency could have a large impact on bottom line costs and resource utilization.

Center (CRG) Program Components

Management Structure

The CRG is expected to require a small administrative/management component at NIEHS. This program will be directed from the Office of the Director, NIEHS, as it will involve both intramural and extramural components of NIEHS.

Repository/Database

The CRG will exist to improve the infrastructure at NIEHS and its sister Institutes for development and study of specific mouse lines that are useful in toxicology research. A main component of that infrastructure is a first class mouse repository/database that solicits, maintains and distributes relevant mouse strains including strains that are highly specialized for specific experimental purposes. All grantees and intramural researchers will utilize this repository, and the mouse models they generate will populate the repository/database.

Services Cores

Many state-of-the-art technologies are needed to characterize mouse models. It would therefore be highly appropriate, as suggested here, to centralize expertise and equipment for basic mouse strain characterization, because this effort will promote efficiency and lower costs. The CRG proposes to evaluate providing selected core services, such as: DNA/protein sequencing, global gene expression analysis (Le., microarray, proteomics), pathology/histopathology, transgenic strain construction (knock-ins, knockouts) and imaging. Effort will be made to eliminate redundancy within NIEHS and other ICs for these services, and all NIEHS scientists working with rodent models will be encouraged to utilize the CRG or other NIH service cores.

Ongoing eRG Activities in Mouse Toxicogenetics

Resequencing Project

The laboratory mouse population includes more than 50 highly inbred laboratory strains and thousands of mutant mouse strains that have been selected for specific phenotypic traits. The inbred laboratory mouse strains each have a unique fixed genotype, so they can be manipulated in the laboratory as a group of homogeneous experimental subjects, with reproducible phenotypes and defined allelic composition. Despite the many advantages of the inbred mouse strains commonly used in laboratory research, the genetic factors that determine strain specific differences remain poorly characterized. In addition, genetic linkage studies in inbred mice can be difficult and it remains a tedious process to map genetic interactions in the mouse. Recognizing this fact, a recent discussion of the future of mouse genomics stated that adequate future progress requires "improved methods to map [and identify] mutant genes" and that "technology for genotyping SNPs may yield the necessary cost, scale and efficiency to map large numbers of mutant genes." [Science 291. 1253. (2001).]

The phenotypes of many inbred mouse strains are characterized by unique responses to environmental toxicants and pharmaceuticals. The molecular mechanisms for such strain specific properties are well understood only in a limited number of cases. Therefore, the laboratory strains are a rich source of experimental material for gene and pathway discovery, and valuable insight into toxicological mechanisms might be gained if these strains were systematically studied using genotype-phenotype association approaches, and if the genetic characterization of these strains were also accelerated.

Therefore, to maximize the usefulness of laboratory mouse strains and to stimulate use of the laboratory mouse in gene-environment interaction research, the NIEHS is establishing a mechanism to create a dense SNP map of the mouse genome by sequencing the non-repetitive portion of the genome in up to fifteen mouse strains chosen for their applicability to environmental health research and toxicology. Construction of this map will be initiated shortly, using high-throughput DNA sequencing. Based on preliminary sequencing experiments using genomic DNA from several mouse strains, it is estimated that the mouse SNP map will be remarkably dense, with approximately 1 polymorphic site per 150-400 bp. The CRG will coordinate this project with other related strain characterization activities and will ensure that the SNP data are widely available to mouse geneticists via the CRG database/website and other sources.

Extramural Research Activities

NIEHS currently supports over 250 extramural research initiatives that use or generate mouse models for mechanism-based environmental health research, studies of disease-associated susceptibility factors and toxicology. Two of the most important of these projects are (a) investigator-initiated research grants and (b) the Comparative Mouse Genomics Centers Consortium (CMGCC) (part of the Environmental Genome Project or "EGP"). The CMGCC has assembled a nationwide team of participating academic research centers, each headed by a prominent environmental scientist with specific research interests related to gene-environment interactions. Five centers are

currently operating under this arrangement. These activities already contribute to advances in mouse toxicogenetics research.

The main function of the CRG will be to stimulate additional research activity involving rodent models through various approaches. These approaches will be identified through a series of workshops that will include interactions with the Institute's National Advisory Council.

Institute-wide Training

NIEHS has been a leader in the use of rodent models in toxicology. Therefore, there is significant expertise in both mouse genetics and toxicology in the NIEHS portfolio at present. However, it will be important to encourage and provide incentives to scientists to enter this field. This is especially important given the rapid rate of change in the technologies that are available for toxicogenetic research. Thus, the CRG proposes to enhance training opportunities in toxicogenetics, whose purpose will be to recruit and retain outstanding students and professional scientists in this field of research. A small intramural project currently targets postdoctoral trainees who enter a laboratory setting with the dual objectives of carrying out hypothesis-driven bench research and evaluative studies of environmental agents via existing experimental methods. The expanded program will target entry-level toxicologists as well as senior investigators. Career advancement opportunities will also be promoted, including seminar programs, workshops, and an annual symposium at relevant national meetings.

Comparative Mouse Genomics Centers Consortium (CMGCC)

The goals of the Consortium are:

1) To identify relevant and feasible mouse models to be developed by the Consortium;

2) To identify mouse models that are relevant to human environmental health; and

3) To validate mouse models that are relevant to human environmentally-induced disease.

The Environmental Genome Project (EGP) was established by NIEHS to study how variation in human DNA sequences (genetic polymorphism) influences susceptibility to environmentally-induced disease. The knowledge developed by the EGP will be used to improve understanding of gene-environment interactions, and provide an enhanced science-based framework for environmental policy. The ultimate goal of the EGP, and of policies based on EGP research, is to prevent adverse effects from environmental exposure and to protect subset of individuals who are at higher risk for these adverse events.

The CMGCC was initiated by the EGP to develop transgenic and knockout mouse models based on human DNA sequence variants in environmentally responsive genes. These mouse models are tools to improve understanding of the biological significance of human DNA polymorphism. Initially, CMGCC is focusing on variation in genes involved in DNA repair or cell cycle control. These were chosen because many of them are well-characterized environmentally responsive genes and function in pathways that

have been validated by association with human disease phenotypes. Environmentally responsive genes also play roles in cell division, cell signaling, cell structure, gene expression, apoptosis, membrane channels, and metabolism.

Mutant mouse models generated by CMGCC to date include: CHK 2, Cyclin D1 b, Rb, msh2, msh6 ,mlh1, pms2, pcna, pol gamma, eta, zeta, mu, Fen1, XPV, Cyclin D1, p21, E2F1, Brca1, PTEN, p53, Pol beta, Ercc1, Xpa, Ercc2 (XPD), XRCC1, ATM, MGMT, WRN, OGG1, APEX, p27, PRKR, Ligase 4.

Intramural Research Activities

NIEHS commercial contracts are already in place for generating selected mouse targeted genetic mutant strains as proposed by intramural scientists. These activities will be monitored within the coordinated CRG program as appropriate. Some activities under the topic of service cores (Le., bioinformatics) may require additional contract or grant support.

Mouse models carrying an engineered or spontaneous alteration in a single gene are important tools for determining the role of a gene in a particular biochemical pathway. Gene deletions ("knock-out mice"), additions ("transgenic mice") and time-tissue-or sequence-specific alterations ("knock-in" or "conditional knockout" mice) are engineered using recombinant DNA technology, which allows virtually any mouse gene to be systematically altered. The recombinant mice carry the genetic mutation in all cells including germ line cells, enabling the defect to be transmitted to all progeny. The NIEHS intramural program has a contract mechanism in place for generating such transgenic/knockout mice on an as needed basis. The contract will generate up to 26 genetically engineered mouse lines per year.

When complete deficiency of a gene is lethal or when it interferes with normal development, a knockout model is not sufficient to analyze the function of that gene. In these cases, a conditional knockout has the potential to be much more informative. These animals are engineered to lose gene function in a tissue-or time targeted manner. NIEHS has identified approximately 40 mouse genes for which conditional knockout mouse lines will be especially valuable for ongoing research in environmental health issues.

National Toxicology Program Activities

The mission of the NTP is to coordinate toxicological evaluation programs within the Department of Health and Human Services (DHHS); strengthen the science base in toxicology; develop and validate improved testing methods; and provide information about potentially toxic chemicals to health regulatory and research agencies, the scientific and medical communities, and the public.

A number of testing modalities are used by the NTP, but an especially well-known one is the rat and mouse bioassay for carcinogenesis potential. Therefore, to fulfill its mission, the NTP has developed the capacity to produce and maintain uniform lines of mice. All mice used in NTP research must meet rigorous quality control standards. These mouse lines are monitored for the research needs of the NTP, including specifics of genotype/strain, size, weight, number, and gender. Animals are routinely tested for genetic homogeneity, microbial and parasitic status, viral and mycoplasma serology

profiles and pathological changes. Moreover novel mouse genetic mutant strains can be evaluated using the unique histopathology and compound susceptibility capabilities of the NTP for comparison of new models with earlier findings. This capacity is unique to NIEHS and can be leveraged to facilitate efforts of the CRG.

Strategic Plan Outline

Overtapping Phases in the NIEHS Coordinating Center for Rodent Genetics

Phase I: Investigational (Years 1-5)

- To achieve certain scientific milestones in three areas

-Toxicogenetics and
Environmental exposure and susceptibility
-Molecular genetics

Mechanisms -Comparative
genetics
& human biomarkers,predictive cell lines

Phase II: Translational Component Added (Years 3-8) -

Epidemiology, Population Analysis, NTP tests

Phase nl: Interventional Component Added (Years 6-10) -

Therapeutic, Regulatory gUidance

Summary

Rodents are major animal models for the study of human disease. Mouse models have proven especially useful for studying gene-environment interactions, have allowed us to understand risk factors for environmentally-associated disease and have provided opportunities to develop biomarkers of disease pathobiology and environmental exposure. It is well recognized that mouse and rat models are critical experimental tools for fulfilling the promise of modern toxicogenetic and pharmacogenetic research. Therefore, a mechanism to promote and coordinate use of rodent models in toxicology and other biomedical research will be invaluable to the entire scientific community. The NIEHS has therefore established the Center for Rodent Genetics (CRG), as an institutional and national resource that will stimulate research in rodent toxicogenetics and related fields. The CRG will foster state-of-the-art mouse repositories/databases, provide service cores to the research community, promote communication regarding mouse toxicogenetic research, and foster investigator-initiated research and training opportunities within the extramural scientific community. The existing infrastructure at
NIEHS is conducive to establishing and managing the CRG .

FEATURED ACTIVITIES *of DERT*
May 2004

MEETINGS

Obesity: Developmental Origins and Environmental Influences
2004 Spring Symposium, Duke University Integrated Toxicology Program
National Institute of Environmental Health Sciences, NIH, DHHS
Friday, February 20,2004
Duke University, Searle Center

Organizers: Edward D. Levin, Duke University and Jerry Heindel, COSPB

Background

Overweight and Obesity have reached epidemic proportions. This symposium focused on an underdeveloped aspect of the etiology of obesity that relates directly to the mission of NIEHS: the role of exposure to environmental chemicals *in utero* or neonatally in the development of obesity. In a recent review, Bailie-Hamilton presented data on the role of chemical toxins in the etiology of obesity and showed the current epidemic coincides with the marked increase in chemical use in the environment. It is also apparent obesity is more prevalent in rural areas and inner cities where inhabitants are more exposed to environmental chemicals.

The first talk focused on epidemiological studies that have demonstrated a direct relationship between birth weight and BMI reached later in life. Fetal under-nutrition in mid to late gestation may particularly lead to obesity and the related metabolic changes. Similarly higher than average birth weight leads to increased BMIlater in life. In addition, gestational diabetes leads to offspring that weigh more and are at increased risk of obesity later in life.

The increase of adipose tissue mass that accompanies obesity is due both to an increase in adipocyte number and size. Both processes can be mimicked *in vitro* using established stem and preadipocyte lines in culture. Using an immortalized multipotent stem cell line, C3H-10T1/2, researchers have shown that exposure to bone morphogenetic protein 4 leads to commitment to adipocytes. These preadipocytes can then be clonally expanded into adipocytes via treatment with cAMP, glucocorticoid and IGF-1.

Data on the role of estrogen and phytoestrogens in adipose tissue development and number show that estrogen in the adult is antilopolytic. Male and female estrogen receptor knockout mice have a 170% increase in adipocyte number. While the mechanism by which estrogen may inhibit increase in adipocyte number is unclear, recent data suggests a role for p27 and p21. A crucial question that remains unresolved is whether exposure of developing animals and humans to environmental estrogens such as phytoestrogens including genestein could alter adipocyte development and/or adult adipocyte number. Since so many human infants are fed soy based formula this is a question that has serious public health implications and needs investigation.

Fetal exposure to very low doses of the estrogenic chemical bisphenol A, which is the monomer used to make polycarbonate plastic, results in increased postnatal growth. As the amount of estrogenic contaminants in casein based animal feed increased, the amount of body fat decreased in mice indicating that particular attention must be paid to the contents of feed when one is studying obesity. In a related finding casein-based diets with no estrogenic activity resulted in higher estrogen levels in the pups, which were were born heavier. These animals grow up to be fatter and heavier and appear to develop the metabolic syndrome of obesity, diabetes, and insulin resistance. Some of these animals have been shown to have high leptin levels indicating leptin resistance. These data suggest that *in utero* estrogens may be adipogenic, an effect opposite that found in adults.

In utero and neonatal exposure to diethylstilbestrol (DES), a synthetic estrogen, affected body weight. High doses neonatally caused a decrease in body weight in the adult while low doses of DES (.001 mg/kgld) caused a significant increase in body weight in mice. The body weight of DES treated pups was normal after treatment but increased gradually over the lifetime of the mice. In adulthood the weight of the mice was 3-4 times normal. Neonatal exposure to genestein, a phytoestrogen, caused a significant increase in body weight by three months of age.

Environmental chemicals may also affect obesity via the sympathetic nervous system. Central and sympathetic norepinephrine systems are critically involved in the control of adipose tissue metabolism and appetite. A low dose of nicotine administered to mice during gestation results in significant weight gain after birth. This effect may be mediated via blunting of sympathetic and central norepinephrine systems which normally act to increase lipolysis and reduce appetite.

Outcomes
After the day long meeting the presenters participated in a brainstorming session to analyse the state of the art and suggest research needs. Several points were raised:

- There are sufficient data to warrant further study of the role of *in utero* exposures to environmental chemicals in the etiology of obesity. Focus should be on environmental chemicals with estrogenic activity as well as agents that can alter central nervous system function so that control of appetite in addition to direct effects on adipose tissue development and differentiation would be assessed.
- There should be a focus on developing the data on the safety of *in utero* and neonatal exposures to phytoestrogens, via soy formula, on later onset of obesity.
- Diet is critical when studying *in utero* effects of environmental chemicals on obesity. Thus synthetic diets should be encouraged. Studies on the interaction of diet and environmental chemical exposures should also be encouraged.
- Mechanistically, NIEHS should encourage studies of altered gene expression during development after exposure to environmental chemicals and to assess epigenetic changes that could result in altered tissue function later in life.
- NIEHS should be encouraged to stimulate this field via specific initiatives. (Note: NIEHS has added obesity to the latest iteration of the Fetal Basis Program Announcement as a result of this recommendation)
- NIEHS should be encouraged to work with NIDDK to develop a larger more comprehensive meeting on obesity with a focus on the fetal basis of obesity for 2005.

******* Workshop on Structural Determination of Environmentally Responsive Gene Products**
April 12 -13,2004 Snowbird,
Salt Lake City, Utah

Organizers: Les Reinlib, PhD (SPHB), David Balshaw, PhD (CRIS), Pat Mastin, PhD (COSPB)

Objectives The objective of this workshop was to bring together experts in genomics, structural biology, pharmacology, and related cutting-edge technologies (computer modeling, X-ray crystallography, NMR, mass spectroscopy) to identify the optimal routes to solving 3-dimensional structures of environmental

response gene (ERG) products and protein pathways. This information is expected to stimulate new avenues of research on understanding how gene variations underlie altered protein structures and functions. Ultimately, these studies are expected to lead to insights into susceptibility to environmental diseases and to improved ligand and drug design for research, patient therapy, and screening. The workshop recommendations will be published as a guide to the NIEHS in program development and to the research community.

Recommendations

The Workshop Participants recommended support of integrated projects to exploit the talents of mathematicians, computer scientists, and biologists. Outstanding workers in these fields approach their sUbject matter from disparate viewpoints and appear to speak in different languages. The participants strongly recommended training of young investigators as an important component of new initiatives. Trainees with backgrounds in biochemistry, molecular biology, physiology, etc. would gain valuable skills in mathematics and computer science courses that could be well applied to the issues central to environmental health sciences.

Highest Priorities

- Support studies of structure, analysis, control, and design of conformational and functional states at molecular resolution for environmentally-responsive molecules and complexes.
- Encourage integrated experimental and computational approaches
- Promote understanding of dynamics, kinetics, and ligand responses
- Investigate the mechanisms and steps in post-translational modifications, protein partnering, impact of genetic polymorphisms on structure/function, and ligand interactions

Mid-level Priorities

- Improve the production of protein samples and macromolecular assemblies (e.g. environmentally responsive membrane proteins)
- Develop optimal processes for design, production, and assembly of macromolecular complexes

Lower Priorities

- Encourage studies on protein-protein (macromolecules) interactions
- Examine assemblies and pathways rather than individual proteins

21st International Neurotoxicology Conference: Infant and Child Neurotoxicity Studies

February 10-14, 2004
Honolulu, Hawaii

Background

A number of NIEHS staff attended and participated in this conference organized by Dr. Joan Cranmer, Professor of Pediatrics, University of Arkansas, and member of the National Environmental Health Sciences Advisory Council. A significant highlight was that for the first time all the major longitudinal children's studies addressing the important persistent pollutants were presented together. This provided a unique opportunity to make significant advances in our understanding of the subtle and latent effects that these chemicals -alone or in combination -may be posing to children. The overall program focused on mechanisms and consequences of developmental neurotoxicity in children and experimental animals from exposure to persistent pollutants (e.g., pesticides, metals and industrial chemicals) during development (Le., embryonic, fetal, neonatal, infant, child and/or adolescent). The conference debated the most recent basic and clinical research advances, risk-assessment approaches, pediatric cognitive/neurobehavioral tests and batteries, problems and interpretation of issues unique to epidemiological studies of children, ethical/legal issues and related information concerning children's health and exposure to persistent pollutants. Products of the conference will be peer-reviewed and rapidly published papers in

Neurotoxicology.

Conference Objectives

The Conference met each of its specific aims:

- To provide an internationally recognized, interdisciplinary scientific forum for presentation of the major longitudinal children's studies investigating the low-level and long-term effects of methylmercury, PCBs, lead, heptachlor, other pesticides and mixtures.
- To conduct an Open Public Forumrrown Meeting for clinical and basic scientists, clinicians and the citizens of Hawaii who were involved in the 20-year heptachlor studies. To facilitate communication between the researchers and the parents and children from Hawaii who were exposed to heptachlor in pineapple chop and contamination of the milk supply and to discuss the implications of study results.
- To convene scientists from different scientific domains to exchange data and theories regarding the etiology, mechanisms, diagnosis, treatment and prevention of environmentally-induced diseases and disorders of the nervous system in the fetus, infant, child, adolescent, and adult (latent effects). To provide ample time and an environment for informal scientific exchange to promote collaborations and networking worldwide.
- To encourage and recognize student research endeavors by offering pre-doctoral and post-doctoral awards (cash and plaques) and travel scholarships and to provide mentoring and networking opportunities

The internationalization of children's environmental health was a reoccurring theme throughout the Conference. Dr. Henry Falk, Director, National Center for Environmental Health/CDC and Assistant Administrator, ATSDR, gave a Keynote Address focusing on the international perspective to children's environmental health. Dr. Suk, CRIS, and Dr. J. Satayavivad, Chulabhorn Research Institute, Bangkok, Thailand, organized and co-chaired a session on emerging issues in children's environmental health from an international perspective.

A significant part of the Conference was dedicated to the NIEHS/EPA Children's Centers. Dr. Collman, SPHB, and Dr. Chris Saint, U.S. EPA organized and co-chaired a series of sessions focusing on the critical results coming from these research and prevention programs. Dr. Collman provided an overview of this Center's program. Dr. Dick Jackson, Senior Advisor to the CDC Director gave a Keynote Address on children's health in relationship to obesity, urban and suburban sprawl and environmental health issues.

The final Keynote Address was given by Dr. Duane Alexander, Director, National Institute of Child Health and Human Development, NIH, whose presentation focused on the National Children's Study and its importance in reducing the risk of childhood diseases as well as future risk of chronic diseases in childhood.

The Conference was sponsored by the NIEHS, the National Center for Environmental Health/CDC, and the National Center for Environmental AssessmenVU.S. EPA; co-sponsors included the National Institute of Child Health and Human Development, the National Institute on Aging, and the NIEHS Superfund Basic Research Program; contributors included ATSDR, Arkansas Children's Hospital, Chulabhorn Research Institute, and Society of Toxicology.

Following the Conference NIEHS sponsored a Town Meeting entitled "Environmental Health Concerns in Hawaii" to stimulate effective dialogue between the citizens of Hawaii and local, state and national environmental public health scientists, practitioners and policy makers. Dr. Ken Olden, Director, NIEHS, gave the Keynote Address entitled "Bringing the Benefits of Environmental Health Research to the Public." Dr. Bruce Anderson moderated sessions dealing with environmental health concerns of the Hawaii population. Panels of experts presented on the respiratory health effects of volcanic gases, human health and the ocean environment, the long-term effects of the Hawaii heptachlor contamination, and autism and the environment. General discussion of environmental concerns followed.

Outcomes
Papers from this meeting will be published in a peer-reviewed special issue of *Neurotoxico/ogyentitled* "Infant and Child Neurotoxicity Studies."

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NIEHS Nanotechnologies Workshop: Technologies for Improved Risk Stratification and Disease Prevention
March 11-12, 2004
Rodbell Auditorium, NIEHS

Drs. Balshaw and Suk, CRIS, organized a panel of experts charged with assessing the current state of the science in nanotechnologies and formulating a list of specific recommendations for applying nano-and micro-scale devices in the environmental health sciences. The ultimate goal of the initiative is to develop tools to improve public health through improvements in risk assessment, individual risk stratification and the prevention of environmentally induced disease. The workshop was divided into three separate topics: Sensors and BioMEMS (microelectromechanical systems) for risk assessment, tools for mechanistic and functional investigations, and nanoscale devices for environmental remediation. The group agreed that it is important to be broad in defining nanotechnology, focusing on the benefits gained in decreasing scale, both in reagent utilization and in the emergent physical and chemical properties rather than focusing on a particular range of dimensions. This brief report summarizes the highlights of the meeting with a full report being prepared for publication.

Meeting Highlights
Decreasing the experimental scale has a number of advantages, both in terms of practical benefits and the emergence of novel chemical and physical properties. The practical benefits include decreased requirements for expensive reagents including probes and enzymes and an increased ability to automate and multiplex experiments. There are also a number of emergent chemical and physical properties that emerge at the nanoscale, most notably in the optical properties of nanoengineered fluorophores, which have extremely long fluorescence lifetimes, high quantum yields and often, as in the case of quantum dots, tunable emission and excitation profiles.

Environmental monitoring: One of the major barriers in the environmental health sciences is the relative lack of monitoring tools that are both highly specific to known agents and that have sufficient throughput to allow comprehensive 'real time' assessment. It is currently possible to develop micro-and nano-scale arrays, primarily based on affinity reagents that can detect specific sets of harmful agents in the environment. Provided adequate informatics support; this monitoring can be done in 'real time' and remotely accessed. These micro-and nano-scale environmental monitoring systems can also be extended to the individual level, detecting individual exposures and tissue distributions of toxins and environmental agents, and can possibly be coupled with catalytic or chelating activity. The resulting 'smart' sensors could represent an NIEHS specific platform technology, the development and use of which will enhance our ability to link relevant exposures to populations, and thereby, aid epidemiologic investigations and improve public health.

Relating physiological responses to environmental perturbations: Perhaps the major challenge facing the environmental health sciences as a whole is the ability to relate a given internalized dose of toxin to a phenotypic response. Understanding this relationship will require the development of tools for monitoring the signaling mechanisms involved in the pathological response with quantitative data with high temporal and spatial resolution. A number of nanoscale tools are emerging to accomplish this including primarily fluorescence based probes targeted towards small molecule second messengers and quantum dots which can be used to tag specific proteins. It is also possible that these tools can be engineered not only to detect physiological responses to exposures but also to intervene and reduce the development of disease or to treat existing disease. Current examples of nanoscale therapeutics include nanoshells, gold coated mica beads that target tumor tissues.

Nanoscale tools for environmental remediation: Within the realm of tools for environmental remediation, no single factor is more important than surface area. Given that volume increases with the cube of radius while surface area increases with radius squared; the ratio of surface area to volume, therefore, increases dramatically at the nanoscale. One specific example given in the workshop was for Self Assembled Monolayers on Mesoporous Supports (SAMMS) for which a 2 tablespoon volume has the surface area of a football field. There are essentially two applications of nanoscale tools for remediation: chelating agents and catalytic agents. Chelating agents, which are particularly useful for metals and radioactive materials, merely bind the hazardous agents with very high affinity effectively immobilizing and concentrating the agent for long-term storage. In some cases these can be landfill approved entities greatly reducing the cost of storage. Catalytic agents on the other hand, convert the hazardous agent into a non-toxic form either through reduction or oxidation or through chemical changes such as dehalogenation of organics.

The Long Range Recommendation: The participants were unanimous in embracing an idea that the NIEHS lead the way in developing a single, small scale platform technology that would combine aspects of each of the above recommendations to prophylactically detect an individual exposure, eliminate the toxin from the system and intervene to reverse any harmful effects that may have been initiated. This may appear to be science fiction from the imaginations of Dan Brown, Michael Crighton or Isaac Assimov; however, the technology to develop such probes is readily achievable within the not too distant future.

DERT IN THE NEWS

Centers for and Human Health
"The National Science Foundation (NSF) and the National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health, have announced funding for four joint Centers for Oceans and Human Health (COHH). The centers will be located at the University of Washington, the University of Hawaii, the Woods Hole Oceanographic Institution in Massachusetts, and the University of Miami.

The centers will bring together experts in biomedical and oceanographic sciences for the first time to study the effects of harmful algal blooms, marine pathogens, and the oceans' vast potential for drug discovery. The combined expertise of the participants will accelerate the pace of scientific discovery, ranging from the development of new sensors for early warning systems to enhanced progress in finding novel compounds with pharmaceutical potential."

See the News Releases web site for the full press release.

Study Shows Effects ofPrenatal Exposure to *Second-Hand Smoke Greater for Socioeconomically Disadvantaged Children*

Researchers at the Columbia Center for Children's Environmental Health report in the March 2004 issue of the journal *Neurotoxicology and Teratology* that "the effects of prenatal exposure to second-hand smoke on mental development are exacerbated in children who experience socioeconomic hardships, such as substandard housing and inadequate food and clothing, during the first two years of life.

While the study results indicate that prenatal exposure to second-hand smoke can be harmful to the unborn child regardless of socioeconomic conditions, the data also suggest that lower-income children may be less able to compensate for these effects over the next few years of life."

See the News Releases web site for the full press release.

First Human Study to *Show Benefits* to *Newborns from Federal Ban* on *Home Use of Two Insecticides*
A federal ban on two insecticides, chlorpyrifos and diazinon, has resulted in a significant reduction in their impact on newborns' birth weight and length, report researchers at the Columbia University Center for Children's Environmental Health.

See the News Releases web site for the complete press release.

The Worker Education and Training Program (WETPj supports the training and education of workers engaged in activities related to hazardous materials and waste generation, removal, containment, transportation and emergency response. Recently two articles highlighted how some of these funds are being used. In Boston, unemployed and underemployed persons are training to become environmental cleanup technicians. For the full article, which appeared in the Boston Globe April 23, see:
http://www.boston.cominews/globe/editoriaLopinionieditorials/articles/2004/04/23/job_training_thacworks/

On April 8, the Times Ledger reported on a three-day hazardous materials training course taken by Jamaica Hospital Medical Center staff. The 30-person class, comprised of emergency room, housekeeping, building maintenance and other staff, was designed to familiarize staff with the process and equipment used to decontaminate patients who might pose a risk to other patients inside the hospital.

New Research Outlines Public Health Consequences of World Trade Center Disaster
Results from longitudinal studies of firefighters, rescue workers and other personnel who responded to the collapse of the World Trade Center show profound exposure-related adverse effects on the respiratory system.

See the News Releases web site for the complete press release.

DERT PAPERS OF NOTE

Oxidase Enzyme Is the Target for Arsenic-Induced Reactive Oxygen Species Production In Leukemia Cells
Michael A. Trush, Ph.D.
The Johns Hopkins University School of Medicine
NIEHS Grants R01 ES03760 and P30ES03819

Background: Arsenic is a naturally occurring metal-like element found widely and in varied forms in the environment. Inorganic forms of arsenic are considered the most toxic and are found in drinking water, soils, and geologic formations. Humans can be exposed to arsenic in a variety of ways; however drinking contaminated water and industrial exposures are the most common. Arsenic is acutely toxic to humans at doses that generally occur through accidental or intentional poisonings. Arsenic is a known carcinogen to humans; skin cancer is the most common form of malignancy; however, other cancers of the lung, bladder, liver, kidney, and prostate can also occur following arsenic exposure. Interestingly, arsenic has been used for centuries in traditional folk remedies and today it is a component of cancer chemotherapeutic agents. Recently, much attention has been paid to the dramatic clinical efficacy of arsenic against acute promyelocytic leukemia.

Advance: Arsenic is known to induce the formation of reactive oxygen species (ROS); however, the mechanism has previously been undefined. Using gene expression profiling, interference RNA, and genetically engineered cells, these investigators determined that an enzyme required for the normal antibacterial function of white blood cells known as NADPH oxidase is the main target for arsenic-induced ROS production. NADPH oxidase can also be stimulated by a compound known as phorbol myristate.

The investigators went on to show that arsenic and a clinically used analog of phorbol myristate, bryostatin 1, synergistically act to enhance ROS production.

Implications: These investigators have shown that very low levels of arsenic and bryostatin 1 can effectively kill leukemic cells. The findings identify the arsenic target of ROS production and provide a new concept for an anticancer treatment that may have decreased adverse side effects. These findings may also provide clues to the carcinogenic potential of arsenic.

Citation: Chou WC, Kie C, Kenedy AA, Jones RJ, Trush MA, Dang CV. Role of NADPH oxidase in arsenic-induced reactive oxygen species formation and cytotoxicity in myeloid leukemia cells. Proc Natl Acad Sci USA. 2004 Mar 30; 101 (13):4578-83.

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Production of a Vaccine for Prostate Cancer Immunotherapy
Maarten C. Bosland, DV.Sc., Ph.D., New York University Medical Center
NIEHS Grant P30ES00260.

Background: The prostate gland is dependent on testosterone produced in the testes for growth and function. Therefore, reducing the production of testosterone is a targeted therapy in prostate cancer patients. Testosterone is produced in response to a hormone from the pituitary gland called luteinizing hormone. luteinizing hormone is released from the pituitary in response to luteinizing hormone-releasing hormone (lHRH), which is produced in the hypothalamus. Each step in this pathway provides an opportunity to block the production of testosterone to slow the growth of prostate tumors. These investigators using resources at the NIEHS-funded Center at the New York University Medical Center describe a vaccine against lHRH.

Advance: The vaccine was created using sophisticated immunological techniques and tested in rodents, dogs, and baboons. The vaccine produced anti-lHRH antibodies in all three species. This vaccine differs from others in use in that it targets lHRH itself and not a carrier protein. The vaccine, in a clinically applicable formulation, controlled the growth of androgen-responsive prostate tumor cells in rats.

Implications: The results of these studies demonstrate an efficient, responsive, and long-lasting decrease in androgen production in three diverse species, one of which is a non-human primate. Further studies are needed to determine if the vaccine is safe and effective at blocking testosterone production and prostate tumor growth in humans. If results from these studies are favorable, the vaccine could be an improved, less invasive method for treating prostate cancer.

Citation: Finstad Cl, Wang CY, Kowalski J, Zhang M, Li Ml, Li XM, Xia WG, Bosland MC, Murphy KK, Walfield AM, Koff WC, Zamb TJ. Synthetic luteinizing hormone releasing hormone (lHRH) vaccine for effective androgen deprivation and its implication to prostate cancer immunotherapy. Vaccine. 2004 Mar 12; 22{9-10):1300-13.

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A Mutation In the Hepatitis B Virus Predicts liver Cancer Development
Alvaro Munoz, Ph.D., Thomas Kensler, Ph.D., and John Groopman, Ph.D.
The Johns Hopkins University Bloomberg School of Public Health
P01 ES06052 and P30ES03819

Background: Liver cancer is the fifth most prevalent form of cancer worldwide causing over 427,000 deaths in 1990. Exposure to the hepatitis B virus is a major risk factor for the development of liver cancer. Previous work by this investigator has shown that hepatitis B exposure causes a 7-fold risk. Exposure to aflatoxin, a mold commonly found in peanuts and grains, increases the risk of liver cancer by 3.5 times. These two agents combined cause a remarkable 60-fold increase in risk of liver cancer. This is an

especially troubling public health problem in China where hepatitis Band aflatoxic exposure are both very high.

Advance: The current study by this NIEHS-supported investigator examines a particular mutation in the hepatitis B virus. Studies were conducted of the prevalence of the mutation in plasma and tumors of from patients living in Qidong, People's Republic of China. Initial studies determined that about three-fourths of the tumors from the patients contained the mutation. The investigators went on to determine that plasma samples contained the virus mutation about half the time before cancer had appeared.

Implications: These findings suggest that detection of the mutated hepatitis B virus is an early warning sign of subsequent liver cancer development. Early detection, even before liver cancer can be detected, is very important in prevention and intervention trials and may lead to better treatment outcomes.

Citation: Kuang SY, Jackson PE, Wang JB, Lu PX, Munoz A, Qian GS, Kensler TW, and Groopman JD. Specific mutations of hepatitis B virus in plasma predict liver cancer development. Proc Nat Acad Sci USA. 2004 Mar 9; 101 (1 0):3575-80.

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Drug Used to Arrest Preterm Labor Sensitizes the Brain to Neurotoxins

Theodore A. Slotkin, Ph.D., Duke University Medical Center
NIEHS Grants T32ES07031, P42ES10356, and R01 ES1 0387

Background: There is a growing body of evidence that suggests that exposure to environmental agents *in utero* or very early after birth can have life-long effects. This phenomenon is referred to as the fetal basis of adult disease. It is of growing concern to NIEHS and environmental health scientists worldwide. Hypertension, diabetes, asthma, and cardiovascular diseases are but a few of the illnesses that have been suggested as possible effects from these early-life exposures. This investigator examined the combined exposures of terbutaline, a drug used to arrest preterm labor, and SUbsequent exposure to the organophosphate pesticide chlorpyrifos on several indices of brain cell growth and function.

Advance: Young rats were given terbutaline on days 2-5 after birth, followed by chlorpyrifos on days 11 14. Neither treatment affected growth or viability of the young rats; however, both elicited alterations in brain cell differentiation and cholinergic innervation at day 15 persisting into adulthood (day 60). Biomarkers of brain cell number, cell size, and neuritic projections were affected by either agent alone; however the combined exposure produced more severe effects.

Implications: These findings suggest that terbutaline is a developmental neurotoxicant much like chlorpyrifos. The authors conclude that the use of terbutaline to prevent preterm labor may be creating a subpopulation that is more sensitive to the adverse neural effects of organophosphate pesticides. Further studies are needed to repeat these findings, but if the results are confirmed, use of these compounds may need additional scrutiny.

Citation: Rhodes MC, Seidler FJ, Qiao D, Tate CA, Cousins MM, Slotkin TA. Does pharmacotherapy for preterm labor sensitize the developing brain to environmental neurotoxicants? Cellular and synaptic effects of sequential exposure to terbutaline and chlorpyrifos in neonatal rats. Toxicol Appl Pharmacol. 2004 Mar 1; 195(2):203-17.

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Economic Benefits of Air Pollution Reduction for Children

Elaine M. Faustman, Ph.D.
University of Washington
P01ES09601

Background: The health effects of air pollution have been reported in many research studies over the past 30 years. These effects include mortality, respiratory and cardiovascular diseases and hospitalizations, changes in lung function, asthma attacks, and days lost from school and work. The need for cost-benefit analyses of environmental regulations has become increasingly important in the U.S. to warrant the high costs. Children are significantly affected by air quality; however, previous environmental regulation has not focused effects seen exclusively in children. These researchers used a meta-analysis approach to determine the child-specific health impacts derived from the U.S. Clean Air Act.

Advance: The researchers determined, based on data from published studies, that reductions in the criteria air pollutants (particulate matter, ozone, carbon monoxide, sulfur dioxide, nitrogen dioxide, and lead) predicted to occur by 2010 in response to Clean Air Act regulations would have the following impacts: "200 fewer expected cases of postneonatal mortality; 10,000 fewer asthma hospitalizations ... with estimated benefits ranging from $20 million to $46 million (1990 U.S.$); 40,000 fewer emergency department visits in children with estimated benefits ranging from $1.3 to $5.8 million; 20 million school absences avoided with estimated benefits of $0.7 to $1.8 billion; and 10,000 fewer infants of low birth weight, with estimated benefits of $230 million." Including the child-specific data "would be expected to add $1-2 billion to the $8 billion in health benefits currently estimated to result from decreased morbidity, and $600 million to the $100 billion estimated to result from decreased mortality."

Implications: The results of this study suggest that air pollution represents a significant health and economic burden to children in the U.S. The authors state that their estimates of health benefits are conservative and conclude that these estimates highlight the need for increased consideration of children's health effects in environmental regulation. They also point out that improved information for children's health effects and health economics are needed for more thorough environmental policy analyses.

Citation: Wong EY, Gohlke J, Griffith WC, Farrow S, Faustman EM. Assessing the health benefits of air pollution reductions for children. Environ Health Perspect. 2004 Feb; 112(2):226-32.

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Inhibition of Testosterone Production by the Environmental Estrogen Bisphenol A is Associated with Decreased Luteinizing Hormone Secretion and Decreased Steroidogenic Enzyme Gene Expression in Leydig Cells

Matthew P. Hardy, Ph.D. Center for Biomedical Research,
The Population Council
R01ES10233

Background: Synthetic estrogens have been implicated in a variety of endocrine related diseases such as hypospadias and testicular, prostate, and breast cancers. These compounds, also called xenoestrogens, are a diverse group of substances that mimic the action of the natural hormone, 17b-estradiol, in estrogen responsive tissues. Agents that cause adverse effects in target organs and tissues act by interfering with the actions of endogenous hormones and receptors. NIEHS-sponsored investigators at The Population Council have identified such effects from exposure to bisphenol A. Bisphenol A is a component of polycarbonate plastics and resins used in food packaging and dentistry.

Advance: These investigators exposed young laboratory rats to bisphenol A at low levels approximating that found in the environment. They found significant decreases in luteinizing hormone (Which stimulates the production of testosterone in Leydig cells in the testis) and testosterone in serum samples. They also

noted a decrease in the gene expression level of pituitary luteinizing hormone receptor and an increase in pituitary estrogen receptor gene expression. *In vitro* experiments with cultured Leydig cells also showed reductions in testosterone production after exposure to bisphenol A. A final set of experiments in which pregnant and nursing rats were administered bisphenol A showed a marked decrease in testosterone in testicular interstitial fluid of their male offspring.

Implications: These studies indicate that the perinatal period is a sensitive window of exposure to bisphenol A. The authors conclude that suppression of steroid hormone synthesis may be responsible for testicular abnormalities associated with bisphenol A in laboratory studies. Although there is no evidence of adverse effects in humans who consume bisphenol A orally from plastic food packaging, this exposure and the extensive use of bisphenol A in consumer products warrants more investigation of this compound at low doses for the purposes of risk assessment.

Citation: Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, and Hardy MP. Inhibition of Testicular Steroidogenesis by the Xenoestrogen Bisphenol A is Associated with Reduced Pituitary Luteinizing Hormone Secretion and Decreased Steroidogenic Enzyme Gene Expression in Rat Leydig Cells. Endocrinology 145:592-603, 2004.

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Risk of Salivary Tumors Following Gamma Radiation Exposure
Oingyi Wei, MD, Ph.D. The University of Texas
M.D. Anderson Cancer Center
R01ES11740

Background: Salivary glands have been shown in previous research to be highly sensitive to radiation exposure. Exposure to gamma radiation (ie. X-rays) is a known risk factor for both benign and malignant salivary gland tumors. However, the precise mechanism for this adverse effect has not been determined. The focus of this study was to determine whether radiation-induced chromosome breaks are a risk factor for benign and malignant tumors and whether there were any differences in risk between the two types of tumors.

Advance: The authors performed a pilot case-control study of 57 salivary gland cancer patients and 105 controls with no history of salivary gland cancer. Blood lymphocytes were collected and cultured from all research participants. The blood cells were exposed to a single dose of gamma radiation. Five-hours later, slides of the exposed cells were prepared so that counts of chromosome breaks could be determined. There were highly significant increases in the number of breaks/cell from the lymphocytes of the salivary cancer patients. The patients with malignant salivary gland tumors were 40 times more likely to have breaks/cell values higher than the median of the controls. Patients with benign tumors were less likely (4.7 times) to have elevated breaks/cell as compared to the controls.

Implications: Although this study was small and needs to be confirmed in larger studies, it does show that exposure to gamma radiation is a likely risk factor for malignant and benign salivary tumors. If larger studies do indeed confirm these results, this finding could have public health implications regarding the frequency of use of gamma radiation in the practice of dentistry.

Citation: Zheng R, Wang LE, Bondy ML, Wei 0, Sturgis EM. Gamma radiation sensitivity and risk of malignant and benign salivary gland tumors: a pilot case-control analysis. Cancer. 2004 Feb 1; 100(3):561-7.

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Expression of DNA Repair Genes Is Sensitive Marker for Oxidative Stress

Ivan Rusyn, MD, Ph.D. and James Swenberg, DVM, Ph.D.
University of North Carolina at Chapel Hill
K22ES11660, U19ES11391, P42ES05948, and P30ES10126

Background: Oxidative damage to DNA is known to be one of the mechanisms leading to the development of cancer after exposure to environmental agents. Studies have shown that chemical carcinogens that increase the production of reactive oxygen species also induce the formation of oxidative DNA lesions. All aerobic organisms have evolved methods to repair this damage known as DNA adducts. Adducts have been used extensively as markers for environmental damage to DNA; however, in many studies oxidants fail to produce adducts. Thus, these researchers thought that expression of genes involved in DNA repair might be a more sensitive marker for exposure and effect.

Advance: To test the hypothesis, mice were given the chemical carcinogen and peroxisome proliferator WY-14,463. Peroxisomes are intracellular organelles that metabolize lipids and are found in high concentrations in liver cells. Peroxisome proliferators are compounds that stimulate a marked increase in the number and size of peroxisomes in liver tissue and are thought to contribute to carcinogenesis by generating reactive oxygen species that damage DNA. Treatment with WY-14,463 failed to produce differences in a number of conventional end points that are commonly used to assess oxidative DNA damage. However, there was a marked increase in the expression of genes responsible for a specific pathway of DNA repair that removes oxidative damage. Furthermore, this novel marker of oxidative DNA damage was used to elucidate how WY-14,463 causes production of oxidants that damage DNA.

Implications: The studies suggest that gene expression analyses can be used as sensitive markers for chemically-induced oxidative DNA damage. In this study, the gene expression changes for a DNA repair pathway specific for removal of oxidized lesions were seen at a dose that did not produce common markers of oxidative damage; therefore, these gene expression analyses could be a used as a more sensitive measure. Additional studies are needed to corroborate these results in other model systems where oxidative damage to DNA is thought to playa role in cancer but no firm experimental evidence is yet available.

Citation: Rusyn I, Asakura S, Pachkowski B, Bradford BU, Denissenko MF, Peters JM, Holland SM, Reddy JK, Cunningham ML, Swenberg JA. Expression of base excision DNA repair genes is a sensitive biomarker for in vivo detection of chemical-induced chronic oxidative stress: identification of the molecular source of radicals responsible for DNA damage by peroxisome proliferators. Cancer Res. 2004 Feb 1;64(3):1050-7.

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SUk, WA, M. Avakian, D. Carpenter, J. D. Groopman, M. Scammell, and C. P. Wild. 2004. Human Exposure Monitoring and Evaluation in the Arctic: The Importance of Understanding Exposures to the Development of Public Health Policy. *Environmental Health Perspectives.* Vol. 112, No.2: 113-120.

SUk, WA, K. Murray, and M.D. Avakian. 2003. Environmental Hazards to Children's Health in the Modern World. *Mutation Research.* Vol. 544 (2-3): 235-242.

Jiang G, Jankowiak R, Grubor N, Banasiewicz M, Small GJ, Skorvaga M, Van Houten B, States JC. Supercoiled DNA promotes formation of intercalated cis-N2·deoxyguanine adducts and base-stacked trans-N2-deoxyguanineadducts by (+)-7R,8S-dihydrodiol-9S,1OR-epoxy-7,8,9,1 O-tetrahydrobenzo[a]pyrene. Chem Res Toxicol. 2004 Mar;17(3):330-9.

GRANTEE HONORS and AWARDS

Dr. Thomas Arcury, Professor, Wake Forest University School of Medicine, will receive the 2004 Outstanding Researcher Award by the National Rural Health Association at the association annual meeting in San Diego, CA, on May 26. This award is based largely on the projects improving the health of migrant and seasonal farm workers he has directed.

Dr. Gerald N. Wogan, Professor of TOXicology and Professor of Chemistry at the Massachusetts Institute of Technology, has been selected to receive the 2004 Distinguished Lifetime Toxicology Scholar Award for his substantial and seminal scientific contributions to the discipline of toxicology.

Dr. Melvin E. Andersen, CIIT Centers for Health Research, received the Arnold J. Lehman Award at the 2004 Annual Meeting of the Society of Toxicology. Dr. Anderson is widely recognized for contributions in strengthening the scientific basis of chemical risk assessment.

The Board of Publications of the Society of Toxicology announced the best paper published in Toxicological Sciences during the past year to be: Inhaled Environmental Combustion Particles Cause Myocardial Injury in the Wistar Kyoto Rat. Urmila Kodavanti, Carolyn Moyer, Allen Ledbetter, Mette Schladweiler, Daniel Costa, Russ Hauser, David Christiani and Abraham Nyska (ToxSci 71,237-245, *2003). Drs. Hauser and Christiani,* both of Harvard University, are NIEHS grantees.

Dr. Jay Gandolfi, Professor of Anesthesiology, Pharmacology, and Toxicology in the Department of Pharmacology & Toxicology at the College of Pharmacy of the University of Arizona was the recipient of the Society of Toxicology's Education Award.. Throughout his academic career he has maintained a strong focus on education, research, and collaborative programs.

The 2004 SOT/ACC Early Career in Neurotoxicology Award is presented to *Nikolay Filipovof* Mississippi State University. Dr. Filipov, an NIEHS grantee, was selected for his proposed research entitled Dopaminergic Toxicity of Chronic Exposure to the Herbicide Atrazine Interfaced with Short-Term Exposure to Maneb. Dr. Filopov plans to continue his research on susceptibility of the aged to environmental chemicals, an area very important for risk assessment.

This year's recipient of the AstraZeneca Traveling Lectureship Award is *Dr. Charlene McQueen.* Dr. McQueen, an NIEHS grantee, is a professor in the Department of Pharmacology and Toxicology, College of Pharmacy at the University of Arizona. Her research focus is currently on fundamental studies of the role of genetic variation in susceptibility to aromatic amine and hydrazine toxicity.

On April 20, 2004 the U.S. EPA recognized organizations and individuals in recognition of their efforts to protect and preserve the environment in 2003. Two of the honorees are affiliated with NIEHS-funded projects. *Ms. Liliana Guzman,* a junior at San Diego High School, "has become an asset to her community and to the local community group Environmental Health Coalition, by taking a leading role in educating, organizing and advocating for environmental health and justice in her community." *Dr. Henry Gong, Jr.,* is a practicing lung physician and past director of the USC Center for Children's Environmental Health. He integrates his clinical and research skills into educating others about the health effects of air pollution. "His extensive clinical research accomplishments provide a foundation for consulting with various groups including the U.S. EPA on its health research program and asthma strategy." A more comprehensive article has been included in the Council Agenda Book or will be available shortly on the EPA website

STAFF HONORS and AWARDS

Kenneth Olden, Ph.D.; Director, National Institute of Environmental Health Sciences and *William A. Suk, Ph.D., MPH;* Director, Center for Risk and Integrated Sciences; Director, Superfund Basic Research Program, National Institute of Environmental Health Sciences were among six leaders in

Federal Agencies where recognized with a Commendation for their contributions to children, environmental health, and the special needs of oceanic peoples at the 21 st International Neurotoxicology Conference: Infant and Child Neurotoxicity Studies, February 10-14, 2004, Honolulu, Hawaii.

STAFF ACTIVITIES

Ms. Beard, WETB, presented "NIEHS Lessons Learned from Advanced Training Technologies" at the American Industrial Hygiene Conference & Expo 2003 (AIHCE 2004) in Atlanta, Georgia on May 8-9.

Dr. Thompson, GRIS, has been invited to serve on the EPA's World Trade Center Health Panel. The purpose of this expert review panel is to obtain greater input on ongoing efforts to monitor health effects for workers and residents impacted by the collapse of the World Trade Center. This panel is convened and led by the EPA. The expert panel will help guide EPA's use of available exposure and health surveillance databases and registries. It will characterize any remaining exposures and risks, identify unmet public health needs, and recommend any steps to further minimize the risks associated with the aftermath of the World Trade Center attacks. For the complete press release and additional information please see http://www.epa.gov/wtc/panel.

Ms. Duke, GMB, was an invited speaker at the National Council of University Research Administrators Region 1 Spring conference held in Sturbridge, Massachusetts, May 5. She presented the NIH Grants Policy Update.

Mr. Hughes, WETB, presented at the DHHS Secretary's Council on Public Health Preparedness Meeting in Washington, DC on May 4.

Ms. Beth Anderson, GRIS, was invited to participate in EPA's 19th Annual Regional Annual Risk Assessors meeting held in Boston Massachusetts, May 3-7. Ms. Anderson presented an overview of the Superfund Basic Research Program and highlighted recent Program advances.

Dr. Van Houten, PAB, was an invited speaker at the fourth International Workshop on DNA Repair, which was held in Smolenice, Siovokia, May 2-5. His lecture was "How do nucleotide excision repair proteins detect and remove DNA damage?" He also presented the final closing remarks to this meeting of 80 participants from more than 10 different countries.

Drs. Kirshner and Lawler, GOSPB, organized and chaired a symposium "New Paradigms For Exploring Gene-Environment Behavior Relationships" on April 28 at the NIEHS Rodbell Auditorium, Research Triangle Park, North Carolina. The goal of the symposium was to identify and enhance research in the field of behavioral toxicology.

Dr. Van Houten, PAB, presented a lecture "DNA damage processing by the UVrABC nuclease system: probing the DNA hand-off using protein-DNA cross-linking agents" on April 23 at Vanderbilt Institute of Chemical Biology Mass Spectrometry Center, Nashville, Tennessee. Dr. Dan Liebler hosted the seminar.

Mr. Hughes, WETB, and staff sponsored a Technical Workshop on Training Partnerships for Prevention, Protection, and Preparedness. This workshop focused on bUilding stronger relationships with the Department of Homeland Security (DHS), the Department of Labor (DOUOSHA), and the Environmental Protection Agency (EPA/OSWER) for the training of responder populations most at risk, partiCUlarly fire fighters, health care workers, and the construction trades needed at disaster response. The workshop was held in Washington, DC on April 22-23. Other staff attending the workshop and participating in various activities included *Ms. Beard, Mr. Outwater, and Ms. Thompson, WETB.* On April 21, the semi-annual WETP Awardee Meeting was held. *Ms. Mason, GMB,* also participated in the meeting.

Dr. Van Houten, PAB, was a co-chair of a 'Workshop on DNA Adducts: Biological Consequences and Application to Risk Assessment, " which was co-sponsored by the International Life Sciences Institute and

NIEHS. The meeting, attended by over 120 scientists from academia, government and private industry was held April 13-14 in Washington, D.C. The day and a half meeting considered the current knowledge of the chemistry and biology of DNA adducts and discussed the use of DNA adducts in developing a more mechanistic risk assessment on the consequences of DNA lesions.

Dr. Van Houten, PAB, gave an invited lecture, "How do proteins find DNA damage: Structure-function studies of nucleotide excision repair proteins," on April 7 at the Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina. Dr. Dorothy Erie hosted his visit.

Mr. Hughes, WETB, presented at the 5th Biennial Freshwater Spills Symposium on April 6-8 in New Orleans, Louisiana, on a session concerning Emergency Response and Counter-Terrorism Issues.

Mr. Hughes, WETB, presented an update on the Worker Education and Training Program at the HAMMER Steering Committee Meeting in Washington, DC on April 2.

Drs. Packenham and Maull, SPHB, organized, managed, and hosted a Mid-Program Retreat entitled "Assessing and Refining Our Program," for the Comparative Mouse Genomics Centers (CMGC) Consortium, held at the National Institute of Environmental Health Sciences on March 26-27. The goal of this retreat was to discuss the past, present and future of the CMGCC. Discussions centered on accomplishments to date, including technical capabilities developed, organizational structure, and potential future directions for the Consortium. Participants included the CMGC Directors and Co-directors, NIEHS Extramural Staff *(Dr. Collman, SPHB, Ms. Winters and Ms. Garcia, GMB, and Dr. Leroy Worth, SRB),* NIEHS Computer Specialist (Mr. Nehls), members of the CMGC Consortium Mouse Task Force, and external reviewers.

Dr. Van Houten, PAB, gave a lecture, "Telomerase present in the mitochondria increases hydrogen peroxide-induced mitochondrial DNA damage" on March 24 at the Center of Excellence in Biomedical and Marine Biotechnology, Florida Atlantic University, Boca Raton, Florida. His hosts were Drs. Herb Weissbach and Zingwei Li.

Dr. Tyson, SPHB, gave an overview of extramural K-12 EHS science education programs and the COEP Resource Center at the NCABR Science Teachers Workshop on March 23 at NIEHS, Research Triangle Park, North Carolina.

Dr. Allen, SRB, was invited to serve as one of five panelists in a Grantsmanship Workshop held March 23, 2004 at Sigma Xi, Research Triangle Park, North Carolina. The workshop was co-sponsored by Sigma Xi (the Research Honor Society) and Office of Fellows' Career Development, Office of the Director, NIEHS/NIH. The panelists spoke about the importance of networking/collaborations (as they relate to writing applications) and the grant review process. Sixteen of the twenty-six participants were NIEHS fellows. This was a great opportunity to help mentor a young scientists from the NIEHS and the Research Triangle Park area.

Mr. O'Fallon, SPHB, worked with Maryland Public Television (MPT) and Johns Hopkins University (JHU) staff to organize the Environmental Health Sciences as an Integrative Context for Learning (EHSIC) grantee meeting in Baltimore, Maryland, March 21-22. The EHSIC grantee meeting was hosted by MPT and JHU in conjunction with the annual Society of Toxicology conference. Grantees focused on three primary themes: (1) strategic planning for publications and dissemination of their curricular materials to school systems, (2) using the media to communicate project activities and to disseminate research findings, and (3) Federal science education directions, policies and programs. *Dr. Anne Sassaman* presented on continued NIEHS commitment to science education. *Ms. Lou Rozier* (NIEHS/Office of Communication and Public Liaison) spoke on the importance of working with NIEHS on development of Press Releases for the dissemination of research findings.

Mr. O'Fallon, SPHB, collaborated with Dr. David Eaton of the University of Washington to organize and moderate a three-hour science education workshop at the Society of Toxicology conference on March 25 in Baltimore, Maryland. The workshop, "Novel approaches to engaging toxicologists in K-12 science education and outreach," highlighted many successful models of NIEHS grantees going into the K-12 classroom to increase awareness of, and enthusiasm for, science (in general) and environmental health (specifically). The workshop also included a hands-on session where meeting participants had the opportunity to interact with grantees and learn about new lessons or activities they can use in the classroom.

Dr. Shreffler, GOSPB, presented a session on Training Opportunities for Students and Institutions and conducted a round table discussion with student mentors at the Undergraduate Education Program on March 21 at the Society of Toxicology Meeting in Baltimore, Maryland. The Undergraduate Education Program is conducted by the Education Committee of the SOT for minority students and their advisors to familiarize them with career opportunities in toxicology, and provide information on graduate schools and the application process.

Dr. Sassaman, 00, was a speaker at the Grantsmanship Forum at the annual meeting of the Society of Toxicology. The title of her presentation was "New Program Opportunities at NIEHS and How to Take Advantage of Them."

NIEHS hosted the current class of NIH Extramural Associates on March 16. *Dr. Ethel Jackson, 00,* coordinated the visit to NIEHS and EPA, and *Dr. Sassaman* presented the Institute's background and extramural programs. This is a program for faculty for minority and women's institutions to become familiar with opportunities for NIH funding and to serve as a resource at their home institutions for faculty research development.

Dr. Tyson, SPHB, was a speaker at the University of Miami Freshwater and Marine Biological Science Center's Research Symposium in Miami, Florida on March 18 and at the Florida International University's ARCH External Advisory Committee Meeting in Miami, Florida on March 19.

Mr. O'Fallon, SPHB, working actively with staff from across the NIEHS, led the development of a crossinstitute science education website (http://www.niehs.nih.gov/science-educationl). The new website targets three primary audiences: students, teachers, and scientists. The purpose of the site is to provide users with easy access to reliable tools, resources and classroom materials. The site was unveiled March 17 in time for Excellence in Science, Technology, and Mathematics Excellence week. This is the first version of the website. It will be updated to make it even easier to find environmental health materials that can be used in the classroom.

Dr. Heindel, GaSPB, and Carol Henry, Ph.D. DABT, Vice President, Science and Research, American Chemistry Council (ACC) organized and co-chaired a meeting of the grantees funded from two NIEHS initiatives. Grantees from the Joint NIEHS/ACC funded Developmental Toxicology RFA and those funded in the first year of the Fetal Basis of Adult Disease program announcement presented their data on March 8-9 at the Marriott Hotel in Research Triangle Park, North Carolina. The goal of this meeting was to assess the success of the Developmental Toxicology RFA and to assess the progress of the grantees funded under the Fetal Basis initiative. In addition, the meeting served to introduce grantees from these separate initiatives in developmental tOXicology to each other with the goal of stimulating cross fertilization and collaborations.

Ms. Duke, GMB, participated as a member in the planning committee for the Annual North Carolina Society of Research Administrators Conference held in Durham, North Carolina, March 2 -4. She was an invited speaker at that conference, presenting a session entitled "NIH Grant Initiatives and Policy Update" which focused on the NIH Roadmap activities as well as new NIH grants policy updates. She also facilitated a roundtable discussion on "Terms and Conditions of NIH Grant Awards."

Dr. Srinivasan, SPHB, served on the National Commission on Community-Engaged Scholarship in the Health Professions to take a leadership role in creating a more supportive culture and reward system for health professional faculty involved in community-based participatory research, service-learning and other forms of "community-engaged scholarship." This Commission was convened by the Community-Campus Partnerships for Health. The Commission met in March 2004 in Washington, DC.

Drs. Heindel, Mastin and Shreffler, GOSPS, presented a grantsmanship workshop for postdoctoral fellows in the NIEHS Intramural Program on March 2. This forum was designed to aid interested IRTA fellows in the preparation of their application to the Transition to Independent Position Grant Program.

Drs. Reinlib, Maull, and Gallman, SPHB, in collaboration with NCI, organized and coordinated, the second planning meeting of the Breast Cancer and the Environment Research Centers Network February 25-26, in Georgetown, Washington, D.C. All official (Biology, Epidemiology, and COTe) and ad hoc (Bioinformatics and Scientific Meeting Planning) subcommittees met and provided updates at the Steering Committee meeting, held on February 26. BC/E Working Group representatives were present at all subcommittee meetings and at the Steering Committee meeting. Ms. Fran Visco, President, National Breast Cancer Coalition, provided remarks to the participants at a working lunch.

Ms. Beard, WETS, participated in the development and evaluation of the OSHAINIEHS Disaster Site Worker Response Training on February 29 in Washington, DC.

Dr. Balshaw, GRIS, organized a meeting of the grantees under the NIEHS Functional Proteomics Initiative May 3-4. The meeting included an afternoon symposium with invited speakers.

UPCOMING MEETINGS and WORKSHOPS

The Office of the Director, NIEHS, is organizing the "Obesity and Built Environment Conference" to be held at the Marriott Wardman Park, Washington DC, May 24-26. *Dr. Srinivasan, SPHS,* is on the Planning Committee for the conference.

Mr. Outwater, WETB, along with *Dr. Mastin, GOSPB,* will participate in the NIEHS co-sponsored national conference entitled "Mold-Related Health Effects: Clinical, Remediation Worker Protection, and Biomedical Research Issues on June 28-29. The purpose of the cross-disciplinary meeting is to bring together experts in clinical science, worker protection and education, and basic research to further efforts to prevent, diagnose, and treat conditions related to exposure to indoor mold.

The third annual Comparative Mouse Genomics Centers (CMGC) Consortium Summer Symposium, "Cell Cycle and DNA Repair Variants" will be hosted by The University of Texas M.D. Anderson Cancer Center CMGC, June 1 -3, in Austin, Texas. The focus of the symposium will be on recent findings concerning the function of DNA repair and cell cycle control genes and how these functions are altered by naturally occurring polymorphisms in the human population. The symposium will highlight the use of molecular epidemiological studies, in vitro assays, and mouse modeling to identify and functionally characterize polymorphisms relevant for environment-related diseases. For additional information please see the meeting website.
Drs. Packenham, Maull, and Gallman, SPHB, will attend.

Dr. Packenham, SPHB, will co-chair a one-day satellite meeting, *Phenotyping Forum,* June3-4,alsoin Austin, Texas. This forum is a coordinated effort with the NIEHS CMGC Consortium, the NCI Mouse Models for Human Cancer Consortium and the NCRR Mutant Mouse Regional Resource Consortium to initiate discussions and begin development of Phenomics protocols for mouse phenotyping. The meeting will bring together a small group of Nationally and Internationally renowned scientists with expertise in mouse pathology to explore new methodologies for mouse phenotyping. *Dr. Maull, SPHB,* will participate in this meeting.

The Superfund Basic Research Program is co-sponsoring a PCB Workshop in Champaign/Urbana, Illinois, June 13-15. This workshop will bring together scientists who are concerned with the physical and chemical as well as the biomedical aspects of the detection, movement, metabolism, toxicity, remediation and risk assessment of PCBs. A primary objective is to encourage interactions and the exchange of information and to compose a new, up-to-date compendium on the very latest findings relating to the chemistry and biology of PCBs and their risk to human health. Other sponsors include the University of Kentucky Superfund Basic Research Program, the Environmental Protection Agency, the Hanson-Drucker Heritage Fund, and the University of Iowa's Environmental Health Sciences Center and Fogarty International Center.

Dr. Maull, SPHB, will participate in the Botanical Research Centers Annual Directors' Meeting, planned for August 5 through 7, 2004. This year's meeting is being hosted by the University of Missouri/Columbia Botanical Center, Dennis Lubahn, Center Director. The Botanical Research Centers Program is a joint program between NIEHS, the Office of Dietary Supplements, and the National Center for Complementary and Alternative Medicine.

Dr. Suk, CRIS, has accepted an invitation to be a member of the International Advisory Board for the upcoming "5th Princess Chulabhorn International Science Congress: Evolving Genetics and Its Impact on the World," to be held August 16-20, 2004, Bangkok, Thailand. He also has been asked to give a plenary lecture on translating genomics to reduce risk of exposure and disease, and he is involved in organizing as symposium on gene-environment interaction.

A meeting on Brownfields 2004: GrOWing a Greener America Conference in St. Louis, Missouri on September 20. *Ms. Beard and Mr. Outwater, WETB,* are planning to conduct a grantee meeting of the Brownfields Minority Worker Training Program in conjunction with this meeting.

The NIEHS Basic Research Program, in conjunction with the Mt. Sinai Superfund Basic Research Program and the Hudson River Foundation, is sponsoring a conference on "Persistent Contaminants: New Priorities, New Concerns" in Bear Mountain, New York, September 29-30. The intent of this conference is to examine the environmental distribution and potential human health risks of persistent contaminants with a focus on two members of a new and increasingly widespread generation of environmental pollutants --the alkylphenol ethoxylates (APEs) and the polybrominated diphenylethers (PBDEs).

The NIEHS Superfund Basic Research Program, in conjunction with the Agency for Toxic Substances and Disease Registry and the Texas A&M University School of Rural Health, is sponsoring the "Central and Eastern European Environmental Health Conference: International Health Sciences Solving Common Problems," to be held in Prague, Czech Republic, October 24-27. The Central and Eastern European Environmental Health Conference has three primary objectives: (1) to gather scientists and students from the US and Central and Eastern Europe to discuss the magnitude of the problem in understanding the health effects that could result from exposure to hazardous substances, specifically in regions of Central and Eastern Europe; (2) to discuss improved methods for assessing exposure including biomarkers of exposure and integrated methods for predicting dose; and (3) to discuss specific health effects associated with exposure to chemicals at these sites with a focus on developmental and reproductive health.

STAFF CHANGES

Recruitments Teresa (Terry) Nesbitt, D.V.M, Ph.D., has accepted the position of Chief, Scientific Review Branch effective May 30. She spent 17 years at Duke before going to NIH/CSR in 1998 to be Scientific Review Administrator for the Surgery and Bioengineering Study Section. She has been chief of review at NIAMS since last year. A more detailed report will be prOVided for September Council.

Sally Tinkle, Ph.D., has accepted the position of Program Administrator for the Respiratory Diseases Program effective June 13. A more detailed report will be provided for September Council.
Ms. Margarita Roque has accepted the lead Administrative Officer position, which will take effect upon the retirement of Mr. Warren Pope. Ms. Roque is currently the second Administrative Officer in DERT.
Ms. Anne Thompson has been selected for a Program Analyst position in the Program Analysis Branch.

Departures:
Mr. Warren Pope, Administrative Officer for DERT, has announced his retirement, effective June 3, 2004.