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
February 10-11, 2003

The National Advisory Environmental Health Sciences Council was convened for its one hundred seventh regular meeting on September 9, 2002, at 8:30 a.m., in Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The meeting was open to the public from 8:30 a.m. until 5:00 p.m.. The meeting was closed for consideration of grant applications on September 10, from 9:30. a.m. until 12:00 p.m.. Dr. Kenneth Olden presided as Chair on September 9-10, 2002.

Members Present:

Daniel Baden, Ph.D.
Deborah Brooks
Charli Coon
Joan Cranmer, Ph.D.
Dale Eastman
George Friedman-Jimenez, M.D.
Michael Gallo, Ph.D.
Bernard Goldstein, M.D.
George Gray, Ph.D.
Frederick P. Guengerich, Ph.D.
Barbara Hulka, M.D., M.P.H.
Phil Iannaccone, M.D., Ph.D.
Peggy Shepard
Martyn T. Smith, Ph.D.
James G. Townsel, Ph.D.

Members Absent:

Deeohn Ferris, J.D.
Daniel Nebert, Ph.D.
Hon. Harriett M. Wieder

Ex Officio Members Present:

Kelley Brix, Ph.D.
Eric L. Stephens

Liaison Members Present:

Robert Spengler, Ph.D.
Drue Barrett, Ph.D. CDC
Elizabeth Ward, Ph.D. for David R. Ringer, Ph.D. ACS

Members of the Public Present:

Marie Lynn Miranda, Ph.D.
John Hildenbrandt, Ph.D.

NIEHS Staff:

Kathy Ahlmark
Janice B. Allen, Ph.D.
Beth Anderson
Lisa Archer
Martha Barnes
Linda Bass, Ph.D.
Sharon Beard
David Brown
Allen Dearry, Ph.D.
Dwight Dolby
Dorothy Duke
Sally Eckert-Tilotta, Ph.D.
Benigno Encarnacion
Lerlita Garcia
Kimberly Gray, Ph.D.
Mike Humble, Ph.D.
Ethel Jackson, D.D.S.
Laurie Johnson
Marian Johnson-Thompson, Ph.D.
Annette Kirshner, Ph.D.
Cindy Lawler, Ph.D.
Charle League
Edith Lee
Francine Little
Carolyn Mason
Patrick Mastin, Ph.D.
Michael McClure, Ph.D.
Roseanne McGee
Elizabeth Maull, Ph.D.
Sheila Newton, Ph.D.
Liam O'Fallon

Ted Outwater
Joan Packenham, Ph.D.
Jerry Phelps
Chris Portier, Ph.D.
Larry Reed
Susan Ricci
Jacqueline M. Russell
Anne P. Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
William Suk, Ph.D., M.P.H.
Anne Thompson
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Brenda Weis, Ph.D.
Laura Williams-Boyd
Samuel Wilson, M.D.
Michelle A. Owens
Carolyn Winters
Leroy Worth, Ph.D.

Other Federal Staff:

Patricia Greenwel, Ph.D. CSR, NIH
Richard Jackson, M.D., M.P.H. CDC

I. CALL TO ORDER AND OPENING REMARKS

The one hundred eighth regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Olden.

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 September 9-10, 2002 MEETING

Council accepted the minutes without change.

FUTURE COUNCIL MEETING DATES

May 19-21, 2003 NIEHS (including Leadership retreat)
September 15-16, 2003 NIEHS
February 23-24, 2004 NIEHS

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

Dr. Olden began his report by commenting on the Fiscal Year 2003 budget, noting that the final amount is likely to be slightly below the President's Budget and thus the 5-year doubling. However, the budget for the NIH overall is generous. He noted that NIH is still operating on a Continuing Resolution. Preparations are ongoing for the Congressional hearings for Fiscal Year 2004. The House hearings will be in early April. Dr. Zerhouni will provide all testimony for the Senate hearings on April 4, 2003.

Dr. Olden mentioned the new IC director for NIAAA, Dr. T.K. Li and he came from the Indiana Alcohol Research Center at the Indiana University School of Medicine, and Dr. Thomas R. Insel for NIMH and he came from the Center for Behavioral Neuroscience at Emory University School of Medicine. He also noted that efforts under the NIH Director's Roadmap Project are continuing, and reminded the Council of the general topics, which include a major focus on clinical research. Finally, in other NIH news, Dr. Olden commented on activities related to the Government Performance and Results Act (GPRA) and advised the Council that three topics submitted by NIEHS made the list of final objectives to be targeted over the coming years. These are animal models of Parkinson's Disease, the CEBS database, and toxicogenomics.

Dr. Olden invited the council to participate in the Planning retreat and to propose topics for three sessions. Recent topics have been the Environmental Genome Project (EGP) and Toxigenomics which resulted in major new programs.

Dr. Olden also noted the Sister Study and the publicity in the Onclology Times. The Marin County Town Meeting on Breast Cancer was also highly visible. The new Breast Cancer and the Environment Centers program will address a major need and hopefully will have collaborations between NIEHS and NCI centers. Dr. Olden was also pleased about the new centers consortium in Parkinson's Disease and the good visibility and publicity that it has received.

The first issue of Environmental Health PerspectivesToxicogenomics was published in January. Dr. Ken Ramos is the editor. There has also been a compilation of "Grand Rounds" from EHP, edited by Howard. Hu, which will be provided to physicians in hopes of stimulating clinical research and providing an educational tool.

In closing, Dr. Olden mentioned a few other current activities of NIEHS:

- Public Service Announcements produced through our Office of Communications will be shown in K-Marts throughout the country.
- Town meetings (list provided) continue to be successful and give NIEHS good visibility. The agendas and development process are the responsibility of the local organizers.

- An upcoming Children's Health Conference in Bethesda will have a prominent representation of centers cofunded by NIEHS and EPA.
- Recent publications from NIEHS grantees relating to identification of polymorphisms are important for public health and are a good example of partnerships that the Institute hopes to foster.

Subsequent discussion with the Council included questions regarding an interest or emphasis on aging, (Dr. Olden is having discussions with Dr. Hodes, Director of the National Institute on Aging); the funding anticipated from the Environmental Protection Agency for the Children's Centers (less that for the last project period); and whether there might be a consortium between the to-be-established Breast Cancer and the Environment Centers and the Sisters Study.

V. REPORT OF THE DEPUTY DIRECTOR, NIEHS Dr. Samuel Wilson

Dr. Wilson began his report by commenting on recent and forthcoming events involving NIEHS, focusing on the second meeting of the NAS/NRC Committee on Emerging Issues and Data on

Environmental Contaminants. The Committee is looking at roadblocks and how to address the roadblocks and problems. An example is the premature use and interpretation of data. The Federal Liaison Group is identifying specific agency needs. (Details are contained in a Newsletter made available to the Council) A Symposium entitled "Advances in Toxicogenomics" sponsored by NIEHS will be held during the annual meeting of the Society of Toxicology, March 11, 2003. A symposium, "Genetic Variation and Gene Environment Interaction" will be held April 16, 2003 on the NIH campus in Bethesda. Finally, Dr. Wilson noted a regional meeting sponsored by the National Academy of Sciences/Institute of Medicine Roundtable on Environmental Health Science Research and Medicine, which will be held March 19 in Pittsburgh. The title of the meeting is "Ensuring Environmental Health in Post Industrial Cities."

The Council responded enthusiastically to these efforts, and in particular commented on the importance of NIEHS leadership in focusing on implications of toxicogenomics for regulation and risk assessment.

VI. THE BUILT ENVIRONMENT AND PUBLIC HEALTH - Dr. Richard Jackson

Dr. Jackson began his presentation with several relevant facts:

- There are 1.2 million homes in the US with significant lead hazards which house low income families with children under the age of 6. Reducing the blood lead levels by 10 mg/dL raises IQ by 2.5 points.
- As population numbers increase greatly, there is a concomitant large impact on the environment and health.

He then defined "syndemic" as two or more epidemics, interacting synergistically, contributing to excess burden of disease in a population. The great population increase enormously impacts the environment and the health of people. There are links between mental health, physical health

and the built environment. For example, paving has increased run-off of water and the creation of "heat islands" which create their own weather, lead to increased ozone levels, increased electrical demand, and decreased rain.

In another example of the relationship between the built environment and health, pedestrian safety is being ignored traffic fatalities that are pedestrians are at 13% and the Federal transportation spending for pedestrians is at 0.6%. In addition to the safety issue, transportation scenarios which limit sidewalks and create these dangerous situations also discourage walking and exercise and contribute to the epidemic of obesity in the US. The impact of obesity and type 2 diabetes has increased in every age group in the population and diabetes is now listed as the 7th leading cause of death.

"Social capital" is defined as social networking and engagement which generate trust and reciprocity. Decreased social capital leads to declines in health status in a community. Syndemic diseases require "syn-solutions"or solving multiple problems simultaneously. We need to get this message outside of the health community to agencies at all levels, including the local planners. Dr. Jackson noted that this may be a may be a new way to view translation research.

VII. USES OF GIS IN STUDIES OF LEAD CONTAMINATION - Dr. Marie Lynn Miranda

Dr. Miranda began her presentation by discussing the GIS-based strategies for addressing the Children's Environmental Health Initiative. The age of the house, race, income, if the occupants are receiving public assistance and other factors are used to overlap with various maps. The system can be used at different levels, e.g: state, county, zip code, census block, or single address as well as ecologically oriented locations, such as a flood plain. She described how her approach is being used to target areas of high lead contamination in housing in Durham, North Carolina. The translational aspects of this research are that it leads to targeted screening and intervention and the best use of resources.

Dr. Miranda is also working with the Department of Housing and Urban Development and other related agencies for prevention and to address issues of environmental justice and children's environmental health. Dr. Miranda's abstract can be found at Attachment B.

VIII. THE SISTER STUDY: ENVIRONMENTAL AND GENETIC RISK FACTORS FOR BREAST CANCER Dr. Dale Sandler

The NIEHS Sister Study will examine environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Sisters of women who have had breast cancer have about twice the risk of developing breast cancer as other women.

The environmental risk factors are not understood and there are few clues to environmental and occupational exposures. Other complications are the long latency, timing, susceptibility and the fact that most studies have measured only those things that can practically be measured. The

Sister Study is a practical way to approach looking at large number of factors in a highly motivated population. Dr. Sandler's abstract and slides can be found at Attachment C.

IX. NEW MODELS FOR TOXICOLOGY Dr. Christopher Portier

Dr. Portier discussed the National Toxicology Program's (NTP) organization and partners. Three agencies form the core of the NTP: NIEHS, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH) and the National Center for Toxicological Research of the Food and Drug Administration (NCTR). The NTP Executive Committee provides oversight to the NTP for policy issues.

The NTP was established to coordinate toxicological testing programs within the Department of Health and Human Services and to strengthen the science base in toxicology, develop and validate improved testing methods and provide information to the public.

One of the efforts to develop better test methods has been the development of transgenic mouse models for studies of carcinogenicity, which is ongoing. However, it is reasonable to continue looking further for models to add to existing methods. A workshop on February 21 will look at when to use transgenics and how to report the results.

One possible new model for toxicological screening is the free-living nematode, C. elegans. It is a simple invertebrate about which there is a wealth of knowledge. In addition, there are studies demonstrating chemically-induced developmental and/or neurological changes, and a wealth of C. elegans-specific tools. Furthermore, there are possibilities for high through-put and imaging capabilities using this model.

The NTP has proposed a project to develop C. elegans as a high through-put technology; evaluate 200 known or suspected developmental and/or neurological toxicants; obtain and /or create transgenic C. elegans lines to improve specificity and sensitivity; develop and implement microarray methodologies for C. elegans; and develop methods for selective inactivation of genes using DNA interference techniques.

The NTP is also working with the National Center for Toxicogenomics and will use RNA from testing contracts for genomic analysis, another tool for toxicity testing in the future.

X. SUPERFUND BASIC RESEARCH PROGRAM EXTERNAL ADVISORY GROUP REVIEW AND PLANS FOR THE FUTURE Dr. William Suk, Dr. Claudia Thompson and Mr. Larry Reed

Dr. Claudia Thompson gave a brief overview of the Superfund Program. The program is currently working with a $45M/year budget with nineteen (19) programs that cover most of the United States. There are approximately 1000 researchers and students involved.

The SBRP will be phasing from a onceeveryfiveyear award cycle into an annual award cycle and the timeline for this demonstrates the need to initially make 3,4,5 and 6 year awards. From FY07

and beyond the program will be positioned to make awards on an annual basis. Dr. Thompson provided the timeline and details of the proposed transition.

Mr. Larry Reed discussed the Superfund Basic Research Program External Advisory Group (EAG) which is being chaired by Dr. Dan Baden, to conduct an independent assessment of the contributions of the SPRP. The EAG will serve as a Working Group of the Council and report back to Council later on in the year.

XI. REPORT OF THE DIRECTOR, DIVISION OF EXTRAMURAL RESEARCH AND TRAINING (DERT) - Dr. Anne P. Sassaman

Dr. Sassaman called the Council's attention to the written report from the Division (Attachment D) and commented on staff changes, introducing new staff, and highlighting a few special activities since the last Council meeting. She alerted the Council to a new data sharing policy to be forthcoming from NIH, which emphasizes the NIH's expectation and support of the timely release and sharing of final research data from NIH studies for use by other researchers. This policy will be limited to applications requesting $500,000 or more in direct costs for any single year.

She then presented the fiscal report on extramural grant activities from Fiscal Year 2002. (See attachment E) She noted that there have been no major shifts in distribution of the budget among various categories, and that once again, the NIEHS success rate was very close to that of the NIH overall.

The final part of the Report of the DERT Director consisted of the presentation of a report to the Council on complicance with the NIH policy on inclusion guidelines, which was certified by the Council, and the annual review of Council Delegated Authorities and Guidelines for Staff Actions for the coming year. The Council approved the latter which included one change to delete the reference to Council review of fellowship applications. (See attachment F)

CLOSED PORTION OF THE MEETING

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).

XII. REPORT OF THE DIRECTOR, DIVISION OF INTRAMURAL RESEARCH - Dr. Lutz Birnbaumer

The first part of the closed session was devoted to a report from the Director, Division of Intramural Research (See Attachment G) and the Report from the Board of Scientific Counselors of recent Board reviews of the Laboratory of Reproductive and Developmental Biology, The Laboratory of Molecular Toxicology, the Laboratory of Women's Health, and the intramural research component of the National Center for Toxicogenomics.

XIII. REVIEW OF APPLICATIONS

The Council considered 301 applications requesting $65,665,028 in total cost. The Council recommended 179 applications with the total cost of $43,271,698.

XIV. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 11:30 on February 11, 2003.

ATTACHMENTS:

A. Council Roster
B. Abstract of Dr. Miranda; *Adobe Acrobat* Format
C. Abstract (Word) and slides of Dr. Sandler's presentation
D. Report of the Director, Division of Extramural Research and Training (WordPerfect)
E. Extramural grant activities FY02 (Slides)
F. Council Delegated Authorities and Guidelines for Staff Actions (Word)
G. Report of the Director, Division of Intramural Research; *Adobe Acrobat* Format

The Sister Study

Dale P. Sandler, PhD, Clarice Weinberg, PhD
Epidemiology Branch and Biostatistics Branch, NIEHS

The NIEHS Sister Study will prospectively examine environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 ***sisters of women who have had breast cancer***. Such sisters have about twice the risk of developing breast cancer as other women. The frequency of any relevant genes and shared risk factors will also be higher, increasing the statistical power of the study to detect risks. Sisters are expected to be highly motivated and response rates and compliance over time are expected to be high. Thus, studying sisters will enhance our ability to assess the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. The prospective design will allow us assess exposures before the onset of disease and avoid biases common to retrospective studies. The study will create a framework from which to test new hypotheses as they emerge.

Cancer-free sisters will be recruited nationally through health professionals, breast cancer advocates, the Internet, and a national advertising campaign. Recruitment strategies will be designed to maximize inclusion of minorities and high-risk women. Data on potential risk factors and current health status will be collected using computer assisted telephone interviews and mail questionnaires. Blood, urine, and environmental samples will be collected and banked for future use in nested studies of women who develop breast cancer (or other diseases) and a sample of those who don=t. The cohort will be followed prospectively for 10 or more years. Annual questionnaires will update medical history and changes in exposures. Medical records and tumor tissue will be retrieved for those who develop cancer. Medical records will also be sought to facilitate the study of other diseases of importance to women.

About 300 new cases of breast cancer are expected to occur in the cohort each year, with 1,500 cases after 5 years of follow-up. At that time, analyses will assess the independent and combined effects of environmental exposures and genetic polymorphisms that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors (e.g. smoking, occupational exposures, alcohol, diet, obesity) and include measurement of phthalates, phytoestrogens, and metals in blood and urine, insulin, growth factors, vitamins and nutrients, and genes. Ancillary studies will explore risk for other diseases (e.g. heart disease, osteoporosis, other hormonal cancers, and autoimmune diseases) and explore genetic and environmental effects on breast cancer prognosis by continuing to follow women in the cohort who develop breast cancer.

FEATURED ACTIVITIES of DERT
February 2003

MEETINGS

Thyroid Hormone and Brain Development Conference
September 23-25, 2003
Research Triangle Park, North Carolina

Recently, the NIEHS/NIH/DHHS jointly co-sponsored a conference entitled, "Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk," with the US EPA, NIH Office of Rare Disease, Agency for Toxic Substances and Disease Registry (ATSDR), American Chemistry Council, and the Center for Neuroendocrine Studies at the University of Massachusetts. This meeting, which included more than 150 clinicians, endocrinologists, epidemiologists, toxicologists and molecular biologists, as well as representatives of several advocacy groups, examined the current state of emerging multidisciplinary knowledge relevant to the role of thyroid hormones in brain development and the effects of environmental agents on this system. A summary of the science presented, a list of recommendations for future research directions and research challenges are summarized here.

- Thyroid hormone effects on brain development are receptor-mediated and vary with the time of development. Further, there are multiple types of thyroid receptors that play different roles in development, and the timing of thyroid insufficiency is associated with different neurological deficits. More laboratory-based studies are needed to understand both the relative sensitivity of various thyroid hormone-responsive endpoints in the developing brain to small changes in circulating levels of thyroid hormones as well as temporal windows of sensitivity to thyroid hormones.

- There are environmental chemicals, some PCBs for example, that can interfere with thyroid hormone action during brain development. It is likely they can affect signaling through selective thyroid hormone receptors thereby affecting brain development in a mosaic pattern. More information is needed to understand the site and mechanism of action of these environmental chemicals during brain development. Thus, it is critical to improve animal models of thyroid disruption as well as our ability to extrapolate animal data to human risk.

- To improve our understanding of the basic biology of brain development, as well as the site and mechanism of action of environmental chemicals that target the thyroid system, there is a need to increase the use of 'omics' technology, develop and use new imaging technologies, develop and use genetic models of thyroid hormone receptor defects or deficiency, and increase multidisciplinary and interdisciplinary research projects.

- It is clear that thyroid deficiency during pregnancy can result in neurological deficits in the children. It is also known that fetal thyroid receptors are present before the onset of fetal thyroid function so the fetal brain development is dependent on maternal thyroid hormone. Thus it may be prudent to know that maternal thyroid status is normal before, as well as during, pregnancy to assure that both the mother and fetus are healthy.

Nursing and Environmental Health Roundtable
August 26-27, 2002
Research Triangle Park, North Carolina

Recognizing the important contributions nurses make to improving public health and reducing health disparities, the National Institute of Environmental Health Sciences (NIEHS), the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Nursing Research (NINR)

collaboratively organized and hosted a roundtable on nursing and environmental health. The roundtable, convened on August 25-26 in Research Triangle Park, North Carolina, brought together representatives from schools of nursing, state and local health departments, schools of public health, national organizations, and federal agencies. The goal of the roundtable was to identify areas for potential collaborative initiatives to advance environmental health nursing in each of the following areas: (1) Research, (2) Education, and (3) Translation to practice.

A final report of this meeting is available on line and upon request. The report highlights the issues discussed by roundtable participants and outlines several proposed priority recommendations to continue advancing work in environmental health nursing. Topics discussed during the roundtable include:

Nursing and Environmental Health Clearinghouse
A centralized repository of environmental health journal articles and educational materials and resources could provide nurses, especially nurse researchers, with a valuable tool. Such a clearinghouse could help raise awareness about nurse involvement in environmental health research and enhance overall dissemination of information.

Integration of environmental health materials into existing curricula
Current requirements at schools of nursing make it difficult for nurses to take elective courses in environmental health. Therefore, participants proposed that more work should be done to integrate environmental health materials into existing coursework. In addition, a document should be developed that spotlights schools and universities that are already successful at doing this.

Partnerships and resources
Participants recognized that many federal agencies support nursing in environmental health in some capacity, yet there is limited interaction among the various programs. Therefore, roundtable participants emphasized the importance and the benefits of increased collaboration among federal agencies, as well as between federal agencies and private organizations that support nursing efforts.

Journals and environmental health nursing
Roundtable participants expressed need for existing nursing journals to showcase important environmental health issues and research advances. Participants also proposed the establishment of a journal specifically targeted to nursing and environmental health.

For more detail on the roundtable and to obtain a copy of the final report, please visit the roundtable website at http://www.niehs.nih.gov/translat/nurse-rt.htm. The roundtable report and website also includes a list of recommended reading materials pertaining to nursing and environmental health.

International Conference on Chemical Mixtures
September 10-12, 2002
Atlanta, Georgia

The NIEHS SBRP was one of several federal and international organizations that co-sponsored the International Conference on Chemical Mixtures. People are generally exposed to mixtures of chemicals rather than to a single chemical. Such exposures occur through various environmental media and through multiple routes of exposure. Mixtures research is an important topic because of its potential impact on how risk is assessed in populations exposed to multiple environmental agents. However the complexities of studying mixtures has limited the ability to effectively assess risk and it remains one of the great challenges of toxicological research. Not only is there a general lack of knowledge concerning the characterization of the exposures to mixtures, to date, there are limited experimental strategies and statistical for assessing interactions of chemical mixtures in the human body. To evaluate the joint toxicity of such complex exposures, strategies must be developed to integrate experimental and computational methods for a more scientifically credible risk assessment of chemical mixtures.

It was the objective of this conference to advance the science by exchanging information, stimulating discussion, and promoting cooperation among scientists worldwide. The sessions were designed to highlight the most recent advances in mixture research and focused on issues pertaining to basic mechanistic research on chemical mixtures, mixtures health risk assessment, and computational modeling of chemical mixtures. The anticipated outcomes from this meeting were the development of better methods to conduct mixtures research, assess risks from exposure to mixtures, and develop interaction physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models of mixtures.

Chemical mixtures research topics included: (1) advances in experimental designs of simple and complex mixtures studies; (2) analysis of low-dose chronic and high-dose acute exposure studies; and (3) novel methods for end-point-specific toxicities incorporating toxicogenomics, proteomics, and integrative research. Sessions on risk assessment focused on qualitative and quantitative methods for health risk assessments of mixtures, the development of databases to include information on toxicology of mixtures and the identification of priority mixture combinations. There were several sessions devoted to computational methods and included application and validation of PBPK/PD models, quantitative structure-activity relationships (QSAR) modeling methodologies and the use of bioinformatics to identify toxic interaction mechanisms.

A workshop entitled “Risk Assessment of Mixtures: Development of Testable Hypotheses” preceded the mixtures conference. This workshop was organized under the auspices of the Society of Toxicology (SOT) and sponsored by NIEHS, EPA, and the Chlorine Chemistry Councils’s Research Foundation for Health and Environmental Effects. This was the final workshop in a series of meetings held over the past two years that has been sponsored by this group. An expert panel was assembled and charged with proposing specific biologically-based hypotheses and experimental approaches that will generate empirical and mechanistic datasets useful to enhancing the scientific quality of future risk assessments and regulatory policies directed at chemical mixtures. The results of the workshop were presented on the opening day of the International Conference on Chemical Mixtures.

2002 Superfund Basic Research Program (SBRP) Annual Meeting: ***Transitioning Basic Science into Practical Applications to Meet Environmental and Public Health Challenges***
November 3-6, 2002
Tucson, Arizona

The theme of the 2002 SBRP annual meeting, sponsored by the National Institute for Environmental Health Sciences, Superfund Basic Research Program and hosted by the University of Arizona, focused on the transfer of technology and the dissemination of information relevant to assessing, evaluating and remediating hazardous substances to reduce the toxicity and the uncertainty of risk. More than 200 participants, including students, staff and researchers from the nineteen SBRP-funded university programs, gathered to learn about technology transfer activities that have evolved from basic laboratory research to practical applications, with discussion on the pathways that investigators have taken to achieve this. Representatives from the Environmental Protection Agency (EPA), the Department of Energy (DOE), the Arizona Department of Environmental Quality, and independent commercial consultancies and research institutes also joined in this year’s conference discussions. Presentations provided an exciting glimpse of innovative tools that can be used to exploit rich data sets generated by genomic, proteomics, imaging and exposure assessment technologies.

Throughout the two and a half day conference, technical sessions highlighted technology transfer activities that have evolved from basic laboratory research to practical applications and the paths that investigators have taken to achieve this. A broad spectrum of research was presented during the sessions, providing a greater understanding of the work currently being performed by the program’s researchers. Major themes from this year’s presentations included:

- Transitioning phytoremediation and bioremediation techniques from the laboratory to the field.
- Emerging biomarkers of toxic exposure and disease in humans.
- Competing goals of researchers and end users when implementing innovative remediation technologies.
- Communicating research results to relevant target audiences.

Continuing its ongoing support for student excellence in science research and training, SBRP sponsored two student poster sessions during the conference, providing graduate and post-doctoral students with the opportunity to present their research findings. All of the research projects represented at the poster sessions were funded in part by the SBRP. Two students were chosen from the total submission pool and presented with an award for outstanding student research.

In addition to the student poster award ceremony, the 2002 Karen Wetterhahn Memorial Award was presented to Elena S. Craft for her research on "Metal Induced Activation of Metallothionein Gene Expression." Ms. Craft is a post-doctoral student at Duke University's Nicholas School of the Environment. The award recognizes her research examining the effect of heavy metals on biological processes and will support Elena's participation in one major upcoming scientific conference.

In addition to the conference's technical and student poster sessions, Administrators and Outreach Core staff from each SBRP university program met concurrently in their own meetings to review information relevant to their roles and responsibilities.

The Outreach sessions addressed subjects of particular interest to those involved in the task of communicating the SBRP's results to the communities and organizations most concerned with hazardous substances. Session topics included:

- Strengthening the SBRP Outreach Cores Network
- Community Partnerships Curriculum
- Measuring the Outcomes of Outreach Programs
- Beyond Publication: Technology and Information Transfer
- Applying Advanced Technologies to Outreach Programs

Administrators met to review details and updates regarding grant proposals and renewal submissions. Several key items were discussed at this year's meeting. Particular emphasis was placed on the new December submission date for annual updates. It was also announced that it is anticipated, beginning in 2004, that an SBRP RFA will be released every year. Applicants will apply for five-year awards; however, based on funds available, awards will be made for 3, 4, 5, and 6 years. Furthermore, it was also announced that it is anticipated that approximately half of the existing grants will re-compete in 2004 and the other half in 2005. NIEHS staff also provided Administrators with a description of the newly created SBRP External Advisory Group, which has been established to provide an independent constructive assessment of the SBRP's effectiveness, role and future directions. This group will provide a summary report of observations, recommendations and conclusions, which will be made available before next year's SBRP annual meeting.

Center Directors' Meeting
October 20-21, 2002
Seattle, Washington

The theme of the 60th Annual NIEHS Core Center Directors Meeting was, "Gene-Environment Interactions Research in the Post-Genome Era: Looking to the Future." Hosted by the University of Washington's Center for Ecogenetics and Environmental Health, this exciting meeting brought together Center Directors, Business Administrators, COEP Directors, NIEHS staff and other interested scientists. In addition,

members of the NIEHS Public Interest Liaison Group (PILG) attended the meeting to learn about the innovative work at Core Centers.

During the scientific symposium, guest presenters addressed the historical perspective of gene-environment interactions, current research and ethical, legal and social implications of gene-environment research. To conclude the symposium, a panel of Center Directors discussed challenges and future opportunities in this research field.

In FY 2002, NIEHS announced two opportunities for supplemental funding. The first addressed genomics, proteomics and ELSI. The second announcement was for WTC response efforts. Centers that received administrative supplements presented their accomplishments to meeting participants.

COEP Meeting
October 19-21, 2002
Seattle, Washington

The annual COEP meeting was convened in conjunction with the 60th Annual NIEHS Core Center Directors' Meeting. This year the meeting focused on the following three topics: community partnerships, government and public policy, and use of the media. In addition, Dr. Mohammed Akhter, former executive director of the American Public Health Association, gave a special keynote address. Dr. Akhter presented a public health perspective on environmental health issues and he urged COEPs to consider the APHA a partner in their mission of translating research into public health applications.

Community Partnerships – this session addressed the issue of: "Community Partnerships: Why they are important and what are some successful models?" In this session, presenters highlighted their efforts to engage community participation in their Center and to address community needs. Specifically, they discussed the use of Town Meetings, community forums, and community-based projects. The presenters then led breakout sessions on those topics.

COEP, Government, and Public Policy — presenters addressed the processes, benefits and challenges of interfacing with government and policy makers. They emphasized the need for Centers and COEPs to be a unbiased source of information. In addition, invited representatives from the American Lung Association of Washington state and from the NIEHS Public Interest Liaison Group (PILG) discussed how their organizations address public policy issues and how they could assist COEPs.

COEP and the Media — this session examined the ways in which COEPs can work with the media to increase public awareness of environmental health issues. The University of Washington Media Relations Coordinator described her work in facilitating the exposure of scientists to reporters and in managing the relationship between the university and the media. She offered advice on delivering scientific information to the media, preparing effective communications, and dealing with difficult individuals and politically-charged issues.

NIEHS Division of Extramural Research and Training Scientific Retreat
November 21-22, 2002
Wilmington, North Carolina

The Division of Extramural Research and Training (DERT) third annual scientific retreat was held in Wilmington, North Carolina on November 21-22. The purpose of the retreat was to explore opportunities in new and existing topics related to the theme "Transitional Research: where basic science has provided mechanisms/tools to intervene/prevent disease," and how these opportunities can be incorporated into current environmental health science research.

The retreat was developed around the following three scientific sessions:

Session 1: Evaluation of Science: Models for Determining Scientific, Public Health Impact and Policy.

In light of recent emphasis on evaluating research impact, this session examined the value and challenges of evaluating science and technology, the power of economic analysis in scientific evaluation, and current mechanisms to support evaluations of NIH programs. Three major points of discussion were:

Research Value Mapping: emphasizes that both **Output/Impact evaluations,** which conform to the expectations of policy makers by focusing on measurable outcomes, and **Capacity evaluations,** which examine the scientific and human capital that result from a project, are valuable methods for research institutions.

Economic data and environmental health policy: demonstrating economic impact of environmental-related disease captures the attention of the public, policy makers and federal funding agencies, and stimulates action (e.g. lead policies). Economic data helps focus research and prevention efforts, puts costs of pollution control into perspective, permits comparisons with other health issues and societal problems, and guides process for setting budget priorities.

Evaluation at NIH: the1% set-aside program provides money to conduct Needs Assessment, Feasibility Studies, Process Evaluations, and Outcome Evaluations. Proposals for trans-NIH evaluations receive greater attention.

Session 2: Arsenic Exposure: Mechanisms, Speciation, and Policy.

This session addressed molecular mechanisms of arsenic exposure, speciation and toxicity of arsenic, and arsenic risk assessment and risk management. Three main points from the presentations included:

New technologies: need to use microarrays/proteomics to examine molecular signatures.

Coordination among researchers: researchers use an array of models (dog, hamster, chick, and mouse) and approaches to understand impact of chronic low-dose arsenic exposure. Need to develop further mechanisms to promote coordination among researchers.

Developmental effects: as a co-genotoxin and co-mutagen, its necessary to examine the impact of arsenic on fetal programming/imprinting.

Session 3: Environmental Medicine: Cases from an Emerging Discipline.

> *Environmental Medicine: "The study of effects upon human beings of external physical, chemical and biologic factors in the general environment."* (Hu, H. and Woolf, *A.* Environmental Medicine as an Emerging Discipline*.* 2003 *draft of EHP Grand Rounds in Environmental Medicine*; 111:1-3.)

This session focused on how basic research can be translated to increase awareness of environmentally-related diseases and to establish prevention programs. Presenters highlighted useful resources, discussed how this approach is currently taking place, and identified gaps and next steps.

Association for Occupational and Environmental Clinics (AOEC): a potential resource for NIEHS collaborations to translate environmental health research into knowledge and tools for use in clinics around the country.

Translating mechanistic research into public health interventions: important to identify biomarkers for early disease detection to have greatest public health impact. DNA found in blood and the blood proteome may serve as an early detection of disease marker.

New challenges in research in pediatric environmental medicine: prevention of disease of environmental origin in children will depend on translation of research findings along with risk assessment, legislation, toxicity testing of chemicals/developmental testing.

Psychosocial stressors and biological/physical exposures: conclusions from recent case studies indicate that psychosocial stressors combined with physical exposures leads to disease. Findings suggest that behavioral factors need to be considered when developing health and safety standards.

Special Keynote Address

Dr. Anne Sassaman, Director, DERT, discussed the process of signing a Memorandum of Understanding (MOU) with Vietnam government officials. It is hoped that the MOU will foster increased US-Vietnam government initiatives on health and environmental impacts of Agent Orange.

DERT PAPERS OF NOTE

Mice Heterozygous for *Blm* Mutation have Increased Tumor Development
Joanna Groden
University of Cincinnati College of Medicine, and Howard Hughes Medical Institute P30ES06096

Background: In traditional Mendelian genetics, dominant and recessive genes exist. For example, the gene for blue eyes is recessive while the gene for brown eyes is dominant. If a person inherits one allele for blue eyes from one parent and one for brown from the other parent, he is said to be heterozygous and in this case, since the blue-eyed gene is recessive, he will have brown eyes.

In cancer biology, there are many tumor suppressor and DNA repair genes that are dominant. Therefore, heterozygous animals are sufficiently protected against certain cancers. The gene controlling the formation of Bloom syndrome is a DNA repair gene known as *Blm*. Bloom syndrome is characterized by small stature, male infertility, a compromised immune system, and increased risk for a variety of tumors including colorectal cancer.

Advance: Researchers at the University of Cincinnati supported jointly by NIEHS, NCI, and the Howard Hughes Medical Institute, report that contrary to the traditional Mendelian inheritance pattern described above, mice heterozygous for *Blm* are at higher risk for cancer development. When challenged with murine leukemia virus, heterozygous mice developed lymphoma earlier than wild-type mice. Also, when cross matings were performed with mice susceptible to intestinal tumors, heterozygous offspring developed twice the number of intestinal tumors.

Implications: These findings describe the increased risk and genetic mechanism for intestinal cancer development in mice heterozygous for *Blm* and have implications for cancer risk in humans. In fact, a companion paper published in the same journal describes an epidemiologic study of Ashkenazi Jews which reports that people heterozygous for the same allele were more than twice as likely to develop colorectal cancer as control subjects.

Citations: Goss KH, Risinger MA, Kordich JJ, Sanz MM, Straughen JE, Slovek LE, Capobianco AJ, German J, Boivin GP, Groden J. Enhanced tumor formation in mice heterozygous for Blm mutation. Science. 2002 Sep 20;297(5589):2051-3.

Gruber SB, Ellis NA, Rennert G, Offit K, Scott KK, Almog R, Kolachana P, Bonner JD, Kirchhoff T, Tomsho LP, Nafa K, Pierce H, Low M, Satagopan J, Rennert H, Huang H, Greenson JK, Groden J, Rapaport B, Shia J, Johnson S, Gregersen PK, Harris CC, Boyd J.
BLM heterozygosity and the risk of colorectal cancer. Science. 2002 Sep 20;297(5589):2013.

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Are Gene Polymorphisms Responsible for Higher Risk of Congestive Heart Failure in African-Americans?

Stephen B. Liggett
University of Cincinnati College of Medicine, and Howard Hughes Medical Institute P30ES06096

Background: Congestive heart failure (CHF) is one of the leading causes of death in the U.S. and is the result of diverse insults to the heart including previous incidences of ischemia, hypertension, and infections. Frequently, no cause can be identified and these patients carry a diagnosis of idiopathic cardiomyopathy. Nearly five million people in the U.S. suffer from the most common forms (idiopathic and ischemic) of heart failure and about half of the patients die within 5 years. Predicting who develops CHF in the general population, or in those with some preexisting cardiac disease, has been an elusive goal. However, racial differences in the incidence, progression, and response to therapy suggest that a genetic component is having an influence.

Physiologically, the presynaptic α_{2c}- and the postsynaptic β_1- adrenergic receptors work in combination to control the release of norepinephrine and the resulting force of the heart muscle contraction. Polymorphic variations in these receptors, which cause increased amounts of norepinephrine release and enhanced activity in the heart, could result in more forceful heart contractions over a period of years, leading to higher incidences of heart failure. These researchers investigated the incidence of these polymorphisms in a group of 348 blacks and whites who were either healthy or heart failure patients.

Advance: In black subjects homozygous for the variant α_{2c} receptor, the risk of developing congestive heart failure was over 5 times higher than those subjects with other receptor types. There was no increase in risk with the β_1 variant alone. However, among subjects who had both variant receptors, the risk for heart failure was over 10 times higher than subjects without the variant receptors. White subjects with either one or the combination of variant receptors had no significantly increased risk. This is most likely due to the fact that the α_{2c} is so uncommon in whites. The allele frequency of the α_{2c} variant occurs is about 40% in blacks and only about 4% in whites.

Implication: Although this was a small study which needs to be replicated in a study with many more subjects, it could have important practical implications. It could explain the higher rates of morbidity and mortality from CHF in blacks than in whites. It suggests that genetic screening would help to determine high risk individuals and families. This knowledge would also have implications in treatment and prevention practices. For instance, for those individuals with both variant receptors, reduction of all other risk factors, such as smoking, high cholesterol, obesity, and inactivity, may be of extra importance. Screening tests for heart enlargement and the possible use of beta-blockers prophylactically could also be indicated.

Citation: Small KM, Wagoner LE, Levin AM, Kardia SLR, Liggett SB. Synergistic Polymorphisms of β_1- and α_{2c}-Adrenergic Receptors and the Risk of Congestive Heart Failure. New England Journal of Medicine. 2002 October 10; 347:(15):1135-1142.

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That Darn Cat. Allergen That Is.
Diane Gold
Brigham and Women's Hospital
R01AI/ES35786

Background: Exposure to cats, or more precisely, exposure to the natural allergens from their skin and hair, has been implicated in the development of asthma in children. Asthma is a serious illness affecting approximately five million children in the U.S. and accounting for more missed school days than any other children's disease resulting in staggering amounts of lost work productivity for parents who must stay home with sick children. Asthma is also a very expensive illness with estimates as high as $11 billion/year in health care costs. Some studies have shown a positive correlation for asthma incidence and exposure to cat allergens while others have shown no correlation. These investigators performed an epidemiologic study with 448 children and their families to study the associations of cat and dog allergens, maternal and paternal history of allergies, and asthma development in these children.

Advance: Supported jointly by NIEHS and NIAID, the research team determined that among children whose mothers had no history of asthma, exposure to cat allergens at 2-3 months of age was associated with a 40% *reduced* risk of wheezing, a symptom of asthma, between age 1 and 5. However, among children whose mothers did have a history of asthma, similar exposure was associated with an 2.4-fold *increased* risk of wheezing at or after 3 years of age. There was no association of wheezing with exposure to dog allergens and the father's asthma/allergy status had no effect.

Implication: These findings suggest that maternal history of asthma affects the relationship between exposure to cat allergen and wheezing among children with a parental history of allergy. The data suggest that women with a history asthma should avoid owning cats to protect their young children from developing asthma.

Citation: Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. Lancet. 2002 Sep 7;360(9335):781-2.

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The Relationship Between Physical Activity and Menstrual Cycle Characteristics
Ellen B. Gold
University of California Davis
K04ES00202

Background: Numerous studies have shown that women who exercise regularly are at decreased risk for breast cancer than women who lead a more sedentary lifestyle. However, the reasons for this difference have not been fully determined. One possible explanation could be an overall more healthy lifestyle for the women who exercise. Regular vigorous exercise can lead to shorter menstrual cycles, and in extreme cases usually involving competitive athletes, missed menstrual cycles, resulting in decreased exposure of breast tissue to circulating estrogens and progesterone at various stages of the cycle. Therefore, because breast cancer is a hormonally mediated disease, these investigators investigated the role of exercise-induced changes in menstrual cycle characteristics.

Advance: Physical activity was associated with increased menstrual cycle lengths. The magnitude of this association was decreased as the body mass index increased, suggesting that the highest benefit is seen in women of normal physical stature.

Implication: The finding that more physical activity was related to longer menstrual cycles is suggestive of a mechanism or mechanisms by which exercise might reduce the risk and incidence of breast cancer. The finding also is supportive of the benefits of promoting regular, even vigorous, physical exercise. To

build upon this finding, future studies should be aimed at assessing the effects of exercise on the control of hormonal feedback and reducing hormone levels.

Citation: Sternfield B, Jacobs MK, Quesenberry CP, Gold EB, and Sowers M. Physical Activity and Menstrual Cycle Characteristics in Two Prospective Cohorts. American Journal of Epidemiology. 2002 September;156(5):402-9.

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Genetic Susceptibility, Maternal Smoking, and Environmental Tobacco Smoke All Contribute to Asthma in Children

Frank Gilliland, W. James Gauderman, and John M. Peters
University of Southern California Keck School of Medicine
P01ES09581 and P30ES07048

Background: Over the past 25 years, the incidence of asthma in children has grown exponentially in the U.S. and other industrialized countries. Many theories based on a plethora of research have been offered for this uncontrolled growth including environmental factors and genetic susceptibility. The evidence that both genetics and the environment play roles in asthma development further suggests changes in specific exposures among genetically susceptible individuals are responsible.

One possible genetic factor is the polymorphic gene for the enzyme glutathione S-transferase (GST) M1. GSTM1 is involved in the detoxification of reactive tobacco smoke metabolic intermediates and reactive oxygen species. In some individuals, the gene for GSTM1 is completely lacking and thus the enzyme is not produced. In an epidemiologic study of 2,950 children in Southern California, this research team investigated the effects of maternal smoking during pregnancy, exposure to environmental tobacco smoke, and the GSTM1 genotype on the development of asthma and children.

Advance: In children lacking the gene for GSTM1, in utero exposure to maternal smoking was associated with an increased prevalence of early onset asthma, persistent asthma, lifetime wheezing, wheezing while exercising, and emergency room visits for asthma symptoms in the previous year. Among children with the GSTM1 gene, in utero exposure to maternal smoking was not associated with asthma or wheezing.

Implication: This study has identified a genetically susceptible population of children at high risk for the development of asthma in response to maternal smoking. Since maternal smoking and the susceptible genotype are common, this study illustrates the need for interventions, such as smoking cessation programs, for the mothers of children in this high risk group.

Citation: Gilliland FD, Li YF, Dubeau L, Berhane K, Avol E, McConnell R, Gauderman WJ, Peters JM. Effects of Glutathione S-Transferase M1, Maternal Smoking during Pregnancy, and Environmental Tobacco Smoke on Asthma and Wheezing in Children. Am J Respir Crit Care Med. 2002 Aug 15;166(4):457-63.

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Anthrax Invades and Evades the Immune System to Cause Widespread Infection

Michael Karin
University of California, San Diego
R37ES04151, R01ES06376, and P42ES10337

Background: The popular press has been filled with reports of anthrax exposure since September 11th. Usually a disease that strikes mostly livestock and wild animals, it has become a household word since its use as a weapon of terror. The most severe form of the disease results from inhalation of Bacillus anthracis spores which are engulfed or phagocytised by macrophages in the lung. Phagocytosis of bacteria by macrophages is a normal and effective method of the innate immune system to fight the

spread of infection. However, in the case of anthrax, the bacteria survive phagocytosis, reproduce within the cells, and use the macrophages as a transport mechanism to invade lymph nodes and eventually the blood stream leading to widespread infection, disease, and death. Until now, the mechanisms by which B. anthracis kills macrophages and avoids detection by the host immune system has been unclear.

Advance: NIEHS supported researchers at the University of California at San Diego have discovered that B. anthracis evades the host immune system, using a toxin called lethal factor (LF) to destroy macrophages and spread throughout the body. Apparently LF cleaves a mitogen activated kinase (MAPK) kinase that activates p38 MAPK by a cellular process known as phosphorylation. If p38 is not activated inside the macrophage the cell dies by apoptosis rather than proliferating. This is quite common in the immune system; if a cell doesn't get all the right signals for proliferation it dies. Since the macrophages do not proliferate, their ability to secrete the signaling agents that rev up the immune system is greatly reduced and thus the natural immune system does not mount the necessary defense to fight the infection. The investigators speculate that many other pathogenic bacteria probably use this approach.

Implication: These results may explain why anthrax infections proceed nearly undetected until the patient is very sick and near death. Since the cascade of events leading to infection is now clearer, this research may clear a path to the discovery of a drug or agent to block the action of LF and therefore, give the immune system, and other therapeutic agents, more time to detect the infection and fight it. Future research by these investigators will focus on the intricate balance of macrophage activation and death since it seems to play a key role in the ability of the bacteria to spread, multiply, and set up a deadly systemic infection.

Citation: Macrophage Apoptosis by Anthrax Lethal Factor Through p38 MAP Kinase Inhibition Jin Mo Park, Florian R. Greten, Zhi-Wei Li, and Michael Karin. Published online August 29 2002; 10.1126/Science.1073163

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Antioxidant Intake is Associated with Paraoxonase Activity
Clement Furlong
University of Washington
R01ES09883

Background: Paraoxonase (PON1) is an enzyme involved in preventing vascular disease. It is physically associated with high density lipoprotein (HDL), the so-called "good" cholesterol, and may have its protective effects by preventing oxidation of low density lipoproteins (LDL) also known as the "bad" cholesterol. The enzyme is also active in chemical metabolism in that it inactivates the toxic metabolites of some insecticides as well as the nerve agents sarin and soman. This multi-purpose enzyme is usually present in lower serum concentrations in patients with coronary artery disease, coronary heart disease, and myocardial infarction. Vascular disease risk factors such as tobacco consumption are also known to depress the concentration of PON1. Free radical oxygen species are products of metabolic activity and are known to depress PON1 activity. Since the antioxidant vitamins C and E destroy free radicals, these investigators wanted to determine if the consumption of antioxidants would have an effect on PON1 activity.

Advance: In an epidemiologic study of 189 subjects, dietary intakes of vitamin C and of vitamin E were significant predictors of PON1 activity. The higher the intake of the vitamins, the higher the concentration of PON1. Current smoking predicted a decrease in PON1 activity. Current statin drug use was also associated with increased PON1 activity.

Implication: Although the effects of PON1 on LDL oxidation appear to be independent of the function of the antioxidant vitamins, vitamins C and E have been shown to inhibit LDL oxidation as well. Therefore any reduction in oxidative stress related to the intake of vitamins C and E may help to maintain PON1 levels and therefore reduce the risk of cardiovascular disease. PON1

activity appears to be a good predictor of the risk of vascular disease; therefore, further studies of other environmental influences on PON1 activity are warranted.

Citation: Jarvik GP, Tsai NT, McKinstry LA, Wani R, Brophy VH, Richter RJ, Schellenberg GD, Heagerty PJ, Hatsukami TS, Furlong CE. Vitamin C and E intake is associated with increased paraoxonase activity. Arterioscler Thromb Vasc Biol. 2002 Aug 1;22(8):1329-33.

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Early Exposure of Mice to DES Causes Developmental and Sperm Function Deficits
Robert G. Halgren
Michigan State University
T32ES07255

Background: Diethylstilbestrol (DES) is a non-steroidal synthetic estrogen that was once used to prevent miscarriages in pregnant women. Tragically, DES was shown to cause cervical clear cell adenocarcinoma, a very rare form of cancer, in the female offspring of women who took it. DES has also been implicated as a cause of several adverse reproductive outcomes in male offspring such as anatomical malformations, testicular cancer, reduced sperm count, and impaired fertility. Estrogen-like compounds in the environment have been purported to cause similar effects in wildlife populations, and human epidemiologic studies suggest that sperm counts are declining and that testicular cancer and reproductive malformations are increasing. These studies have raised the concern that exposure to synthetic and natural endocrine disrupting chemicals has the potential for causing adverse effects on human reproductive health.

The molecular mechanisms responsible for the adverse effects of DES are unclear, although there is evidence that the initiating events involve changes in gene expression. While there is much literature describing the adverse effects of DES, very little is known about its effects at low doses on gene expression. To test the hypothesis that the long-term effects of DES on the male reproductive system are result of lasting changes in testicular gene expression and to potentially identify early biomarkers of adverse effects at later stages of life, these investigators employed a DNA microarray to identify gene expression changes in the testes of affected mice.

Advance: This study demonstrated a long-term decrease in the number of Sertoli cells, epididymal sperm count, and in vitro fertilizing ability in mice after gestational and lactational exposure to DES. Additionally, a number of changes in gene expression were observed including genes involved in steroidogenesis, lysosomal function, and testicular development. Notably, Hoxa10 expression was depressed. Hoxa10 knockout mice manifest bilateral cryptorchidism which ultimately results in defects in spermatogenesis and sterility. Estrogen receptor expression was also significantly depressed.

Implication: This study demonstrates the potential for developmental exposure to DES, and possibly other estrogenic chemicals, to irreversibly alter testicular growth, sperm function, and testicular gene expression. Comparisons of the effects of other estrogenic chemicals to those observed after DES exposure will allow for the development of biomarkers for estrogenic effects on testicular development and sperm function, and add to the knowledge base of the effects of environmental estrogens on male reproductive function.

Citation: Fielden MR, Halgren RG, Fong CJ, Staub C, Johnson L, Chou K, Zacharewski TR. Gestational and lactational exposure of male mice to diethylstilbestrol causes long-term effects on the testis, sperm fertilizing ability in vitro, and testicular gene expression. Endocrinology. 2002 Aug;143(8):3044-59.

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High Amounts of Polycyclic Aromatic Hydrocarbons Found in Dust from The World Trade Tower Disaster

Paul Lioy
University of Medicine and Dentistry of New Jersey
P30ES05022

Background: The attack on the World Trade Towers resulted in an intense fire and the subsequent collapse of both structures. As a consequence, a large plume of dust and smoke developed that released both particles of various sizes and gases into the atmosphere. In the initial 12-18 hours after the disaster, prevailing winds transported the plume to the east and southeast towards Brooklyn. To begin to assess the health risks to the general population and to emergency responders, samples of settled dust were taken in 13 locations around the site within the first few days of the disaster.

Advance: The bulk of the material contained in the dust samples was pulverized building materials consisting of concrete, wood dust, and glass fibers. These materials were of a size that would prevent them from being deposited deep within lung tissue. However, there was a small yet significant percentage of polycyclic aromatic hydrocarbons (PAH) found in the dust. The sources of the PAHs were the fires that consumed a diverse mix of jet fuel, plastics, wood, metals, and other synthetic materials. Based on the samples obtained, the researchers estimate that between 100 and 1,000 tons of PAHs were spread throughout lower Manhattan.

Implication: PAHs are classified as probable human carcinogens. These findings provide conclusive evidence that significant amounts of PAHs were released into the atmosphere. Whether cancers will occur as a result of these exposures has yet to be determined. This study provides baseline data, which may be used in future risk assessments to determine the extent to which adverse health outcomes may result from these exposures.

Citation: Persistent Organic Pollutants in the Dusts That Settled across Lower Manhattan after September 11, 2001. Offenberg, J. H.; Eisenreich, S. J.; Chen, L. C.; Cohen, M. D.; Chee, G.; Prophete, C.; Weisel, C.; Lioy, P. J. Environ. Sci. Technol.; (Article); 2002; ASAP Article; DOI: 10.1021/es025730g

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Erythropoietin Protects the Vascular System by Activating a Protein Kinase and Mitochondrial Modulation of Cysteine Proteases
Kenneth Maiese
Wayne State University
P30ES06639

Background: Erythropoietin (EPO) is a naturally occurring substance most widely known for its ability to stimulate the production of new red blood cells. However, recent research has shown it to have potential as a protectant against toxic stimuli in the nervous system. The focus of the current research effort is to investigate EPO's potential to foster the survival of cerebral microvascular endothelial cells (ECs) and prevent programmed cell death as a result of ischemic injury.

Advance: Using EC cell culture models, the research team determined that EPO prevented damage to cellular DNA and membrane functions. Further experiments with an anti-EPO neutralizing antibody completely blocked the protective effects suggesting that EPO is necessary and sufficient for the prevention of EC apoptosis. Further studies showed that protection was dependent on EPO-induced activation of protein kinase B, the maintenance of mitochondrial membrane potential, and the inhibition of enzymes involved in the release of mitochondrial cytochrome *c* release.

Implication: This work serves to illustrate that EPO offers novel cytoprotection during ischemic vascular injury resulting from strokes. This occurs through modulation of protein kinase B phosphorylation, mitochondrial membrane functions, and cysteine protease activity. Further studies will need to be

conducted to determine whether EPO could prove to be a useful tool for protecting against ischemic injury in humans.

Citation: Chong ZZ, Kang JQ, Maiese K. Erythropoietin is a novel vascular protectant through activation of Akt1 and mitochondrial modulation of cysteine proteases. Circulation. 2002 Dec 3;106(23):2973-9.

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An Endoplasmic Reticulum (ER) Stress-Induced Protein Controls a Protein Kinase—Implications for Viral Infections
David Ron
New York University School of Medicine
R01ES08681

Background: Cells react to environmental stressors by regulation of mRNA translation. A key step in this process is modification of the phosphorylation of a protein known as eukaryotic initiation factor (eIF) 2α. In eukaryotic cells, eIF2α kinases have been identified including protein kinase R (PKR), which is activated during cellular responses to the accumulation of unfolded proteins in the ER. Another is PKR-like ER kinase (PERK). In response to viral infection, host cells stimulate PKR-mediated eIF2α phosphorylation, thus shutting off protein synthesis including the synthesis of viral proteins.

Advance: Previous research in this laboratory identified a PKR inhibitor, $P58^{IPK}$, which is activated after influenza virus infection. The present study sought to gain insight into additional functions of $P58^{IPK}$. Among the findings presented, the investigators report that $P58^{IPK}$ interacts with and inhibits PERK activity and plays a role in the expression of downstream markers of PERK activity in ER-stress response.

Implication: These studies show that with respect to $P58^{IPK}$, the influenza virus has found a way to co-opt a host gene in order for the virus to proliferate in the host cells. Although this is a very basic discovery, it provides insight into the mechanisms by which the influenza virus uses its host's cellular mechanisms to cause infection and illness. This finding may be useful in designing new therapeutic mechanisms to fight infection of influenza viruses.

Citation: Yan W, Frank CL, Korth MJ, Sopher BL, Novoa I, Ron D, Katze MG. Control of PERK eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK. Proc Natl Acad Sci U S A. 2002 Dec 10;99(25):15920-5.

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World Trade Center Cough: Lessons Learned
Lung Chi Chin and George Thurston
New York University School of Medicine
P30ES00260

Background: In the aftermath of the World Trade Center attack and collapse, thousands of people were exposed to high concentrations of gaseous and particulate matter air pollution. This pollution resulted from the release into the atmosphere of millions of tons of pulverized and incinerated building materials, furniture, equipment, and unburned jet fuel. Many residents and emergency responders reported a persistent "World Trade Center cough" despite the pronouncements of safety by a variety of government agencies. This team provides a possible explanation for this disparity.

Advance: One property of the dust that is probably most responsible for its irritancy is its caustic nature. The pH of the bulk of the dust was greater than 10, which is irritating to the mucous membranes found in the nose and throat. The pH decreased as the size of the particles decrease to around neutral pH at 2.5 microns and smaller. The caustic large dust particles caused temporary nose, throat, and upper airway

symptoms; however, they were effectively caught by the body's defenses. Conversely the fine dust that did reach the lungs was lower in concentration and much less caustic. Therefore, although severe acute symptoms were reported, the overall dust exposures probably will not have cumulative health implications for the general population in lower Manhattan.

Implications: The important public health lesson to be learned from this disaster is that government agencies should make wider assessments of exposure to different sizes of particles before making pronouncements as to the safety of situations. Although in this situation the agencies were apparently correct regarding the long-term safety of the exposures, premature assurances in light of a large number of people with a persistent cough may have tended to undermine rather than increase public confidence.

Citation: Chen LC, Thurston G. World Trade Center cough. Lancet. 2002 Dec;360 Suppl:s37-8.

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Factors Influencing Arsenic Availability and Extraction from Groundwater in Bangladesh
Harold Hemond
Massachusetts Institute of Technology
P30ES02109

Background: In the past decade, Bangladesh has shifted its drinking water supply from surface water to groundwater through the drilling of 6-10 million private wells. This was done in an effort to curtail the severe and numerous waterborne disease outbreaks. The incidence of waterborne diarrheal diseases have dropped significantly during this period; however, many of the wells carry high concentrations of arsenic, a known human carcinogen. As a consequence, cancer rates and the rates of other diseases may be increasing in Bangladesh. The purpose of the current study was to determine the source of the arsenic in the groundwater and factors that mitigate its concentration.

Advance: The research team found that arsenic concentrations in the soil and sediment peak at a depth 30-40 meters and that deep wells, in general, are a better source of clean water. The influx of carbon from soil sediments and carbon rich surface water into the wells is also associated with higher levels of arsenic in the water. Thus, massive irrigation pumping, which draws water into the aquifer from surface water sources, may affect arsenic concentrations.

Implication: his study indicates that low arsenic containing water in deeper aquifers is the best source of water in Bangladesh. This could explain differences in arsenic concentrations found in wells of close proximity. However, the relationship of arsenic mobility to inflow of carbon raises important concerns about the proper depth and the proximity to high volume irrigation wells. Although this study does not provide immediate relief for the people of Bangladesh, it does provide public health officials the necessary information to identify the candidate wells to be used for drinking water.

Citation: Harvey CF, Swartz CH, Badruzzaman AB, Keon-Blute N, Yu W, Ali MA, Jay J, Beckie R, Niedan V, Brabander D, Oates PM, Ashfaque KN, Islam S, Hemond HF, Ahmed MF. Arsenic mobility and groundwater extraction in Bangladesh. Science. 2002 Nov 22;298(5598):1602-6.

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Pediatric Leukemia: Newly Identified Gene Translocations

Martyn Smith and Patricia Buffler
P42ES04705, P30ES01896, and R01ES09137
University of California, Berkeley

Background: Pediatric leukemias are caused by a variety of genetic abnormalities. These genetic differences help to categorize the diseases for treatment strategies and prognoses. The identification of individual molecular subtypes is also providing clarity to biological and epidemiological studies, which continue to uncover new information for the causes and potential treatments for leukemia.

Advance: Previous research by this research team has identified specific genetic polymorphisms, present *in utero*, associated with a specific type of childhood leukemia. The current discovery describes a protein, which is the product of the fusion of two genes *E2A* and *PBX1*, which appears to occur after birth.

Implication: This study provides evidence of a unique leukemia in relation to the temporal, ontological, and mechanistic properties of the disease. It reemphasizes the need to differentiate cytogenetic and molecular subgroups of leukemias for studies of causality and for possible different treatment strategies.

Citation: Wiemels JL, Leonard BC, Wang Y, Segal MR, Hunger SP, Smith MT, Crouse V, Ma X, Buffler PA, Pine SR. Site-specific translocation and evidence of postnatal origin of the t(1;19) E2A-PBX1 fusion in childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A. 2002 Nov 12;99(23):15101-6.

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Heme Deficiency in Neurons Causes Metabolic Disruptions Similar to Alzheimer's Disease
Bruce Ames
University of California, Berkeley
P30ES01896

Background: Normal aging of the brain and neurodegenerative changes share certain pathological and physiological changes including mitochondrial dysfunction, oxidative stress, and loss of iron homeostasis. Heme synthesis also declines with age. Heme is the major intracellular functional form of iron. It is synthesized in the mitochondria and the decline in synthesis could explain the loss of iron homeostasis in aging. Heme functions in hemoglobin and in a variety of enzymes as well as promoting the growth of nervous tissue.

Advance: To further investigate the role of heme in nerve cell function, these investigators induced heme deficiency in a nerve cell culture system. Heme deficiency was detrimental to normal mitochondrial function, stimulated oxidative stress by activating nitric oxide synthase, altered amyloid proteins, and inhibited zinc and iron homeostasis. The metabolic changes seen during the heme deficiency were similar to those in dysfunction neurons in patients with Alzheimer's disease.

Implication: Common reasons for heme deficiency are iron and vitamin B6 deficiencies, aging, and exposure to toxic metals such as aluminum. In addition, degradation of heme by heme oxygenase, which increases with age and in the brains of Alzheimer's patients, may be a factor in changes in the metabolism of iron and heme with age. Therefore, heme deficiency may be an important and preventable part of the neurodegenerative process, which deserves more research and attention.

Citation: Atamna H, Killilea DW, Killilea AN, Ames BN. Heme deficiency may be a factor in the mitochondrial and neuronal decay of aging. Proc Natl Acad Sci U S A. 2002 Nov 12;99(23):14807-12.

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Inflammatory Effects of Inhaled Organic Diesel Exhaust Particles

Andre Nel
University of California at Los Angeles
R01ES10553

Background: Numerous epidemiologic studies have demonstrated an association between exposure to ambient particulate matter (PM) and adverse cardiorespiratory effects. These effects include asthma exacerbations and allergic inflammation. Previous research by this group using diesel exhaust particles (DEP) as a model air pollutant have shown that organic chemical compounds play an important role in the pro-oxidative and proinflammatory effects of DEP in the respiratory tract.

Advance: By extracting organic chemicals from DEP and applying them to bronchial epithelial cells in culture, this group demonstrated an induction of oxidative stress by inducing the formation of heme oxygenase and other markers. Macrophages responded in a similar manner; however, epithelial cells produced more superoxide radicals and were more susceptible to cytotoxic effects. The cytotoxicity was determined to be the result of mitochondrial damage, superoxide production, and energy depletion.

Implication: These findings show that organic DEP chemicals induce a range of biological responses in epithelial cells and macrophages that depend on the generation of oxidative stress. This study also sheds light on the mechanisms by which exposure to DEP has adverse effects on the respiratory system.

Citation: Li N, Wang M, Oberley TD, Sempf JM, Nel AE. Comparison of the pro-oxidative and proinflammatory effects of organic diesel exhaust particle chemicals in bronchial epithelial cells and macrophages. J Immunol. 2002 Oct 15;169(8):4531-41.

GRANTEE HONORS and AWARDS

David Schwartz, M.D., M.P.H., Professor of Medicine and Genetics and Director of the Pulmonary and Critical Care Medicine at Duke University, has been chosen for the 2003 American Thoracic Society (ATS) Research Award. He will be giving a talk at the Presidential Session at the annual international ATS meeting in May 2003.

Robert Wells, Ph.D., Director of the Center for Genome Research at the Institute of Biosciences and Technology, Texas A & M University, became president-elect of the Federation of American Societies for Experimental Biology in July 2002.

Timothy Phillips, Ph.D., Professor of Veterinary Anatomy and Public Health, of Texas A & M University, received the 2001 Board for International Food & Agricultural Development (BIFAD) Chair's Award for Scientific Excellence at the October 16, 2002 BIFAD meeting in Washington, D.C. Dr. Phillips was recognized for his breakthrough discovery and application of the properties of clays to deactivate mycotoxins in peanuts. This research is supported by SBRP, the United States Agency for International Development (USAID), and industry. Phillips' scientific contribution is especially notable because the inexpensive and practical technology has critically affected the safety of feeds and the health of people and animals, especially in developing nations. Estimates are that the Phillips technology is now being used in ten percent of animal feeds worldwide

Philip Landrigan, M.D., of the Mount Sinai School of Medicine has received the Haven Emerson Award, the highest honor bestowed by The Public Health Association of New York City. His groundbreaking work in the field of public health was described as a true public health success story at the Association's Annual Dinner on November 21 in Manhattan. Dr. Landrigan gave the keynote address and received the award, which was established in honor of the pioneering public health work of Dr. Haven Emerson in New York during the first half of the 20th century. Dr. Landrigan was honored with this prestigious award for his dedication to public health issues including his earlier work at the Centers for Disease Control, his study of the environmental threats to the health of children, as well as the work of his team at the Mount Sinai

School of Medicine to evaluate the health consequences of the attacks on the World Trade Center. Dr. Landrigan is the Program Director of the Superfund Basic Research Program at Mount Sinai.

STAFF HONORS and AWARDS

Dr. Cindy Lawler, OPD/OSTB, received an NIH Merit Award "For exception scientific and administrative accomplishments in advancing the neruological science and Parkinson's disease research."

Dr. Anne Sassaman, OD/DERT, received an NIH Merit Award "For pioneering a memorandum of understanding establishing a joint US/Vietnam research program on Agent Orange/Dioxin to assess/evaluate research issues germane to disease outcome and prevention modalities."

Drs. Claudia Thompson and William Suk, OPD; and Mr. C. Warren Pope, OD; Ms. Kathy Ahlmark, Ms. Beth Anderson and Ms. Susan Haithcock, OPD; Ms. Jacqueline Russell and Ms. Pamela Moore, OPO/GMB, received a group NIH Merit Award "For exemplary performance managing the SBRP, advancing outstanding fundamental research, and establishing partnerships in a responsive effort to the nation reducing risks from hazardous substances."

Drs. Allen Dearry and Frederick Tyson, and Mr. Liam O'Fallon, OPD/CEMBB, received a group NIH Merit Award "For leadership in development and coordination of the Federal Interagency Working Group for Community-Based Participatory Research."

Dr. Bennett Van Houten, Mr. Jerry Phelps, Ms. Edith Lee and Ms. Martha Barnes, OPD/PAB, and Mr. Paul Jordan, Mr. Bob Hoppin and Mr. Gerald Nehls, CTB, received a group NIH Merit Award "For outstanding efforts in conceptualizing, initiating, and implementing the NIEHS Scientific Publications Information Retrieval System (SPIRES)."

Dr. Tyson, OPD/CEMBB, served as an associate editor for an upcoming special issue of the Journal of General Internal Medicine on Community-based Participatory Research.

STAFF ACTIVITIES

Dr. Sassaman, OD, traveled to Hanoi, Vietnam in October to meet with Vietnamese scientists and government officials to discuss progress on implementation of a Memorandum of Understanding between the two countries to establish a joint research program on the health and environmental effects of Agent Orange/dioxin. This followed a visit in September by a delegation of four Vietnamese scientists to NIEHS and EPA. In related activities, Dr. Sassaman gave presentations on the MOU and its status at a Yale-Vietnam Conference in New Haven, CT in September and at the annual meeting of the American Public Health Association in Philadelphia in November. On her return from Hanoi, she stopped in Taipei, Taiwan to attend sessions of the Asian Conference on Occupational Health, particularly a session on issues around exposures to Agent Orange/dioxin and other persistent organics in Vietnam from the Asian perspective.

Drs. Weis, OPD, and *Van Houten, OPD/PAB*, were invited speakers at the National Academy of Science *Committee on Emerging Issues and Data on Environmental Contaminants* on February 6, 2003. Their presentation on "NIEHS Toxicogenomics Research Consortium: Standardizing Gene Expression" was part of the Committee's workshop on *Generating Useful Information on Toxicogenomics: Focused Efforts,* which included presentations by the Microarray Gene Data Society, Institute for Life Sciences and GeneLogic.

Dr. Mastin, OPD/OSTB, helped organize a workshop entitled, "Environmental Factors in Autoimmune Disease" in Durham, NC, on February 4 and 5, which brought experts in the fields of immunology, immunotoxicology, molecular biology, toxicology, etc., to discussion current research on the role of

environmental agents in autoimmune diseases and to discuss possibilities for future research in this area.

Mr. Hughes, OD/WETP, presented at the 16th Annual NIOSH Education and Research Centers Meeting in Marco Island, Florida on February 4-5. Mr. Hughes' presentation focused on Weapons of Mass Destruction Training Initiative, New Threats, and Skilled Support Personnel Protection.

Mr. Hughes, OD/WETP, presented at the Federal Emergency Management Agency/Occupational Safety and Health Summit on Federal Disaster Response Personnel Safety-Personal Protective Equipment in Washington, DC on December 17.

Dr. Shreffler, OPD/OSTB, organized the biennial meeting of the Directors of the Ruth L. Kirschstein National Research Service Award Institutional Training Grants, which was hosted by the NIEHS on December 12, 2002. Other speakers from the NIEHS included *Drs. Sassaman, OD/DERT; Van Houten, OPD/PAB, and Bass, OPO/GMB*.

Mr. Hughes, OD/WETP, presented at the New York Committee for Occupational Safety and Health Town Meeting in New York City, New York on December 11. Mr. Hughes shared information on the NIEHS Worker Education and Training Program regarding the World Trade Center Cleanup efforts.

Ms. Beard, OD/WETP, attended the U.S. EPA National Environmental Justice Advisory Council (NEJAC) Meeting in Baltimore, Maryland on December 10. Ms. Beard presented on the accomplishments of the NIEHS Worker Training Activities especially the Minority Worker Training and Brownfields Minority Worker Training program to the NEJAC Waste Subcommittee.

Drs. Packenham and Maull,OPD/CEMBB, coordinating with the University of Texas Health Science Center Comparative Mouse Genome Center, organized a mini-symposium focused on the interactions of DNA repair genes and aging, which was held in San Antonio, Texas on December 6.

Ms. Beard and Mr. Outwater, OD/WETP, attended the Brownfields 2002 Conference in Charlotte, North Carolina on November 13-15. This national conference showcased brownfields cleanup, redevelopment and policy issues. During this meeting, they conducted a meeting of the awardees of the Brownfields Minority Worker Training Program to discuss progress in this training program and promote the model of community based environmental job training program. The meeting also provided an excellent setting to promote the WETP Minority Worker Training Program and Brownfields Minority Worker Training Program.

Mr. Hughes, OD/WETP, participated in and presented at the U.S. National Response Team Training Subcommittee in Washington, DC on November 11.

Dr. Tyson, OPD/CEMBB, organized, moderated and presented a session at the American Public Health Association Annual Meeting entitled, "Community-based Participatory Research Approaches in Studying Systemic Lupus Erythematosus (SLE) and other Autoimmune Disorders" on November 12, 2002 in Philadelphia, Pennsylvania.

Mr. O'Fallon, OPD/CEMBB, organized and co-moderated a session on nursing and environmental health at the American Public Health Association annual meeting, which was held November 10-13 in Philadelphia, Pennsylvania . The session, titled "Environmental health research by nurse scientists: breaking new ground," brought together several nurse researchers to discuss their projects and highlight their unique contributions as nurses.

Dr. Brenda Weis, OPD, presented at the Science Education Program's *Rx for Science Literacy* Workshop on November 8, 2002. The workshop was co-sponsored by the NIEHS and the North Carolina Association for Biomedical Research. Her presentation was titled "Toxicogenomics: Genomic Science to Understand

Biological Response to Environmental Stressors" which described gene expression profiling technology and its application in toxicology research.

Ms. Duke, OPO/GMB, presented a session on "Project Budgeting and Expending: An Interactive Team Sport" at the Society of Research Administrators Annual Meeting, Orlando, Florida, October 29-30.

NIEHS (through the Worker Education and Training Program), National Institute for Occupational Safety and Health (NIOSH), Johns Hopkins Education and Research Center for Occupational Safety and Health, and Mid-Atlantic Public Health Training Center co-sponsored a Technical Workshop on the Worker Training in a New Era: Responding to New Threats. This conference drew upon lessons learned from recent terrorist attacks to help attendees better understand and anticipate the safety and health-training needs of workers who would be required to respond to terrorist incidents in the future. The conference was held in Baltimore, Maryland on October 26-27. Staff attending the workshop and participating in various activities included *Mr. Hughes, Ms. Beard, Mr. Outwater, and Ms. Thompson, OD/WETP*. The meeting was preceded on October 25, by the semi-annual WETP Awardee Meeting. Ms. *Mason, OPO/GMB,* also participated in the meeting.

Ms. Duke, OPO/GMB, gave an NIH Grants Policy update as well as a presentation on NIEHS/NIH funding opportunities/areas of scientific interest at the University of Florida on October 24.

Dr. Weis, OPD, presented at the North Carolina Central University's Environmental Science Seminar Series on *Emerging Trends in Environmental Toxicology* on October 1, 2002. The title of her presentation was "Toxicogenomics: Technology and Promises" which described gene expression profiling technology and highlighted recent publications involving applications in toxicology research.

Mr. O'Fallon, OPD/CEMBB, spoke on NIEHS Translational Research programs and NIEHS activities in community-based participatory research at a workshop in conjunction with the annual meeting of the American College of Epidemiology, September 21-24 in Albuquerque, New Mexico.

Dr. Thompson, OPD, presented a talk at the International Conference on Chemical Mixtures held in Atlanta, Georgia, September 10-12, that highlighted the NIEHS research initiatives that have been undertaken in the area of chemical mixtures. As a member of the steering committee, on September 9 she also participated in a workshop entitled “Risk Assessment of Mixtures: Development of Testable Hypotheses.” The report from this meeting was presented at the Mixtures Conference.

UPCOMING MEETINGS and WORKSHOPS

Dr. Tyson, OPD/CEMBB, is organizing the Environment as an Integrative Context for Learning Annual Grantee Meeting in Miami, Florida on February 26-27.

Dr. Gray, OPD/CEMBB in conjunction with staff from DIR, is organizing a workshop on Phthalates and Human Health: Current Knowledge and Future Research Directions to be held on March 26-27 in RTP, NC. The workshop is designed to describe the current state of knowledge on the health effects of phthalates, to identify gaps and deficiencies in our knowledge base, and to identify future directions for exposure assessment, toxicologic and epidemiologic studies. The meeting will bring together scientists with expertise in exposure assessment, toxicology, and epidemiology.

The Worker Education and Training Program will sponsor its 4th National Trainers Exchange (NTX) where trainers affiliated with WETP awardees can learn new, effective teaching techniques, update their technical skills, and share their insights and experiences with fellow trainers. The NTX will be held in Orlando, Florida on March 27-28. A semi-annual WETP awardee meeting will be held on March 26.

STAFF CHANGES

Recruitments:
Dr. Elizabeth A. Maull, joined OPD/CEMBB as a Program Analyst in 2002. Dr. Maull will support the Comparative Mouse Genome Center Consortium and the Breast Cancer and the Environment Research Centers. She received her undergraduate degree from the University of Massachusetts (Animal Science) and a Ph.D. (Food Science and Technology) from Texas A&M University. Dr. Maull has a diverse scientific background including 14 years of laboratory experiences, spanning traditional toxicology studies to molecular biology and virology techniques. Prior to joining DERT, Dr. Maull was employed by the US Air Force where she represented the AF Surgeon General's interests in environmental and occupational health concerns and gained experience in contract oversight and project management. Dr. Maull represented the Department of Defense in trichloroethylene-related issues from 1996 through 2001 and was the recipient of numerous awards based on her work with the Air Force, including the Department of the Air Force Award for Exemplary Civilian Service.

Ms. Yvette Cobb has joined the Worker Education and Training Program as a secretary. She comes to DERT from the Uniformed Service University of the Health Sciences.

Departures:

Ms. Pamela Chaney, OD/WETP, has left DERT to take a position with the U.S. Department of Agriculture, Natural Resources Conservation Service.

COUNCIL DELEGATED AUTHORITIES AND GUIDELINES FOR STAFF ACTIONS

Introduction:

NIH Policy requires an annual review by Advisory Councils of the delegated authorities and operational guidelines under which institute staff operate. These guidelines fall into two general categories. First, Council-delegated staff actions are actions delegated to staff that require no follow up action with Council. Second, Council delegates to staff certain operational actions that are required to ensure the smooth operations of the extramural division in conducting business with our grantees; these actions require the establishment of a threshold level for Council involvement and are listed as section II.

Council-Delegated Staff Actions:

National Institute of Environmental Health Sciences (NIEHS) extramural staff may take the following actions without Council review.

1. Authorize relocation of a currently funded project to a new institution when the principal investigator transfers from one institution to another and the original grantee institution relinquishes the grant. Such projects may be supported at the new institution for a period of up to the remainder of the current project period and in an amount generally not to exceed that previously recommended for the remaining period.

This authorization also applies when the principal investigator moves to a new institution following concurrence with the Initial Review Group (IRG) action by Council, but prior to the time that an award is made.

2. Approve a new principal investigator or program director for a research grant or an institutional training grant, sub-project director or other key personnel on program projects or center grants, for a period equal to the time remaining on the current project. Such changes involving directors of the University-based Environmental Health Sciences (EHS) Centers and Marine and Freshwater Biomedical Sciences (MFBS) Centers will be made on an interim basis pending review and approval by the Centers Subcommittee of Council.

3. Extend a project grant period with additional funds to assure orderly termination of the project or to protect the investment already made.

Staff, in discussion with the principal investigator, will determine the period of support and budget necessary to permit orderly termination of the research project. Special attention will be given to salary for essential staff, for purchase of supplies and for support of experimental animals. The (prorated) supplemental award should not exceed 12 months.

In the case of training grants, stipends may be provided until completion of the training for those trainees already appointed to the program.

In cases where a competing renewal application is deferred by either the Initial Review Group (IRG) or the Council, or when bridging funds are needed until an amended application has been submitted funds may be provided to permit support of the previously recommended research until review is completed and a final decision on the competing

renewal application has been made. If a competing award is made, interim funds and the period of support may be deducted from the budget and budget period of the first year of the continuation award.

4. Authorize supplemental funds in an amount not to exceed $40,000 direct costs to any center, program project, or other multi-disciplinary program grant or cooperative agreement for the purpose of supporting a conference, symposium or scientific workshop. This provision will apply only in those instances in which the principal investigator or center director can show that the meeting is necessary for the scientific community or Institute to react promptly to matters of major importance. The Director, NIEHS, may approve supplementation of these grants, following consultation with members of the Centers Subcommittee of Council when centers are involved.

5. Authorize supplemental direct cost funds to a University-based EHS center or MFBS center in an amount not to exceed 15% of the direct costs recommended for a current annual budget period. This provision will apply only in those circumstances where: 1) the center director can show adequate justification that such funds are required to cover unanticipated costs, or are needed to respond to newly identified problems of urgent program priority, or 2) the supplement is in response to special programmatic or budgetary needs or opportunities identified by the Director, NIEHS. Supplementation of a center grant for the purposes under 1) may be approved only by the Director, NIEHS, following consultation with the Centers Subcommittee of Council.

6. With approval of the Director, NIEHS, make awards as either the primary Institute or through co-funding with another Institute/Center/Division, so long as the direct costs do not exceed $50,000 per year. An application supporting such award must have been reviewed and scored by a chartered NIH initial review group prior to selection for funding by the Director, NIEHS.

7. Authorize the award of funds to research project grants, R25, and S11 grants based on the receipt of a supplemental application to provide support for re-entry into research, disabled or under-represented minority investigators, under-represented minority undergraduate or graduate students to work on research aims previously reviewed during competitive evaluation of the parent grant.

8. Authorize the award of supplemental funds when required to comply with emergency response needs as designated by specific appropriation language or as designated by the Director, NIEHS.

9. Approve continuation of grant under an interim principal investigator during the temporary absence of the principal investigator.

10. Approve extension of grants without additional funds on those grants requiring NIH approval.

11. Award supplements to the Chairperson of the Council committees and to the Environmental Health Sciences Review Committee(s) [chartered or ad hoc] in an amount necessary to carry out the functions of the committee(s).

12. Take final action to increase previously recommended and currently active research and training grants by the amount represented in institution-wide salary increases of

grant-supported personnel or in stipends of grant-supported trainees in accord with NIH policy.

13. Take final action to provide for the employer's portion of mandatory contributions required of employers in their locality when not included in the application and when requested subsequently.

14. Take final action to adjust grants to add summer salaries to current or renewal grants for which authorizing overall policy was adopted by the grantee institution subsequent to the filing of the application.

15. Take final action to provide additional funds not to exceed $150,000 direct costs to research project grants, R25, and S11 grants for increases in the budget for unforeseen administrative costs of research that are within the scope of the approved/funded project or protocol.

~~16. Authorize the award of funds for an individual Fellowship based on the receipt of an application and peer review recommendation regardless of level of support.~~

Reviewed and Approved by NAEHS Council on February 11, 2003.

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Anne P. Sassaman, Ph.D. 02/11/03
Director, DERT, NIEHS

NAEHS COUNCIL REVIEW OF GRANTS

I. Basis for Special Review of Individual Grant Applications:

Applications are presented to the National Advisory Environmental Health Sciences Council (NAEHS) for special consideration when:

1. The research proposed has been identified by either Council or staff as being of particular interest or concern;

2. Some aspect of the recommendation from the IRG has been questioned by either Council or staff, e.g., an apparent discrepancy between the comments in the summary statement and the percentile ranking/priority score;

3. Ethical, hazard, or safety issues or concerns are identified by staff;

4. Concerns about participation of human subjects are raised by the IRG or are identified by staff or Council, regardless of the percentile ranking/priority score;

5. Concerns are raised regarding the principal investigator's inclusion of minorities and women in study populations, regardless of the percentile ranking/priority score;

6. Concerns regarding the treatment of animals are raised;

7. The application is a reviewed foreign application with a fundable percentile ranking;

8. The application is a reviewed center grant application or supplement.

9. All reviewed program project and regular research grant applications with a ranking better than the 40th percentile or a priority score better than 250 and a budget in excess of $500,000 direct costs in any one year will be identified by staff and may be raised for individual discussion by Council.

Applications not identified for individual discussion are reviewed en bloc.

II. Options for Council Action for Special Review:

The following options generally are available to the Council for each application that is identified for individual discussion.

1. Concurrence with the IRG scientific merit review;

2. Change in priority status to HPP (High Program Priority) or to LPP (Low Program Priority). An HPP designation elevates the relative funding position of an application but does not necessarily assure funding. An LPP designation lowers the relative funding position of an application, but does not necessarily prohibit funding. Staff will give special consideration to all HPP and LPP recommendations in making a final funding decision;

3. Deferral to NIEHS staff for additional information for Council consideration at a subsequent meeting;

4. Deferral for reconsideration of the scientific and technical merit of an application by the same or another IRG;

5. Non-concurrence with IRG recommendation for policy, procedure, or administrative reasons; or

In specific cases, additional options may be available. These will be detailed by the staff for the Council's consideration as the need arises.

III. Early Council Concurrence Using the Electronic Council Book:

The purpose of early Council concurrence is to expedite the funding of meritorious grant applications. It is anticipated that the time from submission of an application to eventual funding can be shortened by approximately one month. The following procedure will be available to Council for the May 2002 meeting.

One or more subgroups of Council will be designated as participants in the early concurrence process. Each subgroup will be composed of five Council members with a broad range of expertise and experience. Members of the subcommittees will be solicited and confirmed at the previous Council meeting.

Approximately one month before the Council meeting, staff will identify applications for which there are no issues that would require special review requirements as indicated under item 1 above. These applications will be submitted to a subgroup electronically through the Electronic Council Book.

Council members will be notified electronically of the existence of the panel of applications and a "due date" for their action will be identified. Council members may concur en bloc or may remove any or all applications from concurrence. Any application removed from the early concurrence process by Council members will be held for consideration at the Council meeting. Four of the five Council members on the subgroup are required for further staff action.

Upon early concurrence, as indicated above, staff may initiate the award process for meritorious applications within the pay line. All other applications will be considered at the Council meeting according to the procedures indicated above.

Reviewed and Approved by NAEHS Council on February 11, 2003.

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Anne P. Sassaman, Ph.D. 02/11/03
Director, DERT, NIEHS

DIVISION OF INTRAMURAL RESEARCH

NAEHS COUNCIL UPDATE

FEBRUARY 2003

DIR Recruitments

Chief, Laboratory of Computational Biology and Risk Analysis

An international search is being conducted for a senior tenured investigator to serve as Chief of the Laboratory of Computational Biology and Risk Analysis. The candidate will be expected to:

- Develop and maintain a strong personal research effort in the general area of bioinformatics, particularly as it relates to biological networks, proteomics and genomics.
- Provide overall leadership for the existing principle investigators within the LCBRA who study the combined development of laboratory methods for humans and animals with computational, statistical and mathematical methods to further our understanding of the mechanisms underlying environmental disease.
- Recruit talented investigators to the LCBRA and provide a focus for collaborations within the NIEHS.

The Candidate should be a senior investigator with an international reputation in a specific area within the broad context of bioinformatics and its relationship to the environment. Possible research areas include but are not limited to mathematics, statistics, genetics, bioengineering and molecular biology. The successful candidate will also have an outstanding publication record and proven history of research leadership. A search committee chaired by Dr. Clarice Weinberg, Chief of the Biostatistics Branch should start reviewing applications soon.

Tenure-track Bioinformaticist

The Biostatistics Branch is conducting a nationwide search for a tenure-track investigator with training and experience in bioinformatics. The person selected will focus activities upon developing novel methods related to toxicogenomics, such as developing and evaluating data mining approaches for elucidating characteristic patterns in gene expression array or proteomic data in order to facilitate searches for functionally-coordinated families of genes related to disease processes or response to toxicants. Improved quantitative methods for functional genomics and data mining are needed to make full scientific use of the toxicogenomics data being produced by the NIEHS Microarray Center and the National Center for Toxicogenomics. A search committee chaired by Dr. Douglas Bell, Laboratory of Computational Biology and Risk Analysis has been formed and should start reviewing applications soon.

Tenure-track Immunologist

The Laboratory of Pulmonary Pathobiology is conducting 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). A search committee chaired by Dr. John Drake, Chief or the Laboratory of Molecular Genetics has been formed. Review of applications should begin soon.

Tenure-track Environmental Epidemiologist

The Epidemiology Branch is conducting 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. Applicants with demonstrated research interests in biological mechanisms and etiology of (not limited to) neurodegenerative diseases, diabetes, multiple sclerosis, renal disease, cardio-respiratory diseases; and such exposures as pesticides, metals, and/or solvents are most welcome. A search committee chaired by Dr. Steven Kleeberger, Chief of the Laboratory of Pulmonary Pathobiology has been formed and should start reviewing applications soon.

Staff Scientist Biostatistician

The Biostatistics Branch is conducting a national search for a statistician to collaborate closely with the National Toxicology Program. The successful candidate will provide statistical leadership and consulting support for the National Toxicology Program and will also develop methods related to design and analysis of toxicology studies. Applicants should have with experience in statistical consulting and a demonstrated ability with problems in applied statistics. The search committee, chaired by Dr. John Pritchard, Chief, Laboratory of Pharmacology and Chemistry, is interviewing candidates.

Chief, Laboratory of Molecular Carcinogenesis

An international search has been conducted for a senior tenured investigator to serve as Chief of the Laboratory of Molecular Carcinogenesis. The Candidate should have an international reputation in a specific area within the broad context of molecular carcinogenesis and it's relationship to the environment, an outstanding publication record, and a proven history of research leadership. The search committee, chaired by Dr. Thomas Kunkel, Chief of the Laboratory of Structural Biology selected Dr. Trevor Archer, currently a Senior Investigator in the Laboratory of Reproductive and Developmental Toxicology, who has agreed to accept the position. Final approval is pending at N.I.H.

Tenured or tenure-track Reproductive Epidemiologist

The Epidemiology Branch has conducted an international search for a reproductive epidemiologist who will develop an outstanding research program on reproductive or perinatal health and the effects of environmental factors, including fertility, pregnancy loss, diseases of pregnancy, fetal development, birth defects, and other problems of the neonatal period. Dr. Joanne Promislow, currently a post-doctoral fellow in the Department of Epidemiology, University of North Carolina, has agreed to accept this position.

Tenure-track or tenured Biostatistician--Statistical Genetics

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. Two different candidates were recommended and their respective appointments are pending final approval.

Staff Scientist-Head, Mass Spectrometry Protein Microcharacterization Core Facility

The Laboratory of Structural Biology has conducted a national search for a Staff Scientist to serve as Head of the Mass Spectrometry Protein Microcharacterization Core Facility in the Division of Intramural Research. The successful applicant will be a Staff Scientist in the Laboratory of Structural Biology under the supervision of Dr. K. Tomer and be responsible for the MALDI/MS and capillary HPLC/ESI/MS/MS identification of proteins isolated by 1-D and/or 2-D gel electrophoresis, in-gel digestion, determination of sites of post-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 mass spectrometry. Additional duties will include close interaction with DIR scientists, serving as a mass spectrometry expert during the planning and execution of experiments, and supervision of laboratory technicians. The search committee, chaired by Trevor Archer, Laboratory of Reproductive and Developmental Toxicology, has recommended a candidate and negotiations are currently underway.

Staff Scientist—Protein Expression

The Laboratory of Structural Biology is conducting a national search for a Staff Scientist to serve as Head of the Protein Expression Core Facility. The candidate will manage a facility the purpose of which is to provide proteins for structural and characterization studies conducted by intramural scientists. A search committee chaired by Dr. William Copeland, Laboratory of Molecular Genetics has recommended a candidate. Dr. Robert Petrovich, currently at Syngenta, has accepted an offer to fill this position.

DIR Recruits

Dr. Steven Akiyama
Deputy Scientific Director

Dr. Steven Akiyama has recently been named one of two Deputy Scientific Directors in the DIR. He is also a Senior Investigator in the Laboratory of Molecular Carcinogenesis. His previously served as Associate Director for Research and Training in the DIR. His research focuses on the mechanisms of adhesion and migration of human cancer cells. Cell adhesion and migration contribute to normal processes such as differentiation, embryonic development, and wound healing as well as to the progression of diseases and pathological conditions, such as cancer and inflammatory responses, that can result from either acute or chronic exposure to environmental toxicants and other chemicals. Key mechanistic steps in these processes involve the interactions of adhesive glycoproteins, e.g., fibronectin, laminin, and collagens, with the integrins, a family of heterodimeric adhesion receptors consisting of an α subunit and a β subunit. Integrins are highly regulated receptors that can be directly activated extracellularly (outside-in signaling) and by cytoplasmic signaling pathways (inside-out signaling). His research is focused on characterizing the molecular mechanisms of integrin-mediated adhesion processes, the regulation of integrin activation, and the resulting downstream effect of cell adhesive proteins, such as fibronectin, important for the control of proliferation, adhesion, migration, and invasion of human tumor cells.

One approach that is being used employs a monoclonal antibody (mAb) as a highly specific, high affinity activator of integrin function. MAb 12G10, is an antibody that binds specifically to β1 integrins and induces integrin-mediated cell-cell and cell-substrate adhesion. Binding of mAb 12G10 to β1 integrins stimulates integrin clustering, an increase in intracellular cAMP levels, and a concomitant shift in the localization of the PKA type II regulatory subunits from the cytoplasm to areas of the plasma membrane where integrins expressing the 12G10 epitope are located. MAb 12G10-induced cell-cell adhesion was mimicked by specifically clustering $\alpha 2\beta 1$ integrins or the binding of collagen type IV (an $\alpha 2\beta 1$ ligand) in combination with elevating PKA activity with Sp-cAMPS or forskolin suggesting that the α2 integrin and PKA play a key roles in up-regulation of cell-substrate and cell-cell adhesion.

Selected Publications:

Akiyama, S.K., Yamada, S.S. and Yamada, K.M.: Analysis of the role of glycosylation in the structure and function of the human fibronectin receptor. J. Biol. Chem. 264: 18011-18018, 1989.

Miyamoto, S., Akiyama, S.K. and Yamada, K.M.: Synergistic roles for receptor occupancy and aggregation in integrin transmembrane function. Science, 267: 883-885, 1995.

Newton, S.A., Reeves, E.J., Gralnick, H.A., Mohla, S., Yamada, K.M., Olden, K. and Akiyama, S.K.: Role of integrin fibronectin receptor in metastasis of human breast carcinoma cells in athymic nude mice. Int. J. Oncol., 6: 1063-1070, 1995.

Akiyama, S.K., Olden, K. and Yamada, K.M.: Fibronectin and integrins in invasion and metastasis. Cancer Metast. Rev., 14: 173-189, 1995.
Whittard, J.D. and Akiyama, S.K.: Activation of ı integrins induces cell-cell adhesion. Exp Cell Res., 263: 65-76, 2001.
Whittard, J.D. and Akiyama, S.K.: Positive regulation of cell-cell and cell-substrate adhesion by protein kinase A. J. Cell Sci., 114: 3265-3272, 2001.
Guo, H.-B, Lee, I., Kamar, M. Akiyama, S.K., and Pierce, M.: Aberrant N-glycosylation of beta-1 integrin reduces integrin clustering and stimulates phosphorylation of focal adhesion kinase and cell migration. Cancer Res., 62: 6837-6845, 2002.

Dr. William Schrader
Deputy Scientific Director

NIEHS welcomes Dr. Bill Schrader, who has recently been appointed as Senior Scientist in the Laboratory of Reproductive and Developmental Toxicology and Deputy Scientific Director. Dr. Schrader is a biochemist and molecular endocrinologist by training. He received the Ph.D. degree in Biology from Johns Hopkins University in 1969, and then did post-doctoral research at Vanderbilt Medical School where he published the first papers describing the subunit structure of nuclear receptors. He joined the faculty of Baylor College of Medicine in 1972, was appointed Professor of Cell Biology in 1985 and became Assistant Dean of the Graduate School in 1991. His research interests have dealt with the structure, function and regulation of the steroid receptor superfamily, especially sex hormone receptors and the xenosensor receptors of liver and intestine. His laboratory has developed methods for covalent attachment of steroids to their receptors, for studying receptor-DNA interactions, and for tests of the role of the hormone ligand as a regulatory effector of gene expression. His research group mapped sites of receptor phosphorylation and the mechanisms for ligand-independent gene regulation. He has sat on federal and professional review panels, and as an editor of international scientific journals. He joined Ligand Pharmaceuticals in 1995 as Vice President for Endocrine Research where he directed drug discovery for female and male sex hormone receptor modulators, including both agonists and antagonists for benign and oncologic indications. His programs successfully identified clinical candidate drugs for a number of hormonal conditions in men and women. They range from estrogen modulators for female post-menopausal osteoporosis and breast cancer to progestins for hormone replacement therapy and drugs for androgen-related conditions such as hypogonadism, acne and hirsutism. Several of these drugs have advanced into human clinical trials at Phase I, II or III. In 2000 Dr. Schrader co-founded XenoPharm, Inc., a biotechnology company that developed diagnostic assay methods for evaluating the activity of small molecules as inducers of liver metabolism and drug-drug interactions. At NIEHS he will study the molecular mechanisms underlying the activity of tissue-selective androgen receptor modulators, the “SARMs”. Utilizing a novel set of fluorescent non-steroidal androgens, the studies will use fluorescence microscopy to follow these hormones from initial exposure to elimination from both cells and whole animals. Similarly, the fluorescent molecules will be studied by fluorescence polarization anisotropy, to measure association of the hormone with receptors in the nucleus in real time. These methods will be the basis for a screening system, set up using human cells to detect small molecules that perturb

receptor-hormone interactions, but do so only transiently such that their effects are not detectable by conventional ligand-protein equilibrium methods.

Selected Publications:

Weigel, N.L., Carter, T.H., Schrader, W.T. and O'Malley, B.W.: Chicken progesterone receptor is phosphorylated by a DNA-dependent protein kinase during in vitro transcription assays. Mol. Endocrinol. 6: 8-14,1992.

Polett,i A., Conneely, O.M., McDonnell, D.P., Schrader, W.T. O'Malley, B.W and Weigel, N.L.: Chicken progesterone receptor expressed in Saccharomyces cerevisiae is correctly phosphorylated at all four Ser-Pro phosphorylation sites. Biochemistry 32: 9563-9569, 1993.

Schrader, W.T.: Insight: subunit functions of the steroid/thyroid receptor family. Mol Endocrinol. 7: 1241-1243, 1993.

Edwards, J.P., Zhi, L., Pooley, C.L., Tegley, C.M., West, S.J., Wang, M.W. Gottardis, M., Pathirana, C, Schrader, W.T. and Jones, T.K.: Preparation, resolution, and biological evaluation of 5-aryl-1, 2- dihydro-5H-chromeno[3,4-f]quinolines: potent, orally active, nonsteroidal progesterone receptor agonists. J. Med. Chem. 41: 2779-2785, 1998.

Clemm, D.L., Sherman, L., Boonyaratanakornkit, V., Schrader, W.T., Weigel, N.L. and Edwards,D.P.: Differential hormone-dependent phosphorylation of progesterone receptor A and B forms revealed by phosphoserine site-specific monoclonal antibodies. Mol. Endocrinol. 14: 52-65, 2002.

Dr. Leesa J. Deterding
Structural Biology Staff Scientist – Mass Spectrometry

As a result to a national search, Dr. Lisa Deterding has recently been converted to a Staff Sacientist in support of Dr. Ken Tomer, Laboratory of Structural Biology. She received her M.S. in analytical chemistry from the University of Nebraska-Lincoln and her Ph.D. in analytical chemistry from North Carolina State University. Her Ph.D. dissertation focused on the separation and structural analysis of the HDL apolipoproteins as potential biomarkers of coronary artery disease. Dr. Deterding's initial research efforts at NIEHS were on the development and application of nanoscale separation techniques with mass spectrometry, which have become standard procedures in proteomics and biological mass spectrometry.

Dr. Deterding's current role in the Laboratory of Structural Biology is primarily focused on the application of mass spectrometric techniques to structural problems in biology, including determination of post-translationally modified proteins, identification of complexes via immunoprecipitates, identification of differentially expressed proteins, and interaction of proteins with other biomolecules. Current ongoing projects include mapping the protein:DNA interaction sites on β-polymerase and polymerase iota, determining the extent of and changes in the phosphorylation of specific histone H1 isoforms in response to hormonal induction, and determining the mechanisms of free radical formation on proteins subjected to oxidative stress. Dr. Deterding is also

planning structural studies on the *Bacillus subtilis* transition state regulator protein AbrB that is involved in sporulation.

Selected Publications:

Deterding, L.J., Barr, D.P., Mason, R., and Tomer, K.B.: Characterization of cytochrome c free radical reactions with peptides by mass spectrometry. J. Biol. Chem. 273: 12863-12869, 1998.

Deterding, L.J., Prasad, R., Mullen, G.P., Wilson, S.H., and Tomer, K.B.: Mapping of the dRP lyase active site in DNA polymerase β by mass spectrometry. J. Biol. Chem., 275: 10463-10471, 2000.

Chen, Y.-R., Deterding, L.J., Tomer, K.B., and Mason, R.P.: The nature of the inhibition of horseradish peroxidase and mitochondrial cytochrome c by cyanyl radical. Biochemistry, 39: 4415-4422, 2000.

Banks, G.C., Deterding, L.J., Tomer, K.B., and Archer, T.K.: Hormone mediated dephosphorylation of specific histone H1 isoforms. J. Biol. Chem. 276: 36467-36473, 2001.

Chen, Y.-R., Deterding, L.J., Sturgeon, B.E., Tomer, K.B., and Mason, R.P.: Protein Oxidation of cytochrome c by reactive halogen species enhances its peroxidase activity. J. Biol. Chem., 277: 29781-29791, 2002.

Dr. Mark Gourley
Staff Clinician, Environmental Autoimmunity Group

Dr. Mark Gourley joined the Environmental Autoimmunity Group (EAG) in the Office of Clinical Research, DIR, as a staff clinician at the Warren Grant Magnuson Clinical Center, Bethesda, MD, in August, 2002. Dr. Gourley provides care to patients enrolled in clinical protocols investigating the role of the environment in rheumatic diseases. His clinical research investigates factors in the environment that are implicated in causing or modifying autoimmune disease. While specializing in the autoimmune disease systemic lupus erythematosus (SLE), the EAG will begin to focus research on SLE, rheumatoid arthritis, myositis and scleroderma. It is anticipated that more than 1000 volunteers will be enrolled into a clinical research protocol that seeks to find factors in the environment in the above named diseases along with genetic factors that associate the these illnesses.

Dr. Gourley received his M.D. from Tulane University, completed his residency in internal medicine at Madison, Wisconsin and was trained in rheumatology at the National Institute of Arthritis, Musculoskeletal and Skin Diseases, NIH. Previous to joining NIEHS, he was an Attending Rheumatologist at the Washington Hospital Center where he served as the Acting Director as the section of rheumatology and the director of the lupus clinic. He is board certified in Internal Medicine and Rheumatology.

Selected Publications:

Gourley, M.F., Austin III, H.A., Yarboro, C. H., Vaughan, E.M., Muir, J., Lindahl, M., Boumpas, D.T., Scott, D.E., Klippel, J.H., Balow, J.E. and Steinberg, A.D.:

Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann. Int. Med. 125: 549-557, 1996.
Lefkowith, J.B., Kiehl, M., Rubinstein, J., Di Valerio, R. and Gourley, M.: Heterogeneity and clinical significance of glomerular binding antibodies in systemic lupus erythematosus. J. Clin. Invest. 98: 1373-1380, 1996.
Villalba, L., Hicks, J.E., Adams, E.M., Sherman, J.B., Gourley, M.F., Leff, R.L., Thornton, B.C., Burgess, S.H., Plotz, P. H. and Miller, F.W.: Treatment of resistant myositis: A randomized crossover study of two new cytotoxic regimens. Arthritis. Rheum. 41: 392-399,1998..
Tassiulas, I.O, Aksentijevich, I., Salmon, J.E., Kim, Y., Yarboro, C.H., Vaughan, E.M., Davis, J.C., Scott, D.E., Austin III, H.A., Klippel, J.H., Balow, J.E., Gourley, M.F. and Boumpas, D.T.: Angiotensin I converting enzyme gene polymorphism in systemic lupus erythematosus: decreased prevalence of DD genotype in African American patients. Clin. Nephrol., 50: 8-13, 1998.
Solomou, E.E., Yuange-Taung, J., Gourley, M.F., Kammer, G.M. and Tsokos, G.C.: Molecular basis of deficient IL-2 production in T cells from patients with systemic lupus erythematosus. J. Immunol., 166: 4216-4222, 2001.
Illei, G.G., Austin, H.A., Crane, M., Collins L., Gourley, M.F., Yarboro, C.H., Vaughan, E.M., Kuroiwa, T., Danning, C.L., Steinberg, A.D., Klippel, J.H., Balow, J.E. and Boumpas, D.T.: Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann. Int. Med., 135: 248-257, 2001.
Herdon, T.M., Yuang-Taung, J., Solomou, E.E., Rothwell, S.W., Gourley, M.F. and Tsokos, G.C.: Direct transfer of p65 into T lymphocytes from systemic lupus erythematosus patients leads to increased levels of interleukin-2 promoter activity. Clin. Immunol., 103: 145-153, 2002.

Dr. David Malarky
Staff Pathologist, Laboratory of Experimental Pathology

Dr. David E. Malarkey received his B.S. and M.S. degrees from the University of Bridgeport, Connecticut; D.V.M. from Tufts University School of Veterinary Medicine; Pathology residency training at Angell Memorial Animal Hospital in Boston; and Ph.D. from North Carolina State University. Dr. Malarkey was a Research Fellow under the direction of Dr. Robert Maronpot in the Laboratory of Experimental Pathology at NIEHS from 1993-1997. He has been a Diplomate of the American College of Veterinary Pathologists since 1993 and has particular interest in the areas of toxicological and molecular pathology. Prior to his current position at NIEHS, Dr. Malarkey worked for 5 years as diagnostic pathologist, researcher, and teacher while a faculty member at North Carolina State University College of Veterinary Medicine in Raleigh, NC. His research efforts are in the areas of toxicologic pathology, carcinogenesis, and molecular diagnostic techniques. Primary efforts have been to determine the biological behavior and genetic events involved in chemically induced liver tumors in B6C3F1 mice in order to better define the mouse model for its relevance in assessing human health hazards as well as deciphering the molecular basis of cancer. To date, studies have demonstrated

chemical specific H-*ras* proto-oncogene mutations; specific gene expression patterns in chlordane-associated liver tumor regression using microarray expression analysis with collaborations with the NIEHS microarray center; and evidence that alterations in the putative tumor suppressor gene, *Brca1*, occur in mouse liver tumor progression. Other collaborative efforts have been directed at characterizing the pathology of animal diseases, including transgenic mice, and successfully integrated the fields of clinical medicine and diagnostic pathology by applying molecular research techniques in veterinary clinical applications. Such projects include the use of a PCR-based test for the detection of *Helicobacter hepaticus* infection in mouse liver and a PCR-based clonality assay for aiding in the diagnosis of canine lymphoma.

Selected publications:

Malarkey, D.E., Devereux, T.R., Dinse, G.E., Mann, P.C. and Maronpot, R.R.: Hepatocarcino-genicity of chlordane in B6C3F1 and B6D2F1 male mice: evidence for regression in B6C3F1 mice and carcinogenesis independent of ras proto-oncogene activation. Carcinogenesis, 16: 2617-25, 1995.

Malarkey, D.E. and Maronpot, R.R.: Polymerase chain reaction and in situ hybridization: Applications in toxicological pathology. Tox. Path., 24: 13-23, 1996.

Hailey, J.R., Haseman, J.K., Bucher, J.R., Radovsky, A.E., Malarkey, D.E., Miller, R.T., Nyska, A., and Maronpot, R.R.: Impact of Helicobacter hepaticus infection in B6C3F1 mice from twelve National Toxicology Program two-year carcinogenesis studies. Tox. Path., 26: 602-611, 1998..

Andrews, J.M. and Malarkey, D.E.: Advanced diagnostic techniques: molecular diagnostics. In: Atlas of Canine and Feline Cytology, 1st edition, W.B. Saunders. Raskin, R. and Meyer , D., editors, 2001.

Christensen, J., Romach, E.H., Healy, L.N., Gonzales, A.J., Anderson, S.P., Malarkey, D.E., Cattley, R.C. and Goldsworthy, T.L.: Altered Bcl-2 family expression during nongenotoxic hepatocarcinogenesis in mice. Carcinogenesis, 20: 1583-1590, 1999.

Nyska A., Moomaw, C.R, Foley, J.F., Maronpot, R.R., Malarkey, D.E., Cummings, C.M., Peddada, S., Moyer, C.F., Allen, D.G., Travlos, G. and Chan, P.C.: The Hepatic Endothelial Carcinogen Riddelliine Induces Endothelial Apoptosis, Mitosis, S phase, and p53 and Hepatocytic Vascular Endothelial-Growth-Factor Expression After Short-term Exposure. Toxicol. Appl. Pharmacol., 184: 153-164, 2002.

Training and Mentoring

The Fellows Award for Research Excellence-2003

The Fellows Award for Research Excellence (FARE) was started in 1995 to recognize scientific excellence among NIH intramural trainees. Trainees submit an abstract of their research, which is peer reviewed in a blinded study section competition. The awards are funded by the Scientific Directors, the Office of Research on Women's Health, and the Office of Education. In 2002, 828 applications were received and 203 were funded with $1000 travel awards to attend a meeting in the United States at which they presented their abstract, either as a poster or a seminar. FARE 2003 winners will be invited also to present their work at one of the FARE poster sessions that will follow each of the Wednesday Afternoon Lecture Seminars in Bethesda, and to serve as a judge for FARE 2004.

The NIEHS had 19 winners of FARE 2003 awards:

Winner	*Laboratory/Branch*	*Mentor*	*Abstract Title*
Dr. Lesley Butler	Epidemiology Branch	Dr. Stephanie London	Intake Of Fruit And Asthma Incidence in a Cohort of Chinese Adults in Singapore
Dr. Seung Baek	Laboratory of Molecular Carcinogenesis	Dr. Thomas Eling	Troglitazone, a Peroxisome Proliferator-activated Receptor g (PPARg) Ligand, Selectively Induces Early Growth Response-1 (EGR-1) Gene Independently of Pparg: A Novel Mechanism For its Anti-Tumorigenic Activity
Dr. Jennifer Nixon	Laboratory of Molecular Carcinogenesis	Dr. Thomas Eling	Divergent Effects Of 15-Lipoxygenase-1 on Colorectal Versus Prostate Carcinogenesis
Dr. Petra Koken	Laboratory of Computational Biology and Risk Analysis	Dr. Christopher Portier	A Seasonal Adjustment Method For Analyzing the Impact of Temperature and Air Pollution on Cardiovascular Diseases in Denver
Dr. Liya Qin	Laboratory of Pharmacology and Chemistry	Dr. Jau-Shyong Hong	Roles of NADPH Oxidase in Mediating LPS-Induced Neurotoxicity and the Expression of Pro-inflammatory Factor Genes in Activated Microglia
Dr. Huiming Gao	Laboratory of Pharmacology and Chemistry	Dr. Jau-Shyong Hong	Synergistic Dopaminertic Neurotoxicity of the Pesticide Rotenone and Inflammogen Lipopolysaccharide: Relevance to the Etiology of Parkinson's Disease
Dr. Haiyan Tong	Laboratory of Signal Transduction	Dr. Elizabeth Murphy	The Protective Effect of Phosphatidylinositol-3-kinase and Glycogen Synthase Kinase-3 Beta in the Heart

Dr. Alberto Inga	Laboratory of Molecular Genetics	Dr. Michael Resnick	Characterization of p53 DNA Binding Affinity, Transactivation Capacity and Effects of Post-Translational Modifications Using a Yeast-Based System
Dr. Daniel Tomso	Laboratory of Computational Biology and Risk Analysis	Dr. Douglas Bell	The Influence of Local Sequence Context on Human Single Nucleotide
Dr. Maria Gallardo	Laboratory of Molecular Toxicology	Dr. Jean Harry	Boric Acid Inhibits the Proteolytic Activity of Prostate-Specific Antigen (PSA) In Vitro and Is Effective as a Dietary Supplement to Reduce Proliferative Activity and Local Expression of IGF-1 in Human Prostate Adenocarcinoma (LNCaP) Tumors in Nude Mice
Dr. Diane Klotz	Laboratory of Molecular Carcinogenesis	Dr. Richard DiAugustine	In Vivo Evidence for IGF-1/Estrogen Receptor Cross-talk: Estrogen Receptor-alpha is a Required Intermediate in IGF-1 Stimulated Uterine Proliferative Responses
Dr. Steven Qian	Laboratory of Pharmacology and Chemistry	Dr. Ronald Mason	Optimization of Chromatography Makes a Breakthrough of Radical Identification: LC/ESR, LC/MS, and MS/MS Characterizes in vitro and in vivo POBN Adducts of Carbon-Centered Lipid-Derived Radicals
Dr. Kenichi Imahashi	Laboratory of Signal Transduction	Dr. Elziabeth Murphy	Transgenic Expression of Bcl-2 Reduces Ischemia-Reperfusion Injury and Prevents Cytosolic Acidification During Ischemia
Dr. Jennifer Ingram	Laboratory of Pulmonary Pathobiology	Dr. Jamie Bonner	Interleukin-13-Stimulated Lung Myofibroblast Growth is Mediated by Platelet-Derived Growth Factor-AA in a Stat-6-Dependent Mechanism: Implications for the Development of Airway Fibrosis in Asthma
Dr. Dario Ramirez	Laboratory of Pharmacology and Chemistry	Dr. Ronald Mason	Immuno-Spin Trapping: First application in the detection of protein radical-derived nitrone adducts
Dr. Silvia Ramos	Laboratory of Signal Transduction	Dr. Perry Blackshear	The Zinc Finger Protein Zfp3612 is Critical to Female Fertility and Early Embryonic Development
Dr.Kiyoshi Hidaka	Laboratory of Signal Transduction	Dr. Stephen Shears	Importance to Chondrocyte Differentiation of Changes in Expression of the Multiple Inositol Polyphosphate Phosphatase
Dr. Robert Mohney	Laboratory of Signal Transduction	Dr. John O'Bryan	The Ubiquitin-Interacting Motifs (UIMs) of Epsin Recruit E3 Ubiquitin Ligase Complexes and Target Epsin for Ubiquitination
Dr. Robert Kokoska	Laboratory of Molecular Genetics	Dr. Thomas Kunkel	DNA polymerase IV (Dpo4) of S. sulfataricus generates replication errors by active site misalignment

Awards and Honors for DIR Scientists 2002

Dr. David Armstrong (Laboratory of Signal Transduction) was selected to Chair the inaugural meeting of a new FASEB summer conference on Ion Channel Regulation, which will take place in 2003.

Dr. Douglas Bell (Laboratory of Computational Biology and Risk Analysis) was elected to be Chairman of the Molecular Epidemiology Group, American Association for Cancer Research in 2003; in that position he is serving as Chair-Elect on the Steering Committee.

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) was selected to become the next Editor-in-Chief of *Molecular Endocrinology*.

Dr. Darlene Dixon (Laboratory of Experimental Pathology) was elected to serve a three-year term on the Society of Toxicology Education Committee; and was also selected by Society of Toxicology Council to serve as Chairperson of the K-12 Subcommittee.

Dr. Joyce Goldstein (Laboratory of Computational Biology and Risk Analysis) was selected to join the editorial board of *Drug Metabolism Reviews* and is currently Associate Editor, *Journal of Biochemistry and Molecular Toxicology*.

Dr. Thomas Kunkel (Chief, Laboratory of Structural Biology) has been selected to be the Keynote Speaker at Midwest DNA Repair Symposium, Mayo Clinic and at the Gordon Research Conference on Genetic Toxicology, Oxford, England, both in 2003.

Dr. Larry Lazarus (Laboratory of Computational Biology and Risk Analysis) was on the Organizing Committee, Annual Conference on Opioid Mimetic Analgesics Awaji, Japan, March 2002; and was the Plenary Lecturer. "Dmt (2',6'-dimethyl-L-tyrosine): the universal message determinant for opioidmimetic peptides" Annual Conference on Opioid Mimetic Analgesia, Annual Conference on Opioid Mimetic Analgesia, Awaji, Japan, March 2002.

Dr, Stephanie London (Epidemiology Branch) was elected to the international program committee of the American Thoracic Society and was appointed as an Associate Editor of *Epidemiology*.

Dr. Matthew Longnecker (Epidemiology Branch) has been appointed to the Editorial Board of *Epidemiology* and has been made an Advisory Editor for *Environmental Research* and received a Public Health Service Commendation Medal in recognition of his contributions in the use of Collaborative Perinatal Project data to study environmental effects on children's health.

Dr. Ronald Mason (Laboratory of Pharmacology and Chemistry) was invited to give the Lawrence H. Piette Memorial Lecture, at the 44th Rocky Mountain Conference on Analytical Chemistry in July 2002.

Dr. Fred Miller (Office of Clinical Research) gave the Keynote address at the International Myopain Society, Munich, Germany in May 16 and was reelected to the Board of Directors and as co-chair of the Medical Advisory Board of the Myositis Association of America.

Dr. Elizabeth Murphy (Laboratory of Signal Transduction) has been selected for the Editorial Board of the *Journal of Molecular and Cellular Cardiology*.

Dr. Masahiko Negishi (Laboratory of Reproductive and Developmental Toxicology) received the annual Scientific Achievement Award from the International Society for the Study of Xenobiotics (ISSX) their annual meeting in November 2002.

Dr. Paul Nettesheim (Laboratory of Pulmonary Pathobiology) was received a Humboldt Research Award in recognition of this past achievements by the Alexander von Humboldt Foundation.

Dr. Kenneth Olden (Laboratory of Molecular Carcinogenesis and Director, NIEHS) received the Calver Award from the American Public Health Association in November 2002.

Dr. Allen Wilcox (Epidemiology Branch) was elected President of the American Epidemiological Society for 2002-03 and received the U.S. Public Health Service Distinguished Service Medal, 2002.

Dr. Samuel Wilson (Laboratory of Structural Biology and Deputy Director, NIEHS) was named the Keynote Speaker of the New York Medical College Annual Research Forum and the Mutagenesis Gordon Research Conference; the 21st William B. Kinter Lecturer, Mount Desert Island Biological Laboratory Annual Symposium. Dr. Wilson was also selected to be an Associate Editor for *DNA Repair* and appointed to the Program Committee for the 9th International Conference on Environmental Mutagens; to the Scientific Advisory Board – Program on Structural and Cell Biology of DNA Repair, Lawrence Berkeley National Laboratory; and to the Scientific Advisory Committee, CIIT; and to be Co-Chair of the Marshall Nirenberg Symposium

Dr. Darryl Zeldin (Laboratory of Pulmonary Pathobiology) was elected into American Society for Clinical Investigation (ASCI) in April 2002 and was elected Fellow, American Heart Association, Council for High Blood Pressure Research in May 2002.

Technology Transfer Activities in the DIR for 2002

Material Transfer Agreements (MTAs)

A total of 324 MTAs were reviewed and approved by the NIEHS Office of Technology Transfer. This number represents a 26% increase from FY 2001. Among approved MTAs, 259 (80%) are with academic institutes and the remaining 65 (20%) with pharmaceutical and biotechnology companies.

Cooperative Research And Development Agreements (CRADAs)

Three CRADAs were approved by NIEHS Technology Transfer and by NIH Bethesda:

- "Development and Utilization of cDNA Microarrays for use in Analysis of Gene Expression Changes in Model organisms for Toxicological Studies" by Dr. Richard Paules , National Center for Toxicogenomics, with Boehringer Ingleheim Pharmaceuticals.

- "Proteomic Analysis in Diabetes" by Perry Blackshear, Laboratory of Signal Transduction, with Oxford Glycosciences, Ltd (UK).

- "Tumor Necrosis Factor-Alpha Receptor-1 (TNFR1 or p55) and Tumor Necrosis Factor Receptor-2 (TNFR2 or p75) cDNAs" by Dr. Jean Harry, Laboratory of Molecular Toxicology, with Immunex.

Employee Invention Reports

Four Employee Invention Reports have been or will be filed with the US Patent Office.

- "Effective Activation of poly (A)-specific ribonuclease (PARN) for AU-rich element (ARE)-containing RNA substrates by tristetraprolin (TTP) and related proteins" by Dr. Perry Blackshear, Laboratory of Signal Transduction.

- "Improved Therapy for Asthma Through Increased 1-Phosphatase Activity Against Inositol Pentakisphosphate" by Dr. Stephen Shears, Laboratory of Signal Transduction.

- "A Novel RFX4 Transcript for use in the Diagnosis and prevention of familial Congenital Hydrocephalus" by Dr. Perry Blackshear, Laboratory of Signal Transduction and Dr. Darryl Zeldin, Laboratory of Pulmonary Pathobiology.

- "Mouse Model for Early Onset Cataract" by Dr. Robert Sobol, Laboratory of Structural Biology

Other Activities

License applications.
NIEHS scientists consult with the NIEHS Technology Transfer Office for possible license application regarding NIEHS technology. Licenses may be pursued following NIH OTT review in Bethesda as well as ability to find a commercial sponsor. Five license applications await OTT action.

Foreign country technology transfer.
NIEHS exchanges MTAs with countries throughout Europe and Asia. This year about 15% of MTAs were with researchers abroad.

Confidential disclosure agreements (CDAs).
Commercial organizations will not share data with NIEHS scientists without prior agreement restricting who shares in seeing the data. The NIEHS Technology Transfer Office, NIEHS Deputy Director and the Technology Transfer Service Center in Bethesda review and approve CDAs.

National Toxicology Program
Update February 2003

NTP Workshop on Transgenics

The NTP is sponsoring a workshop, *Genetically Modified Rodent Models for Cancer Hazard Identification: Selecting Substances for Study and Interpreting and Communicating Results*, on February 21, 2003, at the Hamilton Crowne Plaza Hotel, 14th and K Street, NW in Washington, DC. The objectives of this workshop are to solicit comment on

- a process for selection of appropriate nominated substances to undergo cancer hazard evaluation in genetically modified or *transgenic* models
- issues related to the proper interpretation of results from "transgenic" cancer models, the implications of these findings for public health decisions, and the most appropriate interpretive language to describe the results of such studies to the scientific/regulatory communities and the public.

This meeting is open to the public subject to available space. The meeting begins with plenary sessions followed by sessions for two different breakouts designed to address the objectives given above. The meeting will conclude with reports from the breakout groups followed by time for open discussion by all attendees.

The agenda provides time for public comment. Details about the submission of written comments and presentation of oral comments are published in the *Federal Register* (Vol. 68, No. 1, pages 381-382); this notice is posted on the NTP web site. Persons wishing to attend should contact Diane Spencer in the NTP Liaison and Scientific Review Office (919-541-0530 or spencer2@niehs.nih.gov).

10th Edition of the Report on Carcinogens

The Department of Health and Human Services released and made publicly available the Tenth Edition of the Report on Carcinogens (10th RoC) on December 11, 2002. Prepared by the NTP, the RoC identifies substances -- such as metals, pesticides, drugs, and natural and synthetic chemicals -- and mixtures or exposure circumstances that are *known* or are *reasonably anticipated* to be human carcinogens, and to which a significant number of Americans are exposed. This edition of the report adds 16 new listings and brings the total of substances in the report *known* or *reasonably anticipated* to be a cancer hazard to 228. The report makes a distinction between *known* human carcinogens, where there is sufficient evidence from human studies, and *reasonably anticipated* human carcinogens, where there is either limited evidence of carcinogenicity from human studies and/or sufficient evidence of carcinogenicity from experimental animal studies. The report also identifies current regulations concerning these listings in an attempt to address how exposures have been reduced. Additional information and an electronic file of the RoC are available on the NTP web site or by contacting Dr. C.W. Jameson, 919-541-4096. Hard copies are available from Environmental Health Perspectives.

Newly listed as *known* human carcinogens

Steroidal estrogens - A number of the individual steroidal estrogens were already listed as *reasonably anticipated carcinogens* in past editions, but this is the first report to list all these hormones as a group. This group of related hormones controls sex and growth characteristics and is commonly used in estrogen replacement therapy to treat symptoms of menopause and in oral contraceptives. The RoC cites data from human epidemiology studies showing that estrogen replacement therapy is associated with a consistent increase in the risk of endometrial cancer and a less consistent increase in the risk of breast cancer. The RoC also cites evidence suggesting that oral contraceptive use may be associated with increased risk of breast cancer but has protective effects against ovarian and endometrial cancers.

Broad-spectrum ultraviolet radiation - is produced by the sun as part of solar radiation and by artificial sources such as sun lamps and tanning beds, in medical diagnosis and treatment procedures, and in industry for promoting polymerization reactions. Individuals can be exposed to UVR from natural (the sun) and artificial sources. The RoC cites data that indicate a causal relationship between exposure to UVR from natural sources and skin cancer, cancer of the lip and melanoma of the eye. Individuals can be exposed to artificial sources of UVR for cosmetic, medical and occupational reasons and that exposure to these artificial sources (such as sunlamps or sunbeds) is associated with an increased risk of melanoma. The RoC also indicates that skin cancers are observed with increasing duration of exposure and for those persons who experience sunburn.

Wood dust - is created when machines and tools cut, shape and finish wood. Wood dust is particularly prevalent in sawmills, furniture manufacture, carpentry and cabinet making. The RoC cites data from human epidemiological studies that have

consistently demonstrated that wood dust exposure increases the risk of cancers of the nasal cavities and paranasal sinuses.

Nickel compounds - used in many industrial applications as catalysts and in batteries, pigments and ceramics. The RoC listing is based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information that provides evidence of a causal relationship between workers' exposure to nickel compounds and excess mortality from lung and nasal cancers.

Upgraded from *reasonably anticipated* to *known* human carcinogen

Beryllium and beryllium compounds - about 800,000 workers are exposed via inhalation of beryllium dust or dermal contact with products containing beryllium. Workers with the highest potential for exposure include beryllium miners, beryllium alloy makers and fabricators, ceramics workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers. The RoC listing is based on the observed causal relationship between workers exposed to either beryllium or beryllium compounds and lung cancer. The listing states that higher risks for lung cancer are found in groups with greater exposure or longer time since first exposure. These dose-response patterns support a causal relationship and cannot be explained by confounding from smoking or other occupational exposures.

Newly listed as *reasonably anticipated* to be human carcinogens

IQ, or 2-amino-3-methylimidazo[4,5-*f*]quinoline – is one of a series of heterocyclic amines formed during direct cooking with high heat of foods, such as meats and eggs, and is also found in cigarette smoke. The RoC listing is based on findings from oral studies of IQ in experimental animals that produced cancer in multiple organs of multiple species. The report also states that while no adequate human epidemiology studies have been reported that would indicate a human cancer risk specifically associated with exposure to IQ or other HCAs, there are published studies that provide some indication for an increased risk for breast and colorectal cancers related to consumption of broiled or fried foods that may contain IQ and/or other heterocyclic amines.

2,2-bis-(Bromomethyl)-1,3-propanediol (technical grade) - a flame retardant chemical used to make some polyester resins and rigid polyurethane foam is listed as *reasonably anticipated* based on long-term animal feeding studies. The RoC listing is based on findings from long term feeding studies of this chemical in laboratory animals where cancer was observed in multiple organs sites of multiple species of animals.

Ultraviolet A (UVA), Ultraviolet B (UVB) and Ultraviolet C (UVC) Radiation - Broad spectrum ultraviolet radiation contains wavelengths from 100 to 400 nm and is composed of individual components defined as UVA (315 to 400 nm), UVB (280 to 315 nm) and UVC (100 to 280 nm). The major sources of exposure to UVA and UVB are from natural solar radiation and artificial sources such as sunlamps, sunbeds and arc welding. UVC exists in the extraterrestrial solar spectrum, but is completely filtered out by the earth's ozone layer and does not reach the earth's surface. The major source of UVC exposure comes from artificial sources such as germicidal lamps, UV photography, and UV lasers. The RoC listing of UVA, UVB, and UVC is based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals that indicate a causal relationship between exposure to UVA, UVB or UVC and skin cancer.

Chloramphenicol – is an antibiotic with restricted use in the United States because it can cause fatal blood disorders. The RoC listing is based on limited evidence of carcinogenicity from studies in humans showing an increased cancer risk for the occurrence of leukemia after chloramphenicol therapy.

2,3-Dibromo-1-propanol - a chemical used as an intermediate in the production of flame-retardants, insecticides, and pharmaceuticals. Formerly used in the production of TRIS-BP, a now banned flame retardant previously used in children's clothing and other products. The RoC listing is based on findings from skin painting studies of this chemical on laboratory animals that produced cancer in multiple organs of multiple species.

Dyes metabolized to 3,3'-dimethoxybenzidine - dyes that have been used to color leather, paper, plastic, rubber and textiles. The RoC listing is based on the fact that

3,3'-dimethoxybenzidine is carcinogenic in male and female rats, has been listed in the RoC since 1983 as *reasonably anticipated to be a human carcinogen* and that metabolism of these dyes to release free 3,3'-dimethoxybenzidine is a generalized phenomenon that occurs in all animal species studied.

Dyes metabolized to 3,3'-demethylbenzidine – dyes that have been used in printing textiles, in color photography and as biological stains. The RoC listing is based on the fact that 3,3'-dimethylbenzidine is carcinogenic in male and female rats, has been listed in the RoC since 1983 as *reasonably anticipated to be a human carcinogen* and that metabolism of these dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied.

Methyleugenol - occurs naturally in oils, herbs and spices and is used in smaller amounts in its natural or synthetic form in flavors, insect attractants, anesthetics and sunscreens. The RoC listing is based on findings from oral studies of this chemical that produced cancer in multiple organs of multiple species of experimental animals.

Metallic nickel - used mainly in alloys with most exposures by inhalation or skin contact in the workplace. The nickel coin does not contain metallic nickel, but does contain a copper-nickel alloy. The RoC listing is based on findings from studies of this metal in multiple species of experimental animals that produced cancer at multiple organ sites.

Styrene-7,8-oxide - is used in the production of reinforced plastics and as a chemical intermediate for cosmetics, surface coatings, and agricultural and biological chemicals. The RoC listing is based on findings from oral studies of this chemical that produced cancer in multiple species of experimental animals.

Vinyl bromide - used in polymers in making fabrics for clothes and home furnishings, as well as in leather and metal products, drugs and fumigants. The RoC listing is based on findings from inhalation studies of this chemical that produced cancer in multiple organs of experimental animals.

Vinyl fluoride - used in making polyvinyl fluoride and related weather-resistant fluoropolymers. The RoC listing is based on findings from inhalation studies of this chemical that produced cancer in multiple organs of multiple species of experimental animals.

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

Review of Ethylene Glycol and Propylene Gycol

The CERHR serves as an environmental health information resource. It provides timely and unbiased scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, which may be caused by agents to which humans are exposed.

CERHR will hold an expert panel meeting February 11-13, 2003, in Alexandria, Virginia, to evaluate the potential reproductive and developmental toxicities of ethylene glycol and propylene glycol (Federal Register Vol. 67, No. 236, pages 72965 – 72967: December 9, 2002). This meeting is open to the public. Draft expert panel reports on ethylene glycol and propylene glycol are available electronically on the CERHR web site

Ethylene glycol is a high-production-volume chemical used chiefly in the production of polyester compounds. Widespread public exposure occurs through its common use as antifreeze for heating and cooling systems. Propylene glycol, similar in structure to ethylene glycol, is used as antifreeze, in de-icing solutions, and in various paints and coatings. Propylene glycol is also approved for use in various food additives, drugs, and cosmetics.

CERHR Workshop on Chemical-Induced Thyroid Dysfunction and Human Reproduction

CERHR is planning a workshop to address how best to evaluate the potential for chemical-induced thyroid dysfunction to adversely affect human reproduction. Two primary issues for discussion at this meeting are: (1) the appropriate design of relevant toxicity tests for detecting adverse reproductive effects and (2) the appropriate use of rodent data for predicting effects in humans. This one *and* one-half day meeting is planned for late April 2003 in the Washington, DC area. Further details can be obtained from Dr. Michael Shelby, CERHR director 919-541-3455

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

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

The first meeting of the SACATM was held on December 5, 2002, at the Crystal Gateway Hotel in Arlington, Virginia. In response to the ICCVAM Authorization Act of 2000, the NIEHS established the new federally chartered advisory committee SACATM. This committee will provide advice on the statutorily mandated activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and on activities of the NICEATM, including ways to foster partnerships and communication with interested parties. A copy of the charter is posted on the NICEATM/ICCVAM web site or available from the NTP Liaison and Scientific Review Office (919-541-0530 or wolfe@niehs.nih.gov).

Members of SACATM

Daniel Acosta, Ph.D.
University of Cincinnati

Rodger Curren, Ph.D.
Institute for In Vitro Sciences, Inc.

Jack Dean, Ph.D. (chair)
Sanofi-Synthelabo, Inc.

Nancy Flournoy, Ph.D.
University of Missouri – Columbia

Alan Goldberg, Ph.D.
Johns Hopkins University

Sidney Green, Ph.D.
Howard University College of Medicine

Wallace Hayes, Ph.D.
Gradient Corporation

Nancy Monteiro-Riviere, Ph.D.
North Carolina State University

Steven Safe, Ph.D.
Texas A & M University

Jacqueline Smith, Ph.D.
Private citizen

Carlos Sonnenschein, M.D.
Tufts University School of Medicine

Martin Stephens, Ph.D.
The Humane Society of the United States

Katherine Stitzel, D.V.M.
Private citizen

Peter Theran, V.M.D.
Massachusetts Society for the Prevention of Cruelty to Animals

Calvin Willhite, Ph.D.
State of California