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 23-24, 2004

The National Advisory Environmental Health Sciences Council was convened for its one hundred eleventh regular meeting on February 23, at 8:30 a.m., in Building 31, Conference Room 10, National Institutes of Health, Bethesda, Maryland. The meeting was open to the public from 8:30 a.m. until 5:30 p.m.. The meeting was closed for consideration of grant applications on February 24, 9:30 a.m. - 12:30 p.m. Dr. Kenneth Olden presided as Chair on February 23-24, 2004.

Members Present:

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

Members Absent:

Michael Gallo, Ph.D.
Joan Cranmer, Ph.D., ATS
George Gray, Ph.D.

Ex Officio Members Absent:

Eric L. Stephens

Liaison Members Present:

David Ringer, ACS
Marion Ehrich, SOT
Robert Spengler, NCEH/ATSDR

Members of the Public Present:

Patricia Smith - Masi Max Resource, Inc

NIEHS Staff:

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

Joan Packenham, Ph.D.
Jerry Phelps
Warren Pope
Chris Portier, Ph.D.
Les Reinlib, Ph.D.
Margarita Roque
Anne P. Sassaman, Ph.D.
Carol Shreffler, Ph.D.
Shobha Srinivasan, Ph.D.
Deborah Swope, Ph.D.
William Suk, Ph.D., M.P.H.
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Charles Wells, Ph.D.
Brenda Weis, Ph.D.
Samuel Wilson, M.D.
Leroy Worth, Ph.D.

Other Federal Staff:

Caroline Grabner, NHLBI
Kim Brinson, NHLBI
C. Melchoir, CSR
J. Rudolph, CSR
Caroline Dean, FDA

I. CALL TO ORDER AND OPENING REMARKS

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

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

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

III. CONSIDERATION OF MINUTES OF September 15-16, 2003 MEETING

Council accepted the minutes without change.

FUTURE COUNCIL MEETING DATES

May 17-19, 2004 NIEHS with Leadership retreat
September 13-14, 2004 NIEHS
February 14-15, 2005 NIH - Bethesda

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

Dr. Olden began his report by welcoming the new members to the Council and commenting on the importance of the responsibilities of the Council. Dr. Olden reported on Ms. Peggy Shepard's award, the Hines Award for Effective Environmental Advocacy. Ms. Shepard served on the Council until last fall. Dr. Olden also introduced the new Associate Director of Management for NIEHS, Mr. Richard Freed.

Dr. Olden referred to the information that was provided in the folder to the Council members at the table. He commented on the search committee to find his replacement and the roster of the search committee in the folder. Dr. Olden is confident that an outstanding individual will be selected to lead NIEHS.

In several planning sessions, advisory groups were asked to identify the gaps in breast cancer research and in particular how these relate to the environment. From these discussions a Request for Applications was developed, and in October last year NIEHS funded four Breast Cancer and the Environment Research Centers in collaboration with the National Cancer Institute. The four centers funded are: University of California, San Francisco; Fox Chase Cancer Center, Philadelphia; University of Cincinnati; and Michigan State University. The centers have had two meetings since October. The total funding made available was $35 million over a period of 7 years. Although currently no money has been specifically appropriated for this, it is a priority for the NIEHS.

About six years ago at a retreat discussion about what NIEHS intramural research should emphasize, structural biology was identified. Dr. Traci Hall from John's Hopkins was subsequently recruited. She has identified a protein that is involved in circumventing the host mechanism of suppressing the transcription of viral RNA. The publication describing this was provided to the Council .Dr. Olden included a cover of the journal Cell in the information folder and commented on how getting an illustration on the cover of Cell is a major achievement.

Environmental Health Perspectives is the journal for NIEHS. Over the years the journal has evolved and has increased considerably in quality and recognition. There are scientific and lay articles and the Council members were encouraged to submit articles.

Dr. Olden reported that Council Member Dr. Joan Cranmer recently developed an international conference, co-sponsored by NIEHS, on infant and child neurotoxicity studies and the effects of environmental agents on the neurological development of children. The conference was in Hawaii; the attendance was outstanding and the science was good.

Dr. Allen Dearry is taking the lead on the Obesity and the Built Environment Conference to be held in May. The conference is part of an NIH strategic plan to deal with the epidemic of obesity. The strategic plan is being developed as a trans-NIH effort by the Obesity Task Force, and all the institutes and centers are participating. Council members are welcome to attend and participate in the Conference. NIEHS has a particular interest in children and the built environment, as communities are not as people friendly with walking trails and safety from traffic as they should be. The United States needs to develop communities in such a way as to promote good health. NIEHS is also supporting the creation of a television series called "Fitness Fighters" on the model of Sesame Street to get kids interested in good behavior with diet and exercise.

Dr. Olden also spoke about nanotechnology. Since technology is going to revolutionize communication and the practice of medicine, we have a responsibility to make sure the technology is safe. Industry is concerned about identifying the toxic products from the beginning so that they are not put into the market place. Therefore, NIEHS is preparing to test some of these nanotechnological devices in the National Toxicology Program.

In other updates, Dr. Olden mentioned the NIH Roadmap initiatives, in which all institutes are participating, and their relation to ongoing NIEHS activities. The Roadmap is intended to provide tools and resources in support of many areas of science. For the current fiscal year, there is a budget of $128 million. He also mentioned the National Children's Study and some discussions about expanding it to include parents and grandparents. While this would give much more information, it would increase the cost considerably.

Dr. Olden closed with comments on the May retreat and soliciting topics/issues. Almost every program that has been developed has evolved out of the retreats. In addition, the town meetings are a way to let the American have input into the programs.

Mr. Richard Freed, Associate Director for Management, provided some information on the Fiscal Year 2004 and 2005 budgets for NIEHS (Attachment B). NIEHS enjoyed a doubling of the budget from 1998-2003 and the Superfund Program has also increased considerably.

V. REPORT OF THE DIRECTOR, NIH - Dr. Elias Zerhouni

Dr. Zerhouni opened by thanking the Council for the work that they are doing for the Institute. There are over 21,000 individuals who serve on advisory committees every year with very little compensation and NIH could not do its work without them.

Dr. Zerhouni then tackled the question, "Where is the Science"? He mentioned several issues that initiatives in the Roadmap are addressing: complexities in science and the integration of multiple fields; the need to encourage flexibility and innovation in our programs and the peer review process; and improvements in clinical research, for example.

There are other issues related to management and the research workforce. NIH is facing the challenge of the budgets going from 15% increases to 2.8% increases and also changes in the demographics of the scientific workforce. For example, today only 4% of NIH grantees receive new grants under the age of 35. He expressed concern that this indicates a rigidity in our human

capital development. In addition, the need for larger scale science should not overshadow self-assembly of investigator-initiated research and creativity.

In closing, Dr. Zerhouni complimented Dr. Olden on his leadership of the Institute and his contributions to NIH. He mentioned the search committee currently appointed to seek his replacement and noted that he had asked Dr. Olden to stay until the replacement was named. He then responded to questions from the Council and departed.

Dr. Olden then introduced the major topic of the presentations to follow, that is, training and mentoring. He stated that he believes in the investment in people-to look at potential and then make a long-term commitment. The three programs to be discussed are examples of ones that have been successful.

VI. THE MEYERHOFF PROGRAM - Dr. Freeman Hrabowski and Dr. Michael Summers (Attachment C)

The University of Maryland, Baltimore County (UMBC), a predominantly white institution emphasizing science education and research, has a strong commitment of the department chairs to increase diversity. The Meyerhoff Program is a program for minority undergraduates interested in careers in science and is designed to increase the diversity in the sciences. There is a need for minority leadership to address health disparities as well as to participate in the research enterprise in general.

Since the program was created in 1988, the goal has been to build a group of well prepared minority students who will become leading researchers. The importance of the relationships between minority undergraduates and scientist and mentors was emphasized. Since 1993 there have been 243 Science, Engineering and Mathematics (SEM) graduates. In addition to the Meyerhoff Program, UMBC also has a Howard Hughes Medical Institute Program to support high achieving students who plan to pursue a Ph.D. or MD/Ph.D. Each year UMBC supports 5 new students in this program.

Approximately 550 undergraduates have enrolled since the Myerhoff Program began, and approximately 350 students have earned degrees in science with 85 percent going on to graduate and professional programs at universities nationwide.

Following Dr. Hrabowski's description of the Program, Dr. Summers gave a presentation on his research, emphasizing the important role of students and trainees in it.

VII. MOREHOUSE NEUROSCIENCES - Dr. Peter MacLeish and Dr. Byron Ford (Attachment D)

Dr. MacLeish discussed the factors that led to the development of a Neuroscience Institute at Morehouse School of Medicine, which included the emergence of neuroscience as a scientific field; the dearth of under-represented minorities in the neurosciences; and the historic role of Historically Black Colleges and Universities (HBCUs) in training minority professionals. The National Institute of Neurological Disorders and Stroke along with the Office for Research on

Minority Health at NIH developed an approach to increase research capacity for the neurosciences at HBCUs to produce cutting edge research. The Neurosciences Institute at Morehouse is a result of that initiative. Dr. MacLeish was recruited to head the program, and NIH staff played a crucial role through the cooperative agreement mechanism. Dr. MacLeish emphasized the importance of total commitment of the institution, appropriate advisory committees, and a commitment to excellence.

Dr. Ford then presented the results of his research on the role of neuregulins in neuroprotection following acute stroke. He is a young scientist who was recruited into the Institute.(Attachment D2)

VIII. THE RENAISSANCE SCIENTISTS: ENSURING A FUTURE OF DISCOVERY AND INNOVATION Dr. Skip Bollenbacher (Attachment E)

Dr. Bollenbacher described to the Council a post-doctoral training program that provides experiences essential for the success of the future's biomedical researchers: Seeding Postdoctoral Innovators in Research and Education (SPIRE). The University of North Carolina at Chapel Hill, in conjunction with seven historically minority universities (HMUs) in North Carolina, and via the Partnership for Minority Advancement in the Biomolecular Sciences (PMABS), has created a program for post-docs that provides comprehensive training for a new kind of scholar. The training also provides HMU minority students with equal access to knowledge and technology with the goal of contributing to diversity in biomedical careers.

In addition to SPIRE, the Distributed Learning Network (DLN) connects multiple populations of underserved students across North Carolina. The DLN connects each science department within the PMABS via video conferencing classrooms, providing new kinds of learning and training to the future researchers. Through this network, SPIRE fellows are participating in a new paradigm for post-doctoral training and mentoring as well as a new educational model.

IX. RESEARCH PLANNING AT NIEHS: SETTING PRIORITES FOR THE FUTURE Dr. Sheila Newton

The Office of Policy, Planning and Evaluation, Division of Research Coordination, Planning and Translation is an integral part of the research planning at the NIEHS. Setting research priorities for the future is achieved in many ways and may involve Advisory Councils, Boards of Scientific Counselors, national meetings, town meetings, retreats, review committees and brainstorming meetings. Previous reports on the research needs of the NIEHS go back to 1970 and have been done approximately every 6 years. The most recent reports were done in 1998 with a Report of the External Review Working Group and in 2000 with the Working Group Report on the Division of Extramural Training and Research (DERT).

The proposal now is to establish the 5th Task Force with a new question: What are the highest priority investments for the NIEHS to advance the field of environmental health over the next 5-10 years? In developing the NIH Roadmap, the participants were asked the following questions: What are today's scientific challenges, what are the roadblocks to progress and what do we need

to do to overcome these roadblocks? The NIEHS will use these questions in its own priority of investments.

The timeline for the 5th Task Force begins with the February 2004 Council meeting for review and input. In September 2004, the first draft will be presented to Council. In February 2005 the final report will be presented to Council and to the new NIEHS Director.

X. NIEHS FELLOWS PROGRAM - Dr. Deborah Swope (Attachment F)

The NIEHS Office of Fellows' Career Development (OFCD) in the Office of the Director concentrates on the professional development of the postdoctoral and pre-doctoral fellows beyond the skills learned in the laboratory. This program brings career information to the NIEHS fellows in the form of workshops, discussions, seminars and brown-bag lunches. There are challenges at NIEHS by being in North Carolina and not Bethesda, but this Office has made great efforts to provide comparable opportunities to NIEHS trainees.

Dr. Olden complimented Dr. Swope on her energy and effectiveness in developing and promoting the programs for trainees, and pointed out that NIEHS was recently voted one of the top places in the country to do a post-doctoral fellowship.

XI. REPORT OF THE NTP BOARD AND THE NTP VISION - Dr. Stephen Roberts and Dr. Christopher Portier (Attachment G)

Dr. Roberts discussed the National Toxicology Program (NTP) Board's composition and the mandate for the Board. The Board is a federally chartered advisory committee with up to 35 members with broad expertise, including toxicology, medicine and epidemiology. Activities of the Board in 2002-2003 included genetically modified mouse models in NTP studies, establishment of the Center for the Evaluation of Risks to Human Reproduction, concept review and draft NTP Technical Reports. The Technical Reports Review Subcommittee evaluates the findings and conclusions of draft NTP Technical Reports, recommends levels of evidence for carcinogenic activity to NTP on study findings, offers a peer review in public forum with opportunity for public comment and also has subcommittee expertise including pathology, carcinogenesis and toxicology.

Details of the Board's activities are found in the attachment.

Dr. Portier discussed the Vision of the NTP for the 21st Century. The NTP was developed in 1978 to coordinate toxicological testing programs within the Department of Health and Human Services, develop and validate testing methods, develop approaches and generate data to strengthen scientific knowledge about potentially hazardous substances and communicate with stakeholders. The NTP Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

XII. REPORT OF THE DIRECTOR, DIVISION OF EXTRAMURAL RESEARCH - Dr. Anne Sassaman

Dr. Sassaman began her report by referring Council members to the staff activities summary included in her written report, commenting on the many activities in which DERT staff are involved and especially the leadership in a number of these. (Attachment H)

She then moved to present the annual report of the previous fiscal year regarding the profile of grant expenditures, beginning with the comment that approximately 50% of the Institute's budget from its Department of Health and Human Services appropriation is spent on research and training grants of various types. Research Project Grants represent 72% of this budget, a figure that has remained relatively constant over the years. She then pointed out the large impact of the grant funds derived from the separate Superfund appropriation, which accounts for 21% of the total "grants" budget. As a result of ongoing commitments from previous years and new activities begun during the doubling of the NIH budget, the success rate for Fiscal Year 2003 fell to 25.4%, compared with the overall NIH success rate of 30%. However, the new awards for Fiscal Year 2003 included several high priority investments, such as the Breast Cancer and the Environment Centers, Centers for Population Health and Health Disparities, and new research related to the fetal basis of adult disease. New activities are also proposed within the funding plans for Fiscal Year 2004, and she listed some of them.

Next, Dr. Sassaman briefed the Council on a planned assessment of the NIEHS Core Centers (P30) program, which will be undertaken by a working group of Council co-chaired by Dr. Martin Philbert and Dr. Ken Ramos. She summarized some of the history of this program, pointing out that no formal evaluation has taken place since it was started at the time NIEHS was established. Staff has developed an overall strategy that will use existing data in NIEHS databases with additional information obtained from the centers themselves. Issues to be addressed include assessing the center program's success in building research capacity in environmental health sciences, whether the program is adequately configured to meet the needs and challenges of environmental health sciences today and in the future, as well as providing recommendations regarding changes in structure or mechanism that would better address the Institute's priorities for the future. She pointed out that the importance of evaluation was also emphasized in the recommendations of a recent Institute of Medicine study on the NIH extramural centers programs overall. The report on NIEHS centers is scheduled for presentation to the Council in February of 2005.

Council then discussed the proposed assessment process and had several suggestions for consideration by the staff and evaluation committee. Dr. Olden requested that any additional comments or suggestions be sent to him for consideration. Council pointed out that one of the advantages of the centers is that, unlike the department-based academic structure, they can cross boundaries to build interdisciplinary collaborations and this should be examined closely.

The next item for discussion and vote was the annual review of council delegated authorities and operating procedures (Attachment I). No changes were proposed except for editorial changes related to the process for expedited review. New Council members raised questions about how these authorities for staff affected the ability of Council to provide its oversight function, and Dr.

Sassaman provided examples of the types of staff actions that are necessary to be carried out between meetings of the Council and which are routine parts of doing business. She committed to bringing some of the actions taken between the February and May meetings to the attention of concerned members so that they would have a better feel of the types of activities covered by the delegated authorities. Council gave its approval with three negative votes.

The final item on the DERT report was a concept clearance for a new initiative on the built environment and human health (Attachment J). This was presented by Dr. Shobha Srinivasan, and after discussion of this particular initiative and other possible approaches, some of which are being addressed within the activities of the NIH Obesity Task Force, Council unanimously voted approval of the concept.

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).

This also included the Closed Executive Session where the Report of the Director, Board of Scientific Counselors was presented by Dr. John Hildenbrandt.

XIII. REVIEW OF APPLICATIONS

The Council considered 327 applications requesting $112,399,159 in total cost. The Council recommended 186 applications with the total cost of $87,639,283.

XIV. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 12:30 pm on February 24, 2004.

ATTACHMENTS:

A. Council Roster
B. Budget Presentation Slides
C. Meyerhoff Program (Word) *Adobe Acrobat* Format
D. The Development of a Neuroscience Institute at Morehouse School of Medicine (Word)
D2. The Role of Neuregulins in Neuroprotection Following Acute Stroke (Word)
E. The Renaissance Scientist: Ensuring a Future of Discovery and Innovation (Word)
F. NIEHS Fellows Program (WordPerfect)
G. Report of the Director, Division of Intramural Research; *Adobe Acrobat* Format
H. Report of the Director, Division of Extramural Research (WordPerfect)
I. Council Delegated Authorities Word)
J. Concept Clearance for Built Environment and Human Health

Beating the Odds:
Preparing Minority Students for Research Careers in Biomedical Science

Freeman A. Hrabowski, III
President, University of Maryland, Baltimore County

Michael F. Summers
Howard Hughes Medical Institute Investigator &
Professor of Chemistry, University of Maryland Baltimore County

National Environmental Health Science Advisory Council Meeting
National Institutes of Health – Bethesda, Maryland
February 23, 2004

Abstract

Although African American students represent approximately 11 percent of all students enrolled in the nation's colleges and universities, they earn not quite seven percent (6.9) of all bachelor's degrees and less than two percent (1.8) of the doctoral degrees in science and engineering.[i] Colleges and universities, as well as national agencies, companies, and foundations, regularly send representatives to visit the University of Maryland, Baltimore County (UMBC), a predominantly white institution emphasizing science education and research, because of the success over the past decade of our Meyerhoff Scholars Program for high-achieving African American students in science. Our experience is especially noteworthy given the nation's growing diversity and the implications of this development for America's future scientific workforce.

Since creating the program in 1988, our goal has been to build a cadre of well prepared minority students who would become leading researchers. We have focused on creating a climate that attracts serious students, sets high expectations of them, and then takes a proactive approach in helping them to succeed. Most important, our senior faculty have taken ownership of the program and of the student's education, and the students, themselves, comprise a community of young scholars who support each other and focus on the excitement of research.

One of the program's distinguishing features is its assumption that every student competitively selected has the ability not only to graduate – given appropriate opportunities and resources – but also to excel, because the program engenders an expectation of excellence. Its components include (1) recruiting top minority students in science; (2) a summer bridge program; (3) comprehensive merit scholarship support; (4) active faculty involvement in recruiting, teaching, and students' research experiences; (5) strong programmatic values including high achievement, study groups, tutoring, and preparing for graduate or professional school; (6) substantive research experiences for students; (7) intensive academic advising and personal counseling; (8) active involvement of the entire campus; (9) linking students with mentors; (10) a strong sense of community among the students; (11) communication with the students' families; and (12) continuous evaluation and documentation of program outcomes.

This multilevel approach has proven to be highly effective. In fact, *Science* recently listed the Meyerhoff Program among the best academic programs of its kind in the nation.[ii] Approximately 550 undergraduates (including 200 current students) have enrolled since the program began, and approximately 350 students have earned degrees in science, with 85 percent going on to graduate and professional programs at universities nationwide. According to recent data, UMBC ranked first nationally in the number of undergraduate biochemistry degrees awarded to African Americans, producing nearly one-third of the national total several years ago.[iii] Our success at the undergraduate level has led to similarly successful initiatives in our graduate programs.

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[i] American Council on Education, *Minorities in Higher Education, Annual Status Report, 2002-2003*, Washington, D.C., 2003.

[ii] *Science*, Volume 301, August 22, 2003, p. 1030.

[iii] American Society of Biochemistry & Molecular Biology, Graduate Survey, *ASBMS News*, January-February, 2000.

The Development of a Neuroscience Institute at Morehouse School of Medicine

Peter R. MacLeish, Ph.D.

Several factors led to the development of a Neuroscience Institute at Morehouse School of Medicine. The order of listing does not necessarily reflect relative importance among these factors. They were:

1 The emergence of neuroscience as a scientific field. The past forty or so years saw a rapid and profound expansion in our fundamental understanding of the development and functional organization of the nervous system and provided an opportunity to study, systematically, many of the properties of the brain that had intrigued humans for many years. This increase in the knowledge pool also provided the opportunity to understand the molecular and cellular bases of many debilitating neurological and psychiatric disorders and to develop effective interventions.

2. The dearth of under-represented minorities in neuroscience. The number of trainees and researchers from minority groups has been, and continues to be, low. Efforts to increase these numbers through supplements and other mechanisms primarily at majority institutions have met with limited success.

3. Historic role of Historically Black Colleges and Universities (HBCU's) in training minority professionals. HBCU's have been the training sites for many prominent leaders and seemed strategically placed for an investment in focused scientific training.

For the above reasons, the National Institute for Neurological Disorders and Stroke along with the then Office for Minority Health and Research embarked on a bold move to increase research capacity for neuroscience at HBCU's to allow them to undertake cutting edge research. By this action, faculty and students would join in the quest in understanding the workings of the nervous system and in alleviating suffering caused by neurological and psychiatric disorders, particularly those that affected populations disproportionately.

This talk will highlight the development of the Morehouse School of Medicine from 1994 to the present. It will describe the developmental strategies used and will try to identify the essential features for a successful program. It will show that with clear objectives, with productive partnerships with federal and private agencies, and with unwavering institutional support that it is possible to attract and nurture outstanding faculty who are able to mount highly-meritorious research programs. While the immediate beneficiaries are the next generation of students at the institution, the investment has already shown its ability to address some of the most pressing health issues in the nation. Finally, it will attempt to identify the challenges that must be overcome to assure continued success and will underscore the role for long-term commitment from federal and private agencies in maintaining a competitive mature health science enterprise at target institutions.

The Role of Neuregulins in Neuroprotection Following Acute Stroke

Dr. Byron Ford
Morehouse School of Medicine

Stroke is the third leading cause of death in the United States and the major cause of long term disability. However, very little progress has been made in the development of treatment of acute stroke. Neuregulins are a family of growth factors implicated in a number of neuronal functions including development, plasticity, behavior and pathology. Recent work from our lab demonstrated that the expression neuregulin-1 in neurons was induced in the ischemic penumbra by focal stroke in the rat. *In vitro* studies have demonstrated that neuregulin-1 regulates apoptosis as well as cytokine and ischemia-induced gene expression in neuronal cultures. Here, we show that exogenously administered neuregulin-1 completely blocks ischemia-induced neuronal death in the cerebral cortex induced by focal stroke. A single injection of neuregulin-1 (~2.5 ng/kg) was neuroprotective if administered either before or at long as 5.5 hours after stroke. Analysis of DNA fragmentation in brain tissues showed that neuregulin-1 blocked apoptosis in cortical neurons in the penumbra. Neuregulin-1 also prevented macrophage/microglial infiltration and astrocytic activation in the cortex following focal ischemia. The neuroprotective effects of the single administration of neuregulin-1 was seen as long as 2 weeks following treatment. Using microarray analysis and RT-PCR we have observed the induction of a number of genes associated with a variety of cellular mechanisms including inflammation, apoptosis, neuroprotection and neuronal regeneration. We show that neuregulin-1 reversed changes in gene expression in the rat brain following stroke. Our results clearly demonstrate that neuregulin-1 is induced in neurons following ischemic stroke and may be involved in neuroprotection and repair. Neuregulins represent a novel, potent neuroprotective strategy that has potential therapeutic value in treating individuals after acute ischemic stroke.

Dr. Skip Bollenbacher

The Renaissance Scientist: Ensuring a Future of Discovery and Innovation

Seeding Postdoctoral Innovators in Research and Education (SPIRE) is an innovative post-doc training program that provides training experiences essential for success of the future's biomedical researchers. By merging research training with professional development emphasizing learning, education and communication, UNC Chapel Hill, in alliance with 7 NC historically minority universities (HMUs), via the Partnership for Minority Advancement in the Biomolecular Sciences (PMABS), has created a uniquely innovative program for post-docs that provides comprehensive training that is yielding a new kind of scholar. This training contributes to providing HMU minority students equal access to the knowledge and technology revolutions and opportunities with the goal of contributing to achieving diversity in biomedical careers. In addition to these training initiatives, completion of a Distributed Learning Network (DLN) allows SPIRE fellows to teach cutting-edge science content simultaneously to multiple populations of underserved students across NC. The DLN connects each science department within the PMABS consortium via video teleconferencing SMART-classrooms, furthering SPIRE's advance to a significant level of excellence that compellingly demonstrates the importance of providing new kinds of learning and training to today's and tomorrow's researchers. Programmatic integration and innovation documented with tangible outcomes (e.g., success of post-docs and HMU minority students in biomedical careers), built upon evaluation and lessons learned/successes to date, continue to expand and refine SPIRE's original design in a variety of ways, including: 1) modeling a new paradigm for postdoctoral training; 2) increase number of uniquely trained post-docs to meet burgeoning profession and HMU need; 3) diffuse IT innovation broadly to further advance post-doc and student success; 4) expand participation to include outstanding researchers; 5) target disciplines (e.g., genomics, bioinformatics, molecular genetics) to meet the urgent learning needs of HMU students; and 6) expand the exceptional opportunity for sustained post-doc mentoring of minority student research and thus advancement into research careers. SPIRE is poised to begin the needed revolution in post-doc training and diversity which will revitalize US born student interest in biomedical careers.

NIEHS Fellows Program
Dr. Deborah Swope

The NIEHS Office of Fellows' Career Development (located within the Office of the Director, NIEHS) concentrates on the professional development of the postdoctoral and pre-doctoral fellows beyond the skills learned at the laboratory bench. The OFCD brings career information to NIEHS fellows in the form of workshops, discussions, seminars and brown-bag lunches. It acts as a liaison between the NIEHS fellows community and the administration, as well as to outside organizations focused on enhancing postdoctoral training. These programs complement those that have been routinely offered by the NIEHS Trainees Assembly (NTA) for a number of years, including the NTA's "flagship" event, the annual Career Fair, which regularly has about 300 attendees from the RTP area. Recent events organized by the OFCD include the first Survival Skills workshop on "Job Hunting", a seminar on management skills, and a brown bag lunch discussing careers in small biotech companies. This spring, the OFCD is offering a week-long workshop in RTP on grant and proposal writing skills in conjunction with Sigma Xi, the national research honor society. The OFCD has also sponsored a sustaining membership in the National Postdoctoral Association for the NIEHS. In the planning stages are a website, expanded orientation materials, and informational materials for PIs to aid in the recruitment of new fellows.

Division of Intramural Research

NAEHS Council Update

February 2004

DIR RECRUITMENTS

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

Senior Molecular Toxicologist
The Environmental Toxicology Program is conducting a search for a senior tenured investigator to direct research in molecular toxicology. The candidate will be expected to develop and maintain a strong intramural research effort in toxicology, particularly as it relates to defining critical target pathways, genes and cellular/molecular mechanisms of target organ responses to environmental factors and to provide programmatic leadership and council to the initiatives of the Environmental Toxicology and the National Toxicology Program in the candidate's area of expertise. Researchers in the area of developmental toxicology are particularly sought, although qualified individuals in any area of toxicological research are encouraged to apply. The Candidate should be a senior investigator with an international reputation for cutting edge research within the broad context of toxicology, an outstanding publications record, a proven history of research leadership, and demonstration of knowledge of toxicology and human health issues. The search committee chaired by Dr. Robert Maronpot, Chief of the Laboratory of Experimental Pathology, has interviewed candidates.

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. An offer is being made to the top candidate.

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). Dr. Farhad Imani, currently an Assistant Professor of Medicine at the Johns Hopkins University School of Medicine, has accepted this position.

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

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

Tenure-track Investigator - Embryonic Stem Cell Biology
The Laboratory of Molecular Carcinogenesis is conducting a national search for a Tenure-Track Investigator in embryonic stem cell biology with research strengths in, but not necessarily limited to, development and epigenetics. The search committee, chaired by Dr. Jean Harry, Acting Chief, Laboratory of Molecular Toxicology, is interviewing candidates.

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

Tenure-track Investigator—Endocrinology
The Laboratory of Reproductive and Developmental Toxicology is conducting a national search for a Tenure-Track Investigator in hypothalamic–pituitary–gonadal reproductive neuroendocrinology. The individual selected for this position will have a record of accomplishments in the field of mammalian Reproductive Neuroendocrinology, with a research

emphasis on the regulation and function of the hypothalamic–pituitary–gonadal axis in reproduction. A search committee is being formed.

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

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

Staff Scientist--Toxicologic Pathologist

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

Staff Scientist—Pathologist/Laboratory Animal Veterinarian

The Laboratory of Experimental Pathology has conducted a national search for a laboratory animal veterinarian to provide management, oversight, production support, genetic monitoring and disease surveillance of laboratory animals for the National Toxicology Program. Dr. Angela King-Herbert , currently Attending Veterinarian and Manager of Animal Biology in the Department of Regulatory Toxicology, RJ Reynolds Company, has accepted this position.

Staff Scientist—Toxicogenomics

The National Center for Toxicogenomics (NCT) of the National Institute of Environmental Health Sciences is conducting a national search for a Staff Scientist to lead a core facility to support a research program to direct the basic research applications of gene expression technologies within the NCT. The NCT is conducting an aggressive research program to apply genomic technology to toxicology and to facilitate the identification of biomarkers of specific adverse effects of exposure to environmental

agents including drugs, chemicals, and stressors. The activities of the Center will enable other investigators to probe the complexities of the mechanisms of normal genetic and metabolic pathways and to subsequently learn how diseases occur when these pathways malfunction. The position will be filled at the level of a Staff Scientist who will work in support of existing research programs in the Institute's Division of Intramural Research. The search committee, chaired by Dr. Elizabeth Murphy, Laboratory of Signal Transduction, is interviewing candidates.

Staff Scientist--Epidemiology

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

Staff Scientist—Bioethics

The Office of Clinical Research is conducting a national search for a bioethicist to be involved with health policy research on the effectiveness of federal and Institutional Review Board regulations in addressing clinical studies and clinical genetics issues. A search committee chaired by Dr. Ronald Mason, Laboratory of Pharmacology and Chemistry, is conducting interviews.

DIR RECRUITS

Dr. Joanne Promislow, Epidemiology Branch

Dr. Joanne Promislow recently joined the Epidemiology Branch at NIEHS as a tenure-track reproductive epidemiologist. Dr. Promislow was trained in physical chemistry (Ph.D. 1997, Stanford University) before becoming interested in epidemiology. Her epidemiology training was at San Diego State University and the University of North Carolina. Her research has made major contributions to two different areas: (1) the understanding of how dietary factors affect bone mineral density in the elderly residents of Rancho Bernardo, California and (2) nutritional risk factors for spontaneous abortion and preterm birth. She has also examined factors that influence bone loss during pregnancy.

At the NIEHS, Dr. Promislow is now focusing on infant nutrition. Because breast milk is the optimal source of infant nutrition and confers significant health benefits to the infant, and possibly the mother, the American Academy of Pediatrics and the World Health Organization both endorse exclusive breastfeeding for the first 6 months of life and continued breastfeeding for at least 12 months. In the United States, breast-feeding rates fall well short of these goals. Insufficient milk is the most common reason given for weaning. Dr. Promislow is interested in the physiologic determinants of milk production, which could provide valuable insights into breast-feeding practices. Human milk is also an ideal biological fluid for estimating body burdens of environmental chemicals in women and their infants, evaluating the determinants of exposure, and assessing the effect of these contaminants on the health of women and their infants. Dr. Promislow is interested in the elimination kinetics of chemicals from the mother during breast-feeding, a better understanding of which is essential to more effectively evaluate infant exposures and potential health effects. Menstrual cycle function, as a route by which environmental factors could affect women's health, is another topic of interest for.

Selected Publications

Promislow JHE, Makarushka CM, Gorman JR, Howards PP, Savitz DA, Hartmann KE. Recruitment for a Community-Based Study of Early Pregnancy: The Right from the Start Study. (in press, Paediatr Perinat Epidemiol).

Siega-Riz AM, Promislow JHE, Savitz DA, Thorp JM, Jr., McDonald T. Vitamin C intake and the risk of preterm delivery. Am J Obstet Gynecol 2003;189:519-25.

Promislow JHE, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Retinol intake and bone mineral density in the elderly: The Rancho Bernardo Study. J Bone Miner Res 2002;17:1349-58.

Promislow JHE, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Protein consumption and bone mineral density in the elderly: The Rancho Bernardo Study. Am J Epidemiol 2002;155:636-44.

Training and Mentoring

The Fellows Award for Research Excellence

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. The awards are funded by the Scientific Directors, the Office of Research on Women's Health, and the Office of Education. In 2003, 972 applications were received and 243 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 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 the FARE competition next year.

The NIEHS had 14 winners of FARE awards:

Winner	*Laboratory/Branch*	*Mentor*	*Abstract Title*
Bjoern Bauer	Laboratory of Pharmacology and Chemistry	David Miller	The nuclear xenobiotic receptor, PXR, upregulates p-glycoprotein at the blood-brain barrier
Michelle Carey	Laboratory of Pulmonary Pathobiology	Darryl Zeldin	Attenuated immune response and enhanced mortality following influenza virus infection in cyclooxygenase-2 null mice
Gloria David	Laboratory of Pulmonary Pathobiology	Stephanie London	NQO1 and GSTM1 polymorphisms and childhood asthma in a high ozone area: Mexico City
Bonnie Deroo	Laboratory of Reproductive and Developmental Toxicology	Kenneth Korach	Estrogen treatment reduces expression of thioredoxin interacting protein in the mouse uterus through an estrogen-receptor independent mechanism
Marcela Hermoso	Laboratory of Signal Transduction	John Cidlowski	Glucocorticoids and tumor necrosis factor α synergistically regulate Toll-Like Receptor 2 gene expression
Joseph Lundquist	Laboratory of Molecular Toxicology	Serena Dudek	Covalently Bound Extracellular Signal Regulated Kinase Components Revealed Through LTP-Inducing Stimuli

Jeanelle Martinez	Laboratory of Computational Biology and Risk Analysis	Christopher Portier	Up-regulation of EGR-1, a growth regulatory transcription factor by TCDD in human lung cells
Scott McCulloch	Laboratory of Molecular Genetics	Thomas Kunkel	Amino acid substitutions at conserved tyrosine 52 after fidelity and bypass efficiency of human DNA polymerase Eta \
Richard Morris	Biostatistics Branch	Norm Kaplan	Testing for association in nuclear families in the presence of genotyping errors using SNP haplotypes
Francesca Storici	Laboratory of Molecular Genetics	Michael Resnick	Chromosal site-specific double-strand breaks are efficiently targeted for repair by oligonucleotides
Paul Terry	Epidemiology Branch	Jack Taylor	Ancient African haplotypes simplify the study of genetic variation and disease
Daniel Tomso	Laboratory of Computational Biology and Risk Analysis	Doug Bell	Detection of Polymorphic p53 Binding Sites in the Human Genome
Mohamed Trebak	Laboratory of Signal Transduction	Jim Putney	Reciprocal regulation of receptor-activated TRPC3 channels by diacylglycerol and protein kinase C
Jeffrey Vargason	Laboratory of Structural Biology	Traci Hall	Crystal structure and binding specificity of an RNA silencing suppressor

DIR AWARDS AND HONORS

Dr. David Armstrong (Laboratory of Signal Transduction) was named a Guest Professor in the Department of Molecular Neurobiology at the University of Salzburg and will give a course on cell signaling in the nervous system.

Dr. Lutz Birnbaumer (Laboratory of Signal Transduction and Scientific Director) delivered the 2003 "Conferencia Orias" of the Biology Society of Cordoba in Cordoba, Argentina.

Dr. Gary Boorman (Laboratory of Experimental Pathology) will chair a scientific session on "Understanding and Diagnosing Disease Using Large-Scale Differential Gene Expression Technology" at the annual meeting of the Society of Toxicologic Pathology in Salt Lake City in June 2004.

Dr. Jan Drake (Chief, Laboratory of Molecular Genetics) was elected President of the International Genetics Federation for 2003-2008.

Dr. David Dunson (Biostatistics Branch) won the "Best Paper Award" from the American Academy of Fertility Care Professionals.

Dr. E. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) was elected to the Board of Directors, American Society for the Study of Reproduction (2002-2005) and the Executive Council, American Society of Andrology (2003-2006); appointed Associate Editor of Biology of Reproduction; and invited to be an Australian Research Centre Scholar, Australian Centre of Excellence in Biotechnology and Development, Monash Institute of Reproduction and Development, Monash University in 2004.

Dr. Ken Korach (Chief, Laboratory of Reproductive and Developmental Toxicology) was elected to the Editorial Board of the Journal of Molecular Endocrinology by the British Society of Endocrinology, presented the 2003 University Lecture for University of Texas Southwest Medical Center, and was selected as the 30th University of Maryland-Johns Hopkins Lecturer in Reproductive Biology.

Dr. Ronald Mason (Laboratory of Pharmacology and Chemistry) gave the Lawrence H. Piette Memorial Lecture, at the 44th Rocky Mountain Conference on Analytical Chemistry - Denver, CO entitled "In Vivo Lipid-derived Free Radical Formation by NADPH Oxidase in Acute Lung Injury Induced by Lipopolysaccharide - a Model for ARDS."

Dr. Bob Maronpot (Laboratory of Experimental Pathology) has been invited to present the 22nd annual Kuna Lecture at Rutgers University/University of Medicine and Dentistry of New Jersey in April 2004 and as the keynote speaker at the Dutch Society of Toxicology annual meeting in June 2004. He has also been invited to present a talk at the British Society of Toxicology annual meeting in Edinburgh, Scotland, in April 2004 and will chair a scientific session on "Hepatic Morphology and Pathophysiology" at the annual meeting of the Society of Toxicologic Pathology in Salt Lake City in June 2004.

Dr. Ron Melnick (National Toxicology Program) has been named to Who's Who in America.

Dr. Fred Miller gave the Kovacs Lecture at the Royal Society of Medicine, London, UK in March 2003 entitled "New Developments in Pathogenesis and Therapy of the Idiopathic Inflammatory Myopathies".

Dr. Christopher Portier (Chief, Laboratory of Computational Biology and Risk Analysis) was selected to give the Keynote Lecture, Conference on Mechanistic Modeling of Carcinogenesis, Japanese Biometrics Society and Radiation Effects Research Foundation, Kyoto, Japan, March 2003.

Dr. Lisa Rider (Office of Clinical Research) gave the Schlager Family Visiting Professor Lectureship in Juvenile Dermatomyositis at Children's Hospital, Boston, MA in April, 2003 entitled "Juvenile Idiopathic Inflammatory Myopathies: Lessons from the Children."

Dr. Dale Sandler (Epidemiology Branch) received the 2003 Leadership and Distinguished Service Award form the American College of Epidemiology

Dr. Steven Shears (Laboratory of Signal Transduction) was named keynote speaker at the second Japan/Korea conference on cellular signaling, held at Kyushu University, Fukuoka, Japan in June 2003 and appointed to the editorial board of the reviews journal *Essays in Biochemistry*.

Dr. Raymond Tennant (Director, National Center for Toxicogenomics) served as the Co-Chair of the Inaugural Gordon Conference on Toxicogenomics held at Bates College, Lewiston, Maine in June 2003 and was the Keynote Speaker at the NordTox Meeting in Bornholm, Denmark in June 2003.

Dr. Samuel Wilson (Deputy Director and Laboratory of Structural Biology) was the Keynote Speaker at the American Chemistry Council-LRI First Annual Science Meeting and at the Gordon Research Conference on Toxicogenomics; served as a member of the Editorial Board for the Annual Reviews of Medicine and as an Associate Editor for DNA Repair; and served on the Program Committee for the 9th International Conference on Environmental Mutagens, San Francisco, CA; as the Co-Chair of the Biannual US-EU DNA Repair Meeting; as Director of the Radiation Effects Research Foundation (A Cooperative Japan-United States Research Organization managed in the US by the NAS); and as Co-chair of "Advances in Toxicogenomics: NIEHS National Center for Toxicogenomics," a Symposium at the Society of Toxicology Annual Meeting in March 2003.

Dr. Jerrel Yakel (Laboratory of Signal Transduction) has been named to the Editorial Board of the Journal of Molecular Neuroscience.

Dr. Darryl Zeldin (Laboratory of Pulmonary Pathobiology) was named to the Editorial Board of the journal Prostaglandins and Other Lipid Mediators

National Toxicology Program
Update February 2004

Toxicology in the 21st Century: The Role of the National Toxicology Program

The last decade of the 20th century and the turn of the 21st century have produced dramatic technological advances in molecular biology and computer science. In an effort to determine how best to incorporate these new scientific technologies into its research and testing strategies and to broaden scientific knowledge linking mechanism and disease, the National Toxicology Program (NTP) has developed a vision (see attached write-up).

> *The NTP Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.*

The NTP will develop a roadmap or framework to guide the program in implementing its vision. The goal of the roadmap is to position the NTP strategically at the forefront of toxicology in providing scientific data and its interpretation for public health decision-making. In developing the roadmap and milestones toward achieving the vision, the NTP seeks input from all interested stakeholders on issues raised by the following questions:

- *What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?*
- *How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact on the evaluation of public health hazards?*
- *How can we best structure the NTP to provide this information and to ensure its optimal utilization in the protection of public health?*
- *What resources will be needed to realize this vision and how long will it take?*

Vision Activities

On Thursday, January 29, 2004, the NTP held a public meeting to receive comment on the vision and input for a roadmap. This meeting was held at the Lister Hill Center Auditorium (Building 38A), National Library of Medicine, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD, 20892. The meeting was chaired by Dr. Hillary Carpenter, Minnesota Department of Health and member of the NTP Board of Scientific Counselors, and began with an introductory presentation on the NTP vision and roadmap activities by Dr. Christopher Portier, Associate Director of the NTP. These activities include, receiving reports from three groups: an internal NIEHS Working Group, the NTP Executive Committee Working Group, and the NTP Board of Scientific Counselors Working Group, that are independently developing input on the roadmap, holding a retreat this summer, and providing opportunities for additional input by the public and NTP advisory groups. The NTP plans to hold a retreat this summer and rollout the roadmap for the vision in the fall.

A panel composed of the NTP Board of Scientific Counselors Working Group and the chairs of the NIEHS and NTP Executive Committee Working Groups received the public comments. Eight speakers presented oral public comments. Information about this meeting, including copies of any comments received, is posted on the NTP web site at http://ntp-server.nih.gov.

Report on Carcinogens Public Meeting

The NTP held a public meeting on January 27-28, 2004, to receive public comment on the current process for reviewing nominations for listing in or delisting from the Report on Carcinogens (RoC) and on the current listing criteria used for evaluating the nominations. The purpose of this meeting was to obtain input and provide all interested parties the opportunity to express their views and/or to comment on the views expressed by others. All interested parties were invited to participate. A panel that included NTP staff, representatives of the NTP Board of Scientific Counselors and the NTP Executive Committee received the public comments and participate in the discussion.

The meeting was held at the Lister Hill Center Auditorium (Bldg. 38A), National Library of Medicine, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, 20892. Six speakers presented oral comments. Information about this meeting, including copies of public comments received, is posted on the NTP web site at http://ntp-server.niehs.nih.gov.

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee will meet February 17-18, 2004, in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC. The meeting will begin at 8:30 a.m. and is open to the public. The primary agenda topic is the peer review of seven draft NTP Technical Reports, as listed below.

TR#	Chemical
494	Anthraquinone*
520	3,3',4,4',5-Polychlorinated biphenyl 26 (PCB 126)
521	2,3,7,8, Tetrachloro-*p*-dibenzene dioxin (TCDD)
525	2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
526	Dioxin mixture: (PCB 126, TCDD and PeCDF)
527	Malachite Green & Leucomalachite Green
528	1,2,3-Trichloropropane, 2,2-Bis(bromomethyl)-*p*-1,3-propanediol and Nitromethane**

* The Subcommittee reviewed the draft NTP Technical Report on Anthraquinone in May 1999. Subsequent to that peer review, the tested anthraquinone was found to contain a 0.1% contaminant. As a result, additional mutagenicity and metabolism studies were conducted and the findings from those studies are included in the revised draft report. The Subcommittee will evaluate the results from the follow-up studies, use that information to re-examine the carcinogenicity findings from the 2-year studies and make a recommendation on the carcinogenicity of anthraquinone.

**Studies of these compounds are being done in two species of fish (Medaka and Guppy).

The draft NTP Technical Reports will be available for public review, free of charge, through ehpOnline (http://ehp.niehs.nih.gov/).

The public is invited to submit written comments on any report and/or to attend the meeting and give oral comments. Additional details about the meeting, as available, are posted on the NTP web site (http://ntp-server.niehs.nih.gov *see* What's New?).

Scientific Advisory Committee on Alternative Toxicological Methods

The next meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will be held on March 10-11, 2004, at the Hyatt Regency Hotel, One Bethesda Metro Center, Bethesda, Maryland 20814. The meeting begins each day at 8:30 a.m. until adjournment and is open to the public.

Topics included on the preliminary agenda include updates on activities of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on Alternative Methods (ICCVAM), nominations of alternative toxicological methods, a workshop on toxicogenomics, validation of genetically modified mouse models, and performance standards for *in vitro* corrosivity test methods. The agenda and other details of the meeting, as available, will be announced in the Federal Register and posted on the NTP web site (http//:ntp-server@niehs.nih.gov *select* What's New).

The SACATM is a federally chartered advisory committee that provides input to the NIEHS Director, NICEATM and ICCVAM on the statutorily mandated duties of ICCVAM and NICEATM activities. The committee is comprised of 15 members and was established in January 2002.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Updated ICCVAM Submission Guidelines

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces the availability of the publication, "ICCVAM Guidelines for Nomination and Submission of New, Revised, and Alternative Test Methods," September 2003, NIH Publication No. 03-4508. The guidelines are an updated version of guidelines published by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in 1999. The ICCVAM guidelines provide information to sponsors and nominators of new test methods on the framework for organizing the information and the mechanism by which ICCVAM evaluates the validation status of new, revised and/or alternative test methods proposed for regulatory testing use. This framework can also be used to organize information in support of test methods nominated for further evaluation, including proposals for validation studies. The updated ICCVAM guidelines are available electronically (PDF and HTML) on the NICEATM/ICCVAM web site at http:// iccvam.niehs.nih.gov/methods/udp.htm and a limited number of printed guidelines are available from the NICEATM (see contact information).

The ICCVAM established in 1997 coordinates the interagency technical review of new, revised, and alternative test methods of interagency interest, and coordinates cross-agency issues relating to the validation, acceptance, and national/international harmonization of toxicological testing methods. ICCVAM is as a permanent interagency committee of the NIEHS under the NICEATM (ICCVAM Authorization Act of 2000, Public Law 106-545). The Committee is composed of representatives from fifteen federal regulatory and research agencies that use or generate toxicological information. ICCVAM promotes the scientific validation and regulatory acceptance of toxicological test methods that will improve agencies' ability to accurately assess the safety or hazards of chemicals and various types of products, while refining (less pain and distress), reducing, and replacing animal use wherever possible.

NICEATM administers the ICCVAM and provides scientific and operational support for ICCVAM and ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM can be found at the following web site: http://iccvam.niehs.nih.gov

Responses from Federal Agencies to ICCVAM Test Recommendations

The ICCVAM Authorization Act of 2000 requires appropriate federal agencies to review test recommendations from ICCVAM and notify the ICCVAM in writing of their findings, including the identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted. The agencies were sent ICCVAM test recommendations for l) *in vitro* methods for assessing acute systemic toxicity and 2) the revised Up-and-Down Procedure (UDP) for determining acute toxicity. Their responses and other current information relevant to these test recommendations are available electronically (PDF and HTML) on the NICEATM/ICCVAM web site (http://iccvam.niehs.nih.gov).

NTP Satellite Symposium on Hepatic Pathology

The NTP will sponsor a satellite symposium on Saturday, June 12, 2004, before the start of the Society of Toxicologic Pathology Annual Meeting. The annual meeting is scheduled for June 13-17, 2004. The format for the satellite symposium will the same as the one held in Savannah in 2003.

Cases will be available on a web site prior to the meeting and audience response units (for audience voting and instant display of the results) will be provided during the satellite symposium. The emphasis for the cases will be hepatic lesions although non-hepatic lesions will also be included.

Persons interested in attending can obtain information on-line at www.toxpath.org or send a message to stp@toxpath.org

NATIONAL TOXICOLOGY PROGRAM

VISION

Headquartered at the National Institute of Environmental Health Sciences • NIH • DHHS

Toxicology in the 21st Century: The Role of the National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 to coordinate toxicological testing programs within the Department of Health and Human Services, develop and validate improved testing methods, develop approaches and generate data to strengthen scientific knowledge about potentially hazardous substances and communicate with stakeholders. In its 25 years of existence, NTP has become a world leader in providing scientific information that improves our nation's ability to evaluate potential human health effects from chemical and physical exposures. The NTP has maintained a number of complex, interrelated research and testing programs that provide unique and critical information needed by health regulatory and research agencies to protect public health.

The last decade of the 20th century and the turn of the 21st century have produced dramatic technological advances in molecular biology and computer science. The NTP is again ready to evaluate its key activities and in a focused and concerted effort determine how best to incorporate these new scientific technologies into its research and testing strategies and broaden scientific knowledge on the linkage between mechanism and disease. The NTP Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The stimulus for the NTP Vision is to develop a framework that will promote the further development/advancement of toxicology and refine its traditional role as a predominantly observational science. Over the next year, the NTP intends to develop a roadmap for implementation of its vision that will strategically position the program at the forefront for providing scientific data and the interpretation of those data for public health decision-making.

The NTP invites all interested stakeholders to read and comment on its vision and to provide input to a roadmap for its implementation. In developing its roadmap and milestones for tasks and changes to achieve the vision, the NTP seeks input on the issues raised by the following questions:

1. What scientific information should the NTP be producing and what technical capabilities should the NTP have by 2008? By 2013?
2. How do you envision that the refinement/replacement of classical toxicological studies with mechanism-based assays will impact on the evaluation of public health hazards?
3. How can we best structure the NTP to provide this information and to ensure its optimal utilization in the protection of public health?
4. What resources will be needed to realize this vision and how long will it take?

ADDRESS P.O.Box 12233, Maildrop A3-01, Research Triangle Park, NC 27709-2233 **WEB SITE** http://ntp-server.niehs.nih.gov/
NTP LIAISON & SCIENTIFIC REVIEW OFFICE 919-541-0530 **E-MAIL** liaison@starbase.niehs.nih.gov

January 12, 2004

The NTP Vision for the 21st Century:

To move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations

Since its inception in 1978, the NTP has been a leader in toxicological testing and research within the United States and contributed significantly to the scientific knowledge upon which public health decision are based. In 1995, the National Toxicology Program (NTP) initiated a program to use mechanism-based toxicology to develop, evaluate and validate better toxicological test methods. This effort has led to major changes in toxicology at the national and international level. In recent years, mechanism-based toxicology has led to some changes in the scientific basis for public-health decisions; however, it has not dramatically reduced the need for the classical tests developed in the 1970s and 80s that were the basis for many decisions related to product safety, evaluation of environmental and occupational hazards and prioritization of chemicals for further testing. It is now time to focus on changing the scientific basis for decision-making and work toward improving or replacing older classical tests with faster, mechanism-based assays.

Two activities must occur simultaneously if this change is to occur. One, we need to aggressively incorporate new laboratory methods into the NTP testing program and insure that the data produced meet the high quality standards of the NTP. Two, we need to develop strategies for the integration of new types of scientific data into the decision-making process. As a leader in toxicology, the NTP is ready to seize this challenge for improving the scientific basis for public health decision-making.

A core element of the NTP is the design, conduct, evaluation and communication of toxicological tests in a broad number of areas of concern ranging from neurotoxicity to carcinogenesis. Through the testing program, the NTP has been a leader in developing and implementing experimental designs that not only address data gaps for the agent being tested, but contribute to our fundamental understanding of toxicity in the broader context. This strength of the testing program needs to be further developed to insure that every evaluation done contributes to knowledge-based safety evaluations that use the broadest possible range of scientific evidence in reaching a decision. As new methods are developed and gain greater acceptance in developing public health decisions, our dependence on the classical testing paradigms should diminish. During this time of transition, scientific quality and clarity must be preserved to insure that decisions based solely upon new methods do not endanger the health of the public or introduce greater scientific uncertainty than the approaches used in the last century.

Only through a concerted effort focused on the linkage between mechanism and disease will toxicology achieve sufficient predictability to refine or replace disease-specific testing models with mechanism-based assays that are more informative, faster and closely linked to disease incidence and progression. This vision should enable the program to continue its leadership in toxicology and provide the scientific data and knowledge necessary for making appropriate decisions that protect (and improve) public health and the environment.

NTP Roadmap

Over the next year, the NTP intends to develop a roadmap for implementing this vision. The NTP will seek input to this roadmap from numerous groups, including its federal partners, its advisory committees and the public. In developing the framework for implementing the NTP Vision for the 21st Century, the NTP will examine its current activities, examine opportunities for modifying those activities to include recent scientific advances, identify specific activities that need to be accomplished to implement the vision and develop a framework targeted towards achieving the intent of this vision and including the necessary components for implementation, management and communication of changes in NTP activities. In developing this framework, the NTP will 1) identify the tools and technical capabilities needed to utilize new methods, models and approaches within the program; 2) develop strategies for the generation, evaluation and integration of new types of scientific data into the decision-making process; and 3) identify the resources needed to achieve both the short-term and long-term goals for the vision. The NTP will examine each mechanism through which it currently operates and evaluate its functionality toward addressing the vision. Some of the changes and directions in the roadmap will be specific to the NTP, its operations and its personnel, while others will apply to the broader field of toxicology as it is currently practiced. It is envisioned that the acceptance and implementation of this vision in addressing public health priorities will result in better science and ultimately better decisions.

NTP Mission and Goals

The mission of the NTP is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology. The elements of this mission are to provide toxicological evaluations on substances of public health concern, develop and validate improved (sensitive, specific, rapid) testing methods, develop approaches and generate data to strengthen the science base for risk assessment and to communicate with stakeholders (government, public, industry, academia, environmental community) involved in the application and use of scientific data in making decisions about the safety of agents routinely encountered by humans. The overall goal of the NTP, encompassed by these mission elements, is to provide the best science possible for preventing disease due to human exposures. Unfortunately, the changing nature of biological science is such that this goal can never really be attained; however, it is a goal that requires constant diligence to insure that the tools of modern biological science are used appropriately and efficiently.

In its current manifestation, the NTP accomplishes its mission for toxicological testing through several mechanisms:

- Contract laboratories that conduct studies designed by NTP staff and contracts administered by the National Institute of Environmental Health Sciences (NIEHS)
- Collaboration and cooperation with multiple federal agencies, including toxicological research and testing at the National Center for Toxicological Research (NCTR) of the Food and Drug Administration
- Human exposure and toxicity research at the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention
- Biological, toxicological, clinical and epidemiological research in the intramural laboratories of the Division of Intramural Research (DIR) at the NIEHS

- Research grants, contracts and interagency agreements supported through the NIEHS Division of Extramural Research and Training (DERT)
- NTP Centers, including the Report on Carcinogens, the Interagency Center for the Evaluation of Alternative Toxicological Methods, the Center for the Evaluation of Risks to Human Reproduction, and the Phototoxicology Center at the NCTR, and the NIEHS National Center for Toxicogenomics
- Collaboration and support of research with other national and international toxicology and public health agencies
- Review and evaluation of data gaps in our understanding of environmentally induced diseases through the NTP Office of Nominations
- Focused conferences and symposia, and communications to a broad spectrum of stakeholders through public meetings, electronic media and print media managed by the NTP Liaison and Scientific Review Office

FEATURED ACTIVITIES of DERT
February 2004

MEETINGS

Division of Extramural Research and Training Fourth Annual Scientific Retreat
December 4-5, 2003
Southern Pines, North Carolina

The NIEHS Division of Extramural Research and Training held its fourth annual Scientific Retreat December 4th and 5th, 2003 in Southern Pines, North Carolina. Unlike previous Scientific Retreats, this meeting revolved entirely around a single topic: Systems Biology. While the definition of Systems Biology is a matter of some conjecture, the NIEHS has adopted a broadly stated definition that it represents the integration of multiple data streams into a unified model allowing for quantitative predictions of the response of system of interest to various perturbations. The retreat was divided into three sessions ultimately intended to address the question "How can the emerging science of Systems Biology be applied in the Environmental Health Sciences?"

Session 1: Techniques in the Systems Biology Armamentarium
The opening session was intended to serve as an overview of the 'nuts and bolts' tools that are available to researchers to both acquire and analyze data. The discussions included numerous potential data streams but highlighted proteomics and metabolomics as areas ripe for continued development. A common thread from these discussions was that while the research tools are evolving at a rapid pace they are significantly limited in several regards, in particular in their temporal and spatial resolution, quantitative ability, and throughput and automation.

A second topic of discussion in this session was mathematical approaches for analyzing the copious amounts of data resulting from the use of high throughput 'omics' data with the underlying message that the integration and analysis of data will require diverse expertise in multiple mathematical areas including statistics, applied mathematics and engineering.

It became evident from the discussions in Session 1 that Systems Biology is inherently team science and that one of the major barriers to adapting this approach on large scales is a lack of scientists trained in its diverse areas – at least to the point of communicating effectively.

Session 2: Systems Biology Applications in Disease
This session revealed how the tools discussed in session 1 can be applied in different ways to increase our understanding of disease processes and to aid in diagnosis and treatment. With today's technology it is possible to acquire sufficient data to allow the generation of quantitative models of pathways that are known to play a role in a disease process and to use *in silico* techniques to predict the impact of various treatments, perturbations or individual susceptibilities. It is also possible to identify individual markers, or profiles of multiple markers, that can correlate with disease severity and prognosis. However, in both cases it is clear that improvements in technology and training will lead to increases in power and reductions in cost. There is a particular need for the refinement of statistical tools and development of best practices for developing and assessing the appropriateness of *in silico* models.

Session 3: Applications of Systems Biology to Environmental Health
The intent of this session was to highlight how systems biology could be applied to public health issues relevant to the mission of the NIEHS. The discussions emphasized the use of systems biology to predict the risk of developing disease from a given exposure. One paradigm that was presented involved integrating work done at multiple experimental levels, from prokaryotes and lower eukaryotes through patient populations to aid in understanding environmental induced disease. As with the previous session the opinion was expressed that current technologies allow for limited application of these types of studies;

however, there remains a need for refinement. One unique barrier in the application to this arena is encouraging researchers to extend models beyond use as a research tool and into a public health tool.

Special topic discussions
In addition to the three scientific sessions the retreat also included two presentations highlighting special topics not commonly addressed in discussions of systems biology. The first of these highlighted the Ethical, Legal and Social Issues of applying 'omics' to public health issues, and revealed the importance of considering these issues when designing potential public health uses of these tools. The second special topic discussion focused on the development of micro- and nano-biosensors in risk evaluation and the potential for adapting these techniques to systems analyses. These were highly informative sessions which illuminated potential future issues in systems biology.

Conclusions
There was considerable enthusiasm for the involvement of NIEHS in supporting the development of systems biology as a new research paradigm. This approach is quite distinct from the traditional reductionist approach to scientific investigation and as such potential advantages, most notably through the ability to rapidly make quantitative predictions of system responses (i.e. hypothesis generation). While the current state of the art approaches are sufficient for modeling well defined pathways, there is a need for continued refinement of both acquisition and analysis tools that will allow for improved predictions of dynamic systems and integrated models of whole organisms (ultimately humans). Another important aspect of this is the need to support the development and training of interdisciplinary teams of scientists with enough understanding of each others areas of specialty to enable them to work together to design a robust approach to systems investigation. Finally, as one attendee noted "we do not need to be concerned with doing systems biology but rather in tackling problems" – while it is clear that systems biology offers great power it is the potential application to the environmental health sciences which interests the NIEHS.

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Bi-Annual Meeting of the NIEHS Toxicogenomics Research Consortium
December 7-8, 2003
Fred Hutchinson Cancer Research Center
Seattle, Washington

Introduction
The National Institutes of Environmental Health sponsored the Bi-Annual Meeting of the NIEHS Toxicogenomics Research Consortium, held at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington (http://www.niehs.nih.gov/dert/trc/news.htm). Six academic research centers comprise the TRC. They include Duke University, Massachusetts Institute of Technology (MIT), Oregon Health and Sciences University (OSHU), Fred Hutchinson Cancer Research Center/University of Washington (FHCRC/UW), University of North Carolina at Chapel Hill (UNC), and the NIEHS Microarray Group. Research conducted under the TRC serves to expand the knowledge of biological responses to environmental stress through the application of gene expression technologies to toxicology; to develop standards and practices for cross-platform gene expression data validation and interpretation; and contribute to the development of a robust relational database for gene expression profile signature data.

Members of the TRC convene for a scientific meeting twice a year . This meeting was hosted by the FHCRC/UW and served to provide a forum to share recent scientific findings and to foster and strengthen research collaborations. The primary objective of this two-day meeting was to highlight the independent research projects being conducted within the TRC. Platform and poster presentations from individual researchers focused on the application of gene expression technologies to advance science in four research areas: Disease Mechanisms, Susceptibility, Comparative Genomics, and Predictive Toxicology. A series of keynote speakers from outside the consortium provided global perspective on the emerging

technologies of proteomics (David Goodlet, Institute for Systems Biology), metabolomics (Craig Thomas, Lilly) and systems biology (Trey Ideker, University of San Diego) and the integration of these disciplines within toxicogenomics. A panel discussion followed to foster discussions of future research directions and initiatives needed to advance the field.

Following the scientific sessions, Dr. Weis chaired a meeting of the Cooperative Research Program of the TRC to discuss the current findings of the gene expression standardization experiments and establish timelines for continued efforts and publications. A TRC Steering Committee meeting followed to discuss pertinent scientific and administration issues. The Steering Committee elected Bill Kaufmann (UNC) as Chair for 2004. They also discussed the design and conduct of standardization experiment three which will focus on comparative toxicological responses to acetaminophen.

The Meeting Organizing Committee included Helmut Zarbl (FHCRC), Brenda Weis and Mike Humble (NIEHS DERT), Bill Kaufmann (UNC), Dave Eaton and Terry Kavanagh (UW), Jonathan Freedman (Duke), Leona Samson (MIT), Peter Spencer (OHSU) and Rick Paules, NIEHS Microarray Group).

Meeting Highlights

Four scientific research sessions highlighted key advances made by TRC investigators in four focal areas: disease mechanisms, susceptibility, comparative toxicology and predictive toxicology.

Presentations in the *Disease Mechanism Session* addressed the application of gene expression profiling technologies to define the mechanistic underpinnings of environmentally related diseases. Key findings were reported in the areas of genetic and environmental components of disease, elucidation of disease pathways and networks and development of disease models.

Presentations in the *Susceptibility Session* addressed individual and population susceptibilities to exposure and disease as derived from genetic and environmental analysis and integration. Key areas addressed included the identification of gene targets and factors mediating susceptibility, and gender, strain and species susceptibilities.

In the *Comparative Genomics Session,* presentations focused on comparative and integrated responses of organisms to environmental stimuli. Specific findings were reported on cross-species comparisons of biological responses to environmental factors at the gene, transcription, and protein level and their integration in model organisms; conserved biological components, pathways and responses to environmental factors; and computational tools to support comparative toxicogenomics.

In the *Predictive Toxicology Session*, presentations focused on the development and application of gene expression and proteomics technologies in predictive toxicology. Specific focus will be on the development of model systems and research tools and linkage of predictive responses to disease phenotype.

Keynote presentations served to provide global perspective on current topics in toxicogenomics and to stimulate discussion about the scientific direction for future initiatives in this field. The research findings made by the TRC will substantially contribute to advancing the development of new approaches for the detection and prevention of environmental diseases.

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Haplotypes, SNPs, and Disease
December 12, 2003
Vontz Center for Molecular Studies, University of Cincinnati Medical Center, Cincinnati, Ohio

This mini-symposium, organized by Drs. Joan Packenham, Peter Stambrook, and Elizabeth Maull, was hosted by the University of Cincinnati Comparative Mouse Center. The focus of the Comparative Mouse Consortium is to investigate the environmental relevance of single nucleotide polymorphisms (SNPs) in DNA repair and cell cycle control genes, using either in vitro or in vivo methods. This mini-symposium, attended by 70 participants, including a dozen nationally and internationally recognized speakers, was developed to highlight recent developments in understanding and modeling human genetic variation and its impact on human health and disease. Three sessions focused on the following general areas: the impact of SNPs on cardiovascular disease and treatments; technology developments in the areas of microarrays for analyses of transcriptomes, matrix attachment regions, SNP and haplotype discovery; and the use of yeast assays to investigate double-strand break repair, regulation of eukaryotic cell cycle checkpoints, and master regulatory gene, p53.

Meeting Highlights
Three speakers focused on SNPs that either impact aspects of cardiovascular disease or its successful treatments. A SNP resulting in an Arg389 variant in the beta1-adrenergic receptor is a risk factor for heart failure and predicts efficacy of pharmacological therapy with beta1-AR agonists. Polymorphic variants in phospholamban (PLN) affects heart contractility, cardiac hypertrophy, and early death in mice. Although a truncated mutant of PLN is strongly correlated with fibrosis, heart failure and early mortality in homozygous humans, the PLN null mouse is asymptomatic, suggesting that the level of PLN in humans must be precisely controlled for optimal function, while in mice, too little PLN is well-tolerated. Mechanisms of sodium homeostasis, important in hypertension, includes the sodium transporter, epithelial sodium channel (ENaC). One variant, T594M, is hyperfunctional when homeostasis is stressed and, therefore, may have a selective advantage for populations that survived in the desert.

Technological presentations spanned SNP discovery and haplotyping, the use of various types of microarrays, the development of chromosomal cassettes to enable rapid generation of genetically altered cells, and rapid screening of altered cells for genome maintenance pathways. Microarray analysis of the transcriptome of specific, cancer-prone mice demonstrated that the phenotype (phenome) correlated with differential expression of several tumor-related factors and was proposed as a surrogate for genome-wide SNP analysis. Transcriptome analysis was also proposed as a powerful approach for identifying master regulatory genes.

Yeast systems were presented as tools for the study of eukaryotic cell cycle checkpoints and transcriptional master regulator genes. Chk1, a highly conserved protein kinase, is involved in cell cycle checkpoint pathways by monitoring DNA replication, coordination of S-phase completion with mitosis, and promoting restart of stalled replication forks. Human Chk1 SNPs are investigated in yeast prior to incorporation into mouse models to verify functionality. Yeast were also used to investigate p53 transcriptional regulation networks using a sensitive, flexible reporter gene system that relies on an ADE2 reporter construct driven by p53 response elements and a yeast core promoter. Data from these experiments suggest that DNA sequence variation in response elements of p53 garget genes could have significant effects on gene expression and possibly cellular phenotype. Mutations and polymorphic sites in coding and non-coding regions encoding or regulating p53 network components could lead to subtle changes in network connectivity, possibly resulting in phenotypic effects in humans.

Dr. Joanna Groden, member of the NCI Mouse Models of Human Cancers Consortium, provided an after-dinner talk. Groden described two mouse model "success stories," the mouse model for pancreatic duct cancer that recapitulates many characteristics of the human disease, including disease phenotype, and the mouse model for the human autosomal recessive disorder Bloom syndrome. The development of these two models provide investigators tools to investigate the molecular basis of these two diseases.

Pancreatic duct cancer alone afflicts nearly 30,000 Americans annually and is the 5th leading cause of cancer death.

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U.S.-Vietnam Scientific Workshop on Dioxin Screening Bioassays and Bio/Chemical Remediation Methodologies
November 2-5, 2003
Hanoi, Vietnam

Dr. Bill Suk, in collaboration with Dr. Dang Thi Cam Ha, Head, Environmental Biotechnology Lab, Institute of Biotechnology, National Center for Science and Technology, Vietnam, and Dr. Michael Denison, Professor, Department of Environmental Toxicology, University of California at Davis, organized the "U.S.-Vietnam Scientific Workshop on Dioxin Screening Bioassays and Bio/Chemical Remediation Methodologies" November 2-5 in Hanoi, Vietnam. The Workshop's objectives were to assess and apply currently available bioanalytical methods for the detection and relative quantitation of dioxins and related chemicals; to assess and apply remediation strategies and methodologies to degrade/detoxify dioxins and related chemicals; and to establish and enhance real partnerships and research collaborations between scientists in the U.S. and Vietnam in the application of these technologies. The goals of the Workshop were met and, in some instances, exceeded.

The meeting brought together primarily U.S. and Vietnamese research scientists as well as industry representatives to discuss current research in the three areas laid out in the meeting's objective and goals and to develop strategies for addressing specific environmental monitoring and remediation issues. This Workshop is directly related to scientific and health issues contained within the Memorandum of Understanding (MOU) between Vietnam and the United States that was signed in March 2002. The MOU focused on two major areas of research: (1) research on health outcomes from exposure to dioxin; and (2) research on the environmental and ecological effects of dioxin and Agent Orange. This Workshop is directly related to the second major area of research coming out of the March Hanoi 2002 meeting and the MOU.

The Workshop brought together over 70 investigators from government, academia and industry primarily from both countries, with 30 participating from the U.S. The Workshop was sponsored by the NIEHS Superfund Basic Research Program, the National Center for Natural Science and Technology in Vietnam, the U.S. Environmental Protection Agency, the University of California at Davis, the Department of Civil and Environmental Engineering and the Office of International Studies and Programs at Michigan State University, and the Ford Foundation.

The Workshop established and/or enhanced collaborations and partnerships between U.S. and Vietnamese scientists. A meeting report, in both languages, is being written, and a peer-review commentary is to be published providing a research, basic and applied, framework to be set out and agreed upon by both parties. The NIEHS will continue to look for opportunities for collaboration and U.S. technical assistance as an outcome of this meeting.

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2003 Superfund Basic Research Program (SBRP) Annual Meeting
Integrating Perspectives: Interdisciplinary Research and Outreach within the NIEHS SBRP
November 9-12, 2003
Dartmouth College, Hanover, New Hampshire

The Superfund Basic Research Program (SBRP) supports an interdisciplinary approach towards research, application, administration, and outreach strategies. This approach advances our understanding of the

human and ecological risks from hazardous substances and the development of new environmental technologies for the cleanup of Superfund sites.

Hosted by Dartmouth College, the 2003 SBRP annual meeting's theme focused on integrating the perspectives of the diverse disciplines involved in assessing environmental health risks and means for remediation and prevention. Through plenary sessions, symposia, and workshops, invited speakers emphasized current scientific findings and practical applications of SBRP outcomes – which evolve from basic laboratory research and provide a base of information that support the policy and health decisions made at hazardous waste sites. In addition, representatives from the Environmental Protection Agency enthusiastically spoke about opportunities for outreach collaboration and community involvement as well as integrating scientific knowledge with risk assessment and risk management.

Dr. William Suk, Director of the SBRP, welcomed the more than 200 investigators, students, staff, and government representatives participants in the two and a half day conference. Following opening remarks from Dr. Dennis Lang, Deputy Director of the NIEHS Division of Extramural Research and Training, plenary session presentations highlighted several major themes including:

- Developing and applying biomarkers, GIS, and molecular epidemiology approaches to environmental health sciences;
- Improving and applying new biological, chemical, and engineering based approaches to remediation of toxic waste sites; and
- Discussing children's environmental health risks and exposures and chemical and biological threats to homeland security.

Dr. William Glaze, Department of Environmental and Biomolecular Systems, Oregon Health & Science University School of Science & Engineering, who also serves as the Chair of the EPA Science Advisory Board, gave the Keynote Address. In his presentation he discussed his vision for an integrative study of human and environmental health. He lauded the SBRP for its efforts to move beyond public health by incorporating quality of environment in its environmental health studies. He also highlighted the need for more social sciences to complement the biomedical and environmental studies.

In addition to the plenary sessions, the scientific symposia and workshops allowed discussion of other principle messages related to integrating perspectives. These included:

- Discussing recent findings in xenobiotic metabolism, comparative toxicogenomics, and mechanisms of arsenic-induced disease;
- Effectively communicating and translating science to the appropriate audience; and
- Sharing and integrating genomic and proteomic data.

At each SBRP annual meeting, the Program encourages graduate and post-doctoral students to share their research during the Poster Session. Of the nearly 50 posters were presented, the 2003 Student Poster Award recipients, for outstanding student research were:

- Ms. Denise Hill of Texas A&M University for her poster, "Variable Susceptibility to In Utero Arsenic Exposure in Folate Transport Defective Mice."
- Ms. Melinda Wiles of Texas A&M University for her poster, "Matrix-immobilized Organoclay for the Removal of PAHS and Pentachlorophenol from Groundwater."

In addition to the Student Poster awards, the SBRP recognizes an outstanding graduate student or post-doctoral researcher who studies metals and best demonstrates the qualities of scientific excellence to honor and acknowledge the life and scientific accomplishments of Dr. Wetterhahn. The Karen E. Wetterhahn Memorial Graduate Student Award was presented on Tuesday afternoon to Monica Mendez of the University of Arizona. As the sixth recipient of this award, Ms. Mendez briefly spoke about her research, which focused on the cleanup of toxic metals from mine tailings.

This year's presentation took on a special meaning as Dr. Wetterhahn was the founding Program Director of Dartmouth College's SBRP. During the award ceremony, SBRP staff, as well as James Wright, President of Dartmouth College, honored Dr. Wetterhahn's commitment and contributions to science and her efforts to encourage women to pursue careers in the sciences, including mathematics and engineering.

The SBRP annual meeting also affords those involved with the Program the opportunity to meet in small sessions. Each day, Outreach Core and Administrator staff from the SBRP university programs met in their own afternoon meetings to review information relevant to the efficiency, improvement, and advancement of their respective programs.

The Outreach breakout sessions covered a variety of topics of interest. Ms. Anderson of the NIEHS opened the session by providing the audience with a background on the NIEHS and SBRP commitment to serving the community and the importance of expanding SBRP's capacity for communicating science to diverse audiences. Other outreach session topics included:

- SBRP staff's internal and external communication initiatives;
- Working with the EPA on opportunities for collaboration;
- Involving the community in outreach activities;
- Guiding scientists to overcome barriers related to outreach; and
- Conducting an interactive workshop on evaluation.

In concurrent sessions, Administrators met to review details and updates regarding grant proposals and renewal submissions. Several key items such as fiscal administration issues, the SBRP communications initiative, the organization of a program project application, and grant management were addressed.

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Emerging Scientific Issues for Superfund
October 8-10, 2003The International House, at University of California at Berkeley
Berkeley, California

The NIEHS Superfund Quad-University/EPA Region 9 Conference entitled "Emerging Scientific Issues for Superfund" took place on October 8-10, on the campus of the University of California, Berkeley. This meeting was built around the concept of providing an interchange of ideas among investigators from the Four Superfund Basic Research Programs that reside in Region 9 with EPA Region 9 Superfund staff. The goal of the meeting was to address emerging Superfund issues and discuss how SBRP technologies could be brought to bear on these issues. This was the second formal conference organized by SBRP investigators in partnership with EPA Region 9.

There were 100 registrants, including many faculty and students from the quad-universities as well as from the U.S. EPA Region 9 office; the EPA National Exposure Research Laboratory in Las Vegas, Nevada; the EPA Risk Management Research Laboratories in Ada, Oklahoma and Cincinnati, Ohio; and the EPA Headquarters in Washington D.C. The conference opened with welcoming and overview remarks from Dr. Daniel P.Y. Chang, Chair of the Organizing Committee (University of California, Davis) and Mr. Larry Reed, U.S. EPA. Dr. Samuel H. Wilson, Deputy Director of NIEHS and Dr. William H. Farland, Acting Deputy Assistant Director of the U.S. EPA Office of Research and Development provided their perspectives on emerging issues as well as describe their agency's framework for addressing these challenges.

The conference consisted of three sessions, each with overview speakers and experts from both the academic and regulatory communities. The sessions were entitled "Emerging Contaminants – New Threats", "Emerging Issues in Transport & Detection" and "Emerging Issues in Remediation & Treatment." In addition, a workshop was organized to foster interaction between all of the conferees, speakers and

students. This workshop, entitled “Technology - Closing the Gap Between Development & Application,” was an interactive session where attendees discussed the close connections between the research being conducted by the Program with very specific EPA needs. Dr. William Glaze from Oregon Health and Science University was the lunchtime speaker. His presentation focused on the results of the NIEHS Superfund external review and the themes and conclusions that emerged from that review.

Each of the four universities had student and trainee participation at the conference. Of the 100 registered participants, 30 were either pre-doctoral students or postdoctoral trainees. On the first evening of the conference a poster session was held at which the students and trainees were able to interact with conferees.

Plans for distribution of conference proceedings continue to be developed. In the meantime, student/trainee poster abstracts are available upon request, as are speaker abstracts (at superfund@ucdavis.edu). Other documents from the conference may also be requested including the full agenda, and speaker and participant lists.

GRANTEE HONORS and AWARDS

Rick G. Schnellmann, Ph.D., Professor and Chair, Department of Pharmaceutical Sciences, Medical University of South Carolina Charleston, became Editor-in-Chief of the *Journal of Pharmacology and Experimental Therapeutics* on January 1.

STAFF HONORS and AWARDS

Ms. Pamela Moore, GMB, as part of the New Disease Reporting Data Development Process Team, received an NIH Merit Award “For dedicated and meritorious service in creating the database reporting system for NIEHS research investments, allowing timely and accurate responses to Congress and the public.”

Mr. Donald Gula, RCB, received an NIH Merit Award “For exceptional Management of projects and personnel with the Research Contracts Branch.”

Dr. Brenda Weis, CRIS, received an NIH Merit Award “For exemplary efforts in metabolomics, advancing fundamental research and establishing partnerships for the benefit of the entire research community.”

Dr. David Balshaw, CRIS, received received an NHLBI Merit award for "Exemplary leadership and creativity in developing initiatives to improve resuscitation outcomes from out-of-hospital arrest."

Dr. Kimberly Gray, SPHB, received an NIH Merit Award “In recognition of significant contributions to the NIEHS intramural and extramural clinical and epidemiologic research community as the NIEHS Coordinator of Certificates of Confidentiality.”

Drs. William Suk, and Brenda Weis and Ms. Eloise Shephard, CRIS, Dr. Bennett Van Houten, PAB, Dr. Michael Humble COSPB, Ms. Jo Ann Lewis, RCB and Ms. Jacqueline Russell, GMB, received a group NIH Merit Award “For exemplary performance in the management of the Toxicogenomics Research Consortium, advancing outstanding fundamental research for the benefit of the entire toxicology and genomics research community.”

Mr. Warren Pope and Ms. Margarita Roque, administrative officers in the Office of the Director, DDRT, received a group NIH Merit Award “For effectively and collegially engaging and leading DERT in the process of competitive outsourcing of extramural grant staff and related activities to maintain staff morale and commitment.”

Messrs. Joseph Hughes, Theodore Outwater and Rodney Winchel, Mses. Sharon Beard, Patricia Thompson and Yevette Cobb, WETB, and Ms. Carolyn Mason, GMB, received a group NIH Merit Award "For sustained efforts in creating and maintaining high quality health and safety training programs to assure the protection of site disaster responders."

Mr. Joseph Hughes, WETB, and Ms. Beth Anderson, CRIS, received a group NIH Merit Award "For dedicated support in preparing the annual briefing and Superfund program Congressional justification.

Dr. Suk, CRIS, serves on the International Advisory Boards of *Toxicology and Environmental Chemistry* and the *International Journal of Occupational Medicine and Environmental Health.*

STAFF ACTIVITIES

Dr. Sassaman,*Director, DERT,* traveled to Vietnam in November where she represent the United States and the NIEHS in several capacities. She was a member of the US delegation to the annual US/Vietnam Science and Technology Cooperation in Hanoi, where she reported for the workgroup on the environment, was a member of the working group on public health. She also met with Ministers of Natural Resources and the Environment and Science and Technology, as well as one of the Deputy Prime Ministers. Priorities for the Vietnamese for collaboration with the US and an action plan were developed. While in Hanoi, she also presented at a plenary session of the First International Conference on Environmental and Occupational Health, which was sponsored in part by NIEHS and was an activity of the International Training and Research in Environmental and Occupational Health co-funded by NIEHS and the Fogarty International Center. Dr. Sassaman then traveled to Ho Chi Minh City, where she met with researchers at the Institute for Tropical Biology, the Institute of Chemistry, and the Institute of Applied Mechanics, all part of the National Center for Natural Science and Technology. As a follow-up to these meetings, she hosted a delegation of Vietnamese scientists to the US on February 2-4 in Research Triangle Park. The delegation was led by Professor Dang Vu Minh, Director-General of the Vietnamese NCST.

Dr. Tyson, SPHB, served as a co-organizer with program staff from NCI, NIA and OBSSR for the first annual Centers for Population Health and Health Disparities. The meeting took place in Galveston, Texas, February 13-14.

Dr. Carol Shreffler, COSPB, represents the NIEHS on the Liver Diseases Subcommittee of the Digestive Diseases Interagency Coordinating Committee, which is charged with preparing a trans-NIH Liver Disease Research Action Plan to identify needs and opportunities for future research in liver disease across NIH. This plan will be presented to the Director, NIH, and to the Health subcommittee of the House Energy and Commerce Committee. At the first meeting of the Action Plan Committee, which includes members of the Liver Diseases Subcommittee and invited university and NIH intramural scientists, Dr. Shreffler made a presentation on the Initiatives in Liver Disease Research at NIEHS. Dr. John Groopman, Johns Hopkins School of Public Health, an NIEHS grantee and Center Director is a member of the Action Committee.

Dr. Balshaw, CRIS, was selected to chair the NIH Systems Biology Special Interest Group the primary purpose of which is to "Create new pathways for biomedical discovery in the NIH extra- and intramural community by advancing approaches and technologies driven by systems biology."

The NIEHS cosponsored with the Duke University Integrated Toxicology Program a one day Symposium "Obesity: Developmental Origins and Environmental Influences." The meeting was held at the Searle Conference Center, Duke University February 20th. *Dr. Heindel, COSPB,* and Dr. Ed Levin from Duke organized the symposium. Dr. Heindel provided the introduction to the meeting. The goal of this symposium was to present recent data on a possible role of *in utero* exposure to environmental chemicals in the etiology of obesity. There were talks on clinical perspectives and mechanisms of obesity, adipocyte development and control, the developmental basis of obesity focusing on nutrition, role of genomic imprinting in obesity and the role of phytoestrogens and estrogenic environmental agents in altering

susceptibility to the initiation or exacerbation of obesity. The meeting was followed by a Saturday morning brainstorming session, chaired by Dr. Heindel, to determine the state-of-the-science, data gaps and future directions including possible initiatives and future meetings to stimulate the area.

Dr. Humble, COSPB, gave a presentation on "Toxicogenomics and Environmental Health Sciences Research," at North Carolina A&T in Greensboro during their "Environmental Science Education Workshop for Middle School Science Teachers" on Feb 5.

Ms. Beard, WETP, participated in the review of the U.S. EPA Brownfields Job Training Program on February 3-6 in Charleston, South Carolina.

Mr. Hughes, WETB, served on the Occupational Health Panel at the CDC-sponsored Workshop – "Scientific communications needs during a chemical disaster event" in Atlanta, Georgia on February 3-4.

Mr. Outwater, WETB, presented at the 17th Annual NIOSH Education and Research Centers Meeting in Naples, Florida, on February 2. His presentation focused on a review of training activities and an update on the role skilled support personnel play during WMD incidents.

Mr. Phelps, PAB, was an invited speaker at a class entitled *Performance Measurement for Grant Programs* organized by the Applied Learning Institute of Chicago, Illinois. Mr. Phelps made his presentation, *Measuring the Unmeasurable: Developing a Quantitative Approach to Measure Scientific Outcomes,* on January 28th in Arlington, Virginia.

NIEHS , through the Worker Education and Training Program and represented by *Ted Outwater, WETB*, co-sponsored a workshop on January 27-28 to develop national guidance for protecting and training workers who are exposed to mold during remediation efforts. Other sponsors were the Society for Occupational and Environmental Health, Association of Occupational and Environmental Clinics, Urban Public Health Program of Hunter College CUNY, New York City Department of Health and Mental Hygiene, University of Medicine and Dentistry of New Jersey School of Public Health, and the John Hopkins Bloomberg School of Public Health. Representatives from HUD, FEMA, OSHA, NIOSH, EPA participated along with labor, academic, and private sector experts. This was one of three planned meetings. A meeting of physicians at Johns Hopkins on December 11-12 addressed the diagnosis, treatment and management of mold-related health problems. A larger, third meeting, to be held in the summer of 2004, will review the findings of the two earlier meetings with a broader audience. The National Clearinghouse for Worker Safety and Health Training, a NIEHS WETB contractor directed by Dr. Bruce Lippy, has provided significant support to this effort.

Mr. Hughes, WETB , presented at the Annual Briefing of the EPA/Labor Superfund Task Force in Washington, DC on January 21 focusing on disaster response training issues and interagency coordination.

Dr. Weis, CRIS, was an invited participant of the "Workshop on Validation Principles and Approaches for Toxicogenomics-Based Test Systems" held at the European Centre for the Validation of Alternative Methods (ECVAM) in Ispra, Italy on December 11-12. The Workshop convened an expert group of European and U.S. scientists to discuss approaches for validating toxicogenomics-based test systems to support regulatory decision making. The Workshop included three scientific sessions: biological validation, technical validation, and regulatory acceptance. Dr. Weis served as Rappateur for the session on biological validation and co-author of the workshop report to be published in 2004.

Dr. Heindel, COSPB, was an invited speaker at the WHO/IPCS-Japan Workshop "Endocrine Disruptors: Research Needs and Future Directions" December 7-9 in Tokyo, Japan. He presented a talk entitled, "Endocrine Disruptor Research in Reproduction: Current Status and Future Directions."

Dr. Heindel, COSPB, was an invited speaker at the Sixth International Symposium on Environmental Endocrine Disruptors held in Sendai, Japan, Dec 3-5. He presented a talk entitled, "The Developmental Basis of Disease: Role of Endocrine Disrupting Chemicals."

Mr. Hughes, WETB, and staff hosted the NIEHS/Worker Education and Training Program (WETP) semi-annual awardee meeting and technical workshop in Research Triangle Park, North Carolina, on December 3. The focus of the meeting took an inward look at the training, administrative core, and future directions of the WETP. Staff attending and participating in the meeting/workshop in various activities included *Ms. Beard, Mr. Outwater, Ms. Thompson, WETB, and Ms. Mason, GMB.*

Mr. Outwater, WETB, presented on the WETB program at the Paper, Allied-Industrial, Chemical and Energy Worker International Union (PACE) National Health and Safety School in Orlando, Florida, on November 21.

Dr. Srinivasan and Mr. O'Fallon, SPHB, helped organize and attended the annual Health Disparities grantee meeting, which was convened November 19-20. It was hosted by the University of California at San Francisco following the American Public Health Association Meeting (APHA).

Drs. Gray and Srinivasan, SPHB, organized and moderated a session titled “Exposures to Environmental Hazards in the Home,” at the American Public Health Association 131st Annual Meeting, November 16-19 in San Francisco, California. This session highlighted four ongoing NIEHS studies that seek to delineate the environmental health effects of ubiquitous exposures in the home and the role of social and behavioral factors in moderating these risks.

The Superfund Annual Meeting was held November 9-12 in Dartmouth, New Hampshire. *Dr. Thompson, CRIS*, served as a member of the steering committee for the Technical Sessions with Drs. Josh Hamilton and Carol Folt, Dartmouth College, Dr. A.Jay Gandolfi, U of Arizona, Dr. Phil Landrigan, Mount Sinai, Dr. and Dr. James Swenberg, UNC-Chapel Hill. *Ms. Anderson, CRIS*, served on the steering commitee for the Outreach Meeting with Ms. Nancy Serrell, Dartmouth College, Ms. Kathleen Gray, UNC-Chapel Hill, and Mr. Keith Pezzoli, UC-San Diego. *Ms. Ricci, GMB and Ms. Ahlmark , CRIS*, served on the steering committee for the Administrators' Meeting with Ms. J. Sugarman, Dartmouth College and Ms. Kathleen Dooley, UC-Davis.

Ms. Beard, WETB, presented at the 131st American Public Health Association Annual Meeting -- Behavior, Lifestyle, and Social Determinants of Health in San Francisco, California, on November 15. Her presentation was entitled "Training Young Minority Workers: A Comprehensive Approach to Providing Workforce, Health and Safety Skills to a Highly Vulnerable Worker Population." This panel presentation reported the results and strategies utilized to develop a national job-training program for minority workers especially those younger adults from the ages of 18-25. In particular, the panel described why strong connections to apprenticeship programs influence the success of the training and why training programs are successful when they improve basic academic and life skills; enhances safety, health, and environmental justice awareness while providing specific job skills training for employment in the construction, environmental remediation and hazardous materials industries.

Mr. Outwater, WETB, presented at the 131st American Public Health Association Annual Meeting -- Behavior, Lifestyle, and Social Determinants of Health in San Francisco, California, on November 15 during the Oral Session Environmental Toxics - Indoor Air Quality in the Home and Workplace on the topic "Public Housing and Safer Pest Control: Results from a Pilot Program in New York City."

Dr. Humble, COSPB, gave a presentation on “Toxicogenomics and Environmental Health Sciences Research,” to a group of visiting students from North Carolina A&T on Oct 30.

Ms. Beard and Mr. Outwater, WETB, attended the Brownfields 2003: Growing a Greener America Conference in Portland, Oregon on October 26. This national conference was built upon past successes

and continues to offer up-to-date and stimulating information for brownfields practitioners from throughout the United States and overseas. The NIEHS WETP co-sponsored this conference and organized and/or conducted four sessions on brownfields job training, public health, health and safety, and environmental justice efforts of our grantee community. During this meeting, Ms. Beard and Mr. Outwater conducted a grantee meeting of the Brownfields Minority Worker Training Program and a caucus meeting of those attendees interested in environmental job training programs. This caucus meeting was a collaborative effort between the WETP and Mr. Lenny Siegel of the Center for Public Environmental Oversight, who has conducted these very successful caucuses since 1996 at each Brownfield National Conference.

Dr. Collman and Mr. O'Fallon, SPHB, worked with the Environmental Health Sciences Core Center at Johns Hopkins University Bloomberg School of Public Health to develop the meeting agenda and identify speakers for the Center Directors' annual meeting held in Baltimore, Maryland, October 20-21. The focus of this years meeting was on urban environmental health. Unlike past years, the scientific symposium blended scientific presentations with community outreach and education presentations. The three main sessions were: Air Pollutants as an Urban Environmental Health Priority; Host, Genetic and Environmental Susceptibility; and from Bench to Community: Translating Environmental Health Research. As part of the welcome and introductions, Mr. O'Fallon addressed the meeting participants. He highlighted the outcomes and action items of the COEP meeting on October 19 and emphasized the importance of the new symposium format to include COEP. On October 21 Dr. Collman formally introduced herself as the new program administrator for the Core Centers by highlighting her background and research interests. Other NIEHS presentations on the 21st included one from Dr. Sheila Newton (OPPE) on the new Roadmap Initiative and one from Mr. John Peterson (OCPL) on the NIEHS Office of Communication and Public Liaison, and how Centers can effectively use the services provided by OCPL.

Mr. O'Fallon, SPHB, worked with COEPs to organize the annual meeting that was hosted at Johns Hopkins University Bloomberg School of Public Health, October 19-20. The focus of the meeting this year was urban environmental health. Unlike past years, the COEPs presented to Center Directors during the scientific symposium. The new format was well received by all.

Drs. Heindel and Humble, COSPB, gave presentations on "Environmental Chemicals as Hormone Mimics: Role in Disease and Dysfunction," and "Toxicogenomics and Environmental Health Sciences Research," respectively, to a delegation of 20 high school students from Iwate, Japan on October 14. The students, their teachers and chaperones, and their hosts from the North Carolina School of Science and Math, toured the NIEHS facilities and attended presentations from a variety of NIEHS scientists. Their presentations were translated into Japanese for the benefit of these visitors.

Mr. O'Fallon, SPHB, collaborated with program staff from NINR, ATSDR, HRSA, EPA and NIOSH to organize a one-day meeting to discuss on-going programs and consider possible areas for future coordination and collaboration in the area of environmental health nursing. This meeting was a follow-up action item to the 2002 environmental health nursing roundtable.

Ms. Beard, WETB, participated as a technical observer at the TOP-EX 2003 (Total Operational Preparedness Exercise) for more than 500 disaster responders representing over 70 different departments or organizations in Oakland County, Michigan on September 25. This event conducted at the Combined Regional Emergency Services Training (CREST) Center at the Oakland Community College was a County, local community and private section partnership with a focus on emergency response to terrorism or major hazardous material incidents.

Mr. Hughes, WETB, presented at the EPA Emergency Support Function #10 Coordination for National Hazmat Disasters Committee in Washington, DC on September 24.

Mr. Hughes, WETB, addressed a study tour group from South Africa on the NIEHS Worker Education and Training Program in Washington, DC on September 20. This was in support of the U.S. Agency for

International Development 's effort to provide technical services to the South African Department of Labour (DOL) and supporting government institutions.

UPCOMING MEETINGS and WORKSHOPS

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

Dr. Ben Van Houten, PAB, will co-chair the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute's (HESI) "Workshop on DNA Adducts: Biological Consequences and Application to Risk Assessment." The workshop will take place on April 13-14, at the Wyndham Washington DC Hotel. The purpose of the workshop is to consider the biological consequences of DNA adducts, modifiers of DNA adduct levels and of their ultimate effects, and how data for DNA adducts can be utilized in mechanistic studies and in the risk assessment process. The program will feature presentations by international experts and offer opportunities for participant discussion on challenging issues around the biological significance of DNA adducts - particularly at lower exposure concentrations - and how the data on DNA adducts might be incorporated into the risk assessment process.

Mr. Hughes, WETB, and staff will sponsor a Technical Workshop on Training Partnerships for Prevention, Protection, and Preparedness, to be held in Washington, DC on April 22-23. This workshop will focus on building stronger relationships with Department of Homeland Security (DHS), the Department of Labor (DOL/OSHA), and the Environmental Protection Agency (EPA/OSWER) for the training of responder populations most at risk, particularly fire fighters, health care workers, and the construction trades needed at disaster response. The meeting will be preceded on April 21, by the semi-annual WETP Awardee Meeting.

STAFF CHANGES

Recruitments: None.

Departures:
Ms. Mary Butts, GMB branch secretary, departed February 6 to take a position as a budget technician in the NIEHS budget office.

Ms. Tanya Johnson, a program assistant, departed SPHB October 17 to take a promotion position with the U.S. Environmental Protection Agency.

Ms. Eloise Shepherd, a program assistant, departed CRIS October 17 to take a promotion position with the U.S. Environmental Protection Agency.

Ms. Edith Lee, a program analyst, departed PAB December 26 to take a position with the Veterans Administration.

DERT PAPERS OF NOTE

Glutathione Genotype Affects Xenobiotic Enhancement of Allergic Responses
Frank D. Gilliland, Ph.D. and David Diaz-Sanchez, Ph.D.
University of Southern California
P01ES09581 and P30ES07048

Background: Among the health effects associated with particulate matter air pollution is the occurrence of asthma and allergy. Diesel exhaust particles can combine with allergens to cause or exacerbate allergic airways diseases in part by the production of reactive oxygen compounds. The enzyme glutathione-s-transferase is known to metabolize reactive oxygen compounds and to detoxify xenobiotics such as those

present in diesel exhaust. These investigators tested the hypothesis that glutathione genotypes were key determinants in the severity of effects of diesel exhaust particles on allergic response.

Advance: Patients with ragweed sensitivity were challenged intranasally with ragweed pollen alone or in combination with diesel exhaust particles randomly on separate visits. Several markers for allergic response were measured before and 24 hours after challenge. Individuals with *M1* null or *P1* genotypes of the enzyme showed enhanced nasal allergic responses in the presence of diesel exhaust particles. Patients with the *M1* null genotype had about twice the IgE and histamine responses observed in patients with functional *M1* genotypes. The diesel exhaust particle enhancement was largest in patients with both the *M1* null and *P1 I/I* genotypes.

Implications: These experiments indicate that glutathione genotype does indeed modify the effect of diesel exhaust particles on allergic inflammation. The investigators provide evidence that the *M1* and *P1* genotypes play an important part in susceptibility to the combined effects of oxidant pollutants such as diesel exhaust particles. They conclude that "[t]he importance of these results is heightened by the high frequency of polymorphisms of these genes in most populations. These results, therefore, have obvious clinical and public-health relevance especially for sensitized individuals living in urban environments."

Citation: Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. Lancet. 2004 Jan 10;363(9403):119-25.

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Folic Acid Deficiency and Late Gestation Brain Development in Mice
Steven H. Zeisel, MD, Ph.D.
University of North Carolina at Chapel Hill
P30ES19126

Background: Neural tube defects are known to be caused by folic acid deficient diets during the early stages of pregnancy. Women are routinely counseled to take folic acid supplements during the early weeks of their pregnancies. In previous work in laboratory animal studies, these researchers discovered the importance of maternal dietary choline intake late in pregnancy for proper development of the hippocampal region of the brain. Because choline and folate are metabolically interrelated, they speculated that folic acid may also be important at later stages.

Advance: Pregnant mice were given either folate-supplemented, control, or folate-deficient diets from days 11-17 of their 21-day pregnancy. The folate-deficient diets decreased the number of neural progenitor cells undergoing cell division by up to 54% in three regions of the fetal brains. In addition the number of apoptotic cells in the fetal brains was two-times higher in the fetal septum for the folate-deficient mouse pups. Pups from the folate-supplemented group did not differ from the control group.

Implications: These results indicate that progenitor cells in fetal forebrains are sensitive to maternal dietary folate intake during late gestation. Applying these results to human pregnancy suggests that folate availability affects brain development long after neural tube closure, and indicates that it may be very important that women ingest adequate amounts of folic acid throughout pregnancy. This may be especially important in those women with genetic polymorphisms in genes of folate metabolism.

Citation: Craciunescu CN, Brown EC, Mar MH, Albright CD, Nadeau MR, Zeisel SH. Folic acid deficiency during late gestation decreases progenitor cell proliferation and increases apoptosis in fetal mouse brain. J Nutr. 2004 Jan;134(1):162-6.

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Asthma in Rural Iowa Schoolchildren
Peter Thorne, Ph.D. and James Merchant, MD, Ph.D. DPH
University of Iowa
P01ES09607 and P30ES05606

Background: Studies on the prevalence of asthma in children in rural communities have produced conflicting results. While most people have a bucolic image of "life on the farm," there many exposures and dangers that put children at risk for injury and illness. Exposures to dusts and molds from crops and animal feed stuffs have been implicated in children's respiratory disorders including asthma. To further address this issue, this team of NIEHS-supported researchers sought to estimate asthma prevalence and severity in farm and non-farm children.

Advance: The study population consisted of children aged 6-14 years enrolled in 10 school districts in two Iowa counties from 2000-2002. Children who lived on farms were only slightly less likely to have had ever had symptoms of asthma. The same was true for symptoms in the previous year. However, the small protective effect was only seen in one of the study counties. Farm and non-farm children that had experienced symptoms were equally as likely to have been given a diagnosis of asthma.

Implications: Asthma prevalence in these rural counties rivaled that seen in large Midwestern cities including Minneapolis and Chicago. The authors conclude that these findings do not support a protective effect of rural living for the development of asthma in children. To appropriately treat asthma, prompt diagnosis is critical. Less than half of children with frequent symptoms and three fourths with severe symptoms had ever been given a diagnosis of asthma. These findings and those of others suggest that underdiagnosis of asthma is common. When coupled with the high rate of frequent or severe symptoms among those given a diagnosis of asthma, the public health importance of effective rural models for asthma diagnosis and management is evident.
Citation: Chrischilles E, Ahrens R, Kuehl A, Kelly K, Thorne P, Burmeister L, Merchant J. Asthma prevalence and morbidity among rural Iowa schoolchildren. J Allergy Clin Immunol. 2004 Jan;113(1):66-71.

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Estrogen Regulation of Antioxidant Response Element-Dependent Gene Expression
Dennis B. Lubahn, Ph.D. and Mark Hannink, Ph.D.
University of Missouri
R01ES08272, P01ES10535, and R21ES11721

Background: Exposure to chemicals that cause oxidative stress can greatly affect the development of many diseases including cancer. The metabolism of many chemicals has proven to be effective in modulating the degree of oxidative damage. The metabolism of many chemicals involves two distinct types of enzymes known as phase I and phase II.
Phase I enzymes, members of the cytochrome P450 superfamily, metabolically oxidize many chemicals thereby forming intermediates. Phase II detoxification enzymes, such as glutathione-s-transferases and quinone reductase, which are responsible for metabolizing the products of phase I metabolic reactions, degrade these reactive intermediates by conjugation or reduction reactions, thereby protecting cells from oxidative DNA damage.

Understanding how estrogens regulate phase II detoxification enzymes is important in explaining how estrogen exposure increases the risk of developing certain cancers like breast cancer. Phase II enzyme expression is regulated by a DNA sequence known as the antioxidant response element. These

researchers sought to determine whether 17beta-estradiol could regulate the antioxidant response element-dependent gene expression.

Advance: Results indicate that estradiol did repress glutathione gene expression. Additionally, glutathione and quinone reductase activities were significantly lowered in a dose-dependent manner after estradiol exposure in the uteri of mice.

Implications: These experiments conclude that 17beta-estradiol and other estrogens down regulate phase II enzyme activities. This repression may increase cellular oxidative DNA damage that ultimately can result in the formation of cancer in estrogen-responsive tissues like the breast and female reproductive organs.

Citation: Ansell PJ, Espinosa-Nicholas C, Curran EM, Judy BM, Philips BJ, Hannink M, Lubahn DB. In vitro and in vivo regulation of antioxidant response element-dependent gene expression by estrogens. Endocrinology. 2004 Jan;145(1):311-7.

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Long-term Exposure to Particulate Matter and Risk of Death from Heart Disease
George D. Thurston, Sc.D., Ph.D.; NYU School of Medicine
John J. Godleski, MD; Harvard Medical School
R01ES09560, P30ES00260, and P01ES08129

Background: Previous epidemiologic studies by these and other researchers have linked long-term exposure to fine particulate matter air pollution to broad cause-of-death mortality; however, links to specific cardiopulmonary diseases and dysfunctions have not been established. These NIEHS-supported researchers and a colleague at Brigham Young University linked cause-of-death data collected by the American Cancer Society with air pollution data from U.S. metropolitan areas.

Advance: Long-term particulate matter exposures were most strongly associated with death due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest. For these causes of death, a 10 microgram/cubic meter elevation in particulate matter was associated with 8% to 18% increases in mortality risk. Risks for smokers were comparable or larger than for non-smokers. Death attributable to respiratory diseases had relatively weak associations.

Implications: The researchers conclude that particulate matter exposure is a risk factor for specific cardiovascular disease mortality through mechanisms that likely include pulmonary and systemic inflammation, accelerated athersosclerosis, and changes in cardiac rhythms. The study also indicates that although smoking is a much larger risk factor for cardiovascular disease, exposure to fine particulate combined with smoking imposes additional effects.

Citation: Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation. 2004 Jan 6;109(1):71-7. Epub 2003 Dec 15.

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Signaling Pathway Preferentially Induces Mammary Cancers from Progenitor Cells

Bryan Welm and Zena Werb, Ph.D.
University of California San Francisco
T32ES07106

Background: Breast cancer is a complex disease that arises from a variety of cellular alterations with different clinical manifestations. The contributions of different target cells and different cancerous mutations are not well understood. These investigators report that mammary tumors induced by components of the Wnt signaling pathway contain heterogeneous cell types and express early developmental markers, in contrast to tumors induced by other signaling elements. Wnt proteins are a family of signaling molecules that regulate cell-to-cell interactions during embryogenesis.

Advance: Results of their experiments show that expression of the *Wnt-1* protooncogene in mammary glands of transgenic mice causes growth of a population of epithelial cells expressing stem cell markers, keratin 6 and Sca-1. Resulting tumors also express these markers and contain epithelial and myoepithelial tumor cells that share a secondary mutation, loss of *Pten*, suggesting that these cells arose from a common progenitor. Mammary tumors arising in transgenic mice expressing β*-catenin* and *c-Myc*, downstream components of the Wnt signaling pathway, also contain a significant proportion of myoepithelial cells and cells expressing keratin 6. These results suggest that mammary stem cells and/or progenitors to mammary epithelial and myoepithelial cells may be the targets for oncogenesis by Wnt-1 signaling elements. Thus, the developmental heterogeneity of different breast cancers is in part a consequence of differing effects of oncogenes on distinct cell types in the breast.

Implications: These studies provide evidence suggesting components of the Wnt signaling pathway transform mammary stem cells, and that these cells develop into various tumors containing different cell types expressing markers of both mature and immature epithelial cells. Thus, breast cancer heterogeneity may result from transformation of distinct cell types by different oncogenes.

Citation: Li Y, Welm B, Podsypanina K, Huang S, Chamorro M, Zhang X, Rowlands T, Egeblad M, Cowin P, Werb Z, Tan LK, Rosen JM, Varmus HE. Evidence that transgenes encoding components of the Wnt signaling pathway preferentially induce mammary cancers from progenitor cells. Proc Natl Acad Sci U S A. 2003 Dec 23;100(26):15853-8. Epub 2003 Dec 10.

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Protective Effects of Caffeine in Animal Models of Parkinson's Disease
Michael A. Schwarzchild, MD, Ph.D.
Massachusetts General Hospital
R01ES10804

Background: During the past decade several laboratory and epidemiologic studies have suggested that caffeine use reduces the risk of Parkinson's disease by preventing the loss of dopamine producing neurons located in the substania nigra region of the brain. These authors review the evidence that caffeine and other more specific antagonists of the adenosine A2A receptor protect dopamine producing neurons in several animal toxicity models for Parkinson's disease.

Advance: The demonstration that caffeine and more specific A2A antagonists protect dopaminergic neurons in animal models of Parkinson's disease has pathophysiologic, epidemiologic, and therapeutic significance. Understanding the neurobiology of the A2A and other adenosine receptors provides insight into the role of endogenous adenosine in basal ganglia biology and Parkinson's pathophysiology.

Implications: Although the cellular and molecular mechanisms by which A2A receptors contribute to neuronal cell death have not been revealed, several possibilities have emerged. Preliminary clinical data

have substantiated the antiparkinsonian benefits of caffeine and other A2A receptor blockers. Potential neuroprotective benefits from the use of A2A receptor antagonists suggest the possibility of improved treatments and outcomes for Parkinson's disease.

Citation: Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli N Jr, Chen JF. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. Neurology. 2003 Dec 9;61(11 Suppl 6):S55-61.

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Breast Cancer Implications of the Suppression of Estrogen Formation by Components of Red Wine and Grape Seeds

Shiuan Chen, Ph.D.
Beckman Research Institute of the City of Hope, Duarte California
R01ES08258

Background: Many epidemiologic studies have shown that diets high in fruits and vegetables can reduce cancer incidence with multiple studies focusing on wine and grape consumption. Other studies have shown that the production of estrogens in breast cancer tissue plays a major role in tumor progression. Aromatase, a P450 enzyme, synthesizes estrogen by converting 19-carbon androgens into 18-carbon estrogens. Aromatase is highly expressed in breast cancer tissue. Previous research from this and other laboratories has shown that extracts from red wine were shown to inhibit aromatase activity.

Advance: In their current publication, these investigators have identified a class of compounds called procyanidin B dimers as the most abundant aromatase inhibitors in red wine. High levels of these compounds have been found in grape seeds. Further laboratory analyses revealed that the most potent procyanidin B dimer competes with the androgen substrate for binding with the enzyme. Additional *in vitro* studies show that the dimers were able to reduce androgen-dependent tumor growth, indicating that these chemicals reduce the production of estrogens from the androgen substrates.

Implications: This study, and earlier work by the same team, demonstrates that procyanidin B dimers in red wine could be used as chemopreventive agents against breast cancer by inhibiting the conversion of androgens to estrogens in breast tissues. The researchers estimate that a single four-ounce glass of red wine daily could provide enough procyanidin B dimer to inhibit aromatase activity in an average post-menopausal woman.

Citation: Eng ET, Ye J, Williams D, Phung S, Moore RE, Young MK, Gruntmanis U, Braunstein G, Chen S. Suppression of estrogen biosynthesis by procyanidin dimers in red wine and grape seeds. Cancer Res. 2003 Dec 1;63(23):8516-22.

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Folic Acid Intake and Arsenic Biotransformation in Mice

Richard H. Finnell, Ph.D.
Texas A&M University Health Science Center
P30ES09106 and P42ES04917

Background: In most mammals, arsenic transformation occurs by the addition of methyl groups resulting in dimethylarsinic acid being the predominant metabolite excreted in the urine. Previous research by this and other laboratories have established a link between arsenic metabolism and folate biochemistry. These researchers sought to determine if folate binding protein-1 is an important component of arsenic

transformation using transgenic mice lacking the gene for the binding protein. Their experiments also investigated whether dietary folate deficiency in these mice altered arsenic biotransformation.

Advance: Dietary folate deficiency caused reduced excretion of arsenic in the urine of both the transgenic mice lacking the folate binding protein and in wild-type control mice. The transgenic mice excreted more dimethylarsinic acid than the control mice during folate deficiency but not when their diets were folate sufficient.

Implications: These results suggest that inadequate dietary folate may result in decreased transformation and excretion of arsenic. Impaired biotransformation and excretion of arsenic results in increased body retention and exposure in humans. In turn, an increase in arsenic retention is likely to increase the risk of arsenic-induced toxicities, especially in certain at-risk populations due to their genetic predisposition.

Citation: Spiegelstein O, Lu X, Le XC, Troen A, Selhub J, Melnyk S, James SJ, Finnell RH. Effects of dietary folate intake and folate binding protein-1 (Folbp1) on urinary speciation of sodium arsenate in mice. Toxicol Lett. 2003 Nov 30;145(2):167-74.

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Validating the Measurement of Environmental Chemicals in Amniotic Fluid as a Potential Biomarker of Prenatal Exposure

Brenda Eskenazi, Ph.D.
University of California, Berkeley
P30ES01896 and P01ES09605

Background: Use of pesticides in the United States, both agriculturally and residentially, has risen to over one billion pounds annually. Recent studies by this NIEHS and EPA jointly funded Children's Environmental Health Center have demonstrated widespread pesticide exposure to the U.S. population. Pregnant women and children are among those at risk for exposure. Overall, these studies confirm that children are exposed to pesticides prenatally, when they may be particularly vulnerable to adverse health effects during critical periods of development. Exposure and health research has been hampered by the lack of reliable methods to determine fetal exposure. These researchers report the validation of a method using amniotic fluid to provide direct evidence of fetal exposure to commonly used non-persistent pesticides.

Advance: Using one hundred amniotic fluid samples collected during amniocentesis at 18 weeks of gestation and slated for disposal, analytic methods were evaluated for measuring organophosphate and carbamate pesticides and metabolites, synthetic pyrethroid metabolites, herbicides, and chlorinated phenolic compounds. Six phenolic compounds were found including napthol and pentachlorophenol. The organophosphate metabolites diethylphosphonate, dimethylphosphate, and dimethylthiophospadte were also detected in some samples.

Implications: Although the reported levels are low compared to reports in maternal urine and blood and meconium, they indicated direct exposure to the developing fetus possible during sensitive stages of development. These results suggest that amniotic fluid offers a unique opportunity to investigate fetal exposures and health risks.

Citation: Bradman A, Barr DB, Claus Henn BG, Drumheller T, Curry C, Eskenazi B. Measurement of pesticides and other toxicants in amniotic fluid as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect. 2003 Nov; 111(14):1779-82.

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Lead and Psychiatric Symptoms in Aging People
Howard Hu, MD, Sc.D.
Brigham and Women's Hospital
R01ES05257, P42ES05947, and P30ES00002

Background: The effects of lead on cognitive function in children are well documented and have been common knowledge for decades; however, the effects of lead on older people are not well known. Lead is released from its major storage sight, the long bones, during periods of bone turnover such as gestation and lactation and as a result of osteoporosis. Therefore, there is cause to be concerned about the effects of lead in elderly persons as it may be relevant to neurologic diseases and dementia.

Advance: These NIEHS-supported researchers measured blood and bone lead concentrations in middle-aged to elderly men enrolled in the Normative Aging Study and used them to investigate lead's potential effects on psychiatric symptoms such as anxiety, depression, and phobic anxiety. Blood lead levels averaged 6.3 micrograms/dl while tibia and patellar lead levels were 21.9 and 32.5 micrograms/gram respectively. All of these lead levels are considered to be modest levels of exposure. Logistic regression models that adjusted for age, employment status, education, and alcohol consumption indicated that patellar bone lead was significantly associated with an increased risk for phobic anxiety. Similar associations were seen for tibia and blood lead.

Implications: These results led the researchers to conclude that cumulative lead exposure, even at these modest levels, could be a risk factor for the development of psychiatric symptoms in adults. If additional studies confirm these results, screening and treatment for lead exposure could be indicated for adults with similar psychiatric illnesses and symptoms.

Citation: Rhodes D, Spiro A 3rd, Aro A, Hu H. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. J Occup Environ Med. 2003 Nov;45(11): 1144-51.

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Single Nucleotide Polymorphisms in Myeloperoxidase and Catalase Genes Increase Susceptibility for Arsenic-Induced Hyperkeratosis
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Columbia University Health Science
P42ES10349 and P30ES09089

Background: Chronic exposure to arsenic, usually through contaminated drinking water, is known to cause skin and other cancers in humans. This is unfortunately readily apparent in areas of the world where arsenic exposure is high such as Bangladesh and parts of South America. Continuing on previous research in Bangladesh by this team of investigators, this report focuses on whether single nucleotide polymorphisms in two oxidative stress genes are associated with increased risk of arsenic-induced hyperkeratotic skin lesions (precursors of skin cancer) in a case-control study also carried out in Bangladesh.

Advance: Carriers of the susceptible myeloperoxidase and catalase genotypes were at about twice the risk for hyperkeratosis. When combined with high arsenic exposure, carriers of the susceptible myeloperoxidase gene had six times the risk of hyperkeratosis than did subjects with low arsenic exposure and the low-risk genotype. Similarly, high arsenic exposure and high-risk catalase genotype was associated with about a four-fold risk of hyperkeratosis than low exposure and low-risk genotype.

Implications: These studies, although based on small numbers of subjects, suggest that the oxidative stress genes myeloperoxidase and catalase may influence the risk of arsenic-induced premalignant

hyperkeratotic skin lesions. This group is currently conducting a larger epidemiologic prospective cohort study. Findings from this study, if confirmed in the larger study, may have important research and policy implications. Recent estimates suggest that the life-time burden of internal cancers due to arsenic exposure in Bangladesh is expected to be at least doubled. Currently, no specific chemoprevention strategies for preventing arsenic induced cancers are known. Since a vast number of people have already accumulated years of chronic exposure, the study findings may guide researchers in designing and testing specific biomedical/public health interventions by incorporating knowledge of inherent variations in susceptibility to arsenic effects. From the general policy perspective, the findings should reinforce the importance of reducing arsenic exposure in the population.

Citation: Ahsan H, Chen Y, Kibriya MG, Islam MN, Slavkovich VN, Graziano JH, Santella RM. Susceptibility to arsenic-induced hyperkeratosis and oxidative stress genes myeloperoxidase and catalase. Cancer Lett. 2003 Nov 10;201(1):57-65.

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Low-Level Ozone and Particulate Matter Pollution is Associated with Respiratory Symptoms in Children with Asthma

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William S. Beckett, Ph.D., University of Rochester School of Medicine and Dentistry
R01ES07456, R01ES05410, R01ES11013, and P30ES01247

Background: Many studies have shown that children with asthma are particularly vulnerable to adverse health effects from exposure to high levels of the air pollutants ozone and particulate matter. These studies have shown that children with asthma living in areas that regularly experience periods of high levels of these ambient pollutants are at significant risk for respiratory symptoms, the need for asthma medication use, and decreases in lung function. Other epidemiologic studies of children with asthma living in regions with levels of pollution within or near compliance with EPA standards suggest that these standards may not be protective of this more vulnerable group. The current study conducted by NIEHS grantees at the Yale University School of Medicine examines simultaneous effects of ozone and particulate matter at levels below EPA standards on daily respiratory symptoms and rescue medication use.

Advance: Ozone levels, but not particulate matter was significantly associated with respiratory symptoms and rescue medication use among children using maintenance medication. The 1-hour average (59 parts per billion) and 8-hour average (51 parts per billion) levels of ozone were significantly lower than the EPA standards of 120 and 80 respectively. No exposure-dependent associations were observed for any outcome by either pollutant among children not using maintenance medication.

Implications: The finding that asthmatic children are particularly vulnerable to ozone at levels below current EPA standards has major public health implications. On days when the ozone levels are considered safe for the general population, this at-risk group may need to take additional precautions. Parents and physicians need to be aware of ozone alert forecasts and may need to take measures to limit outdoor activity and exercise for children with asthma on days when ozone is elevated but not exceeding accepted standards.

Citation: Gent, JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett, WS and Leaderer, BP. Association of Low-Level Ozone and Fine Particles with Respiratory Symptoms in Children with Asthma. JAMA, 2003; 290:1859-1867.

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Trends of Persistent Pollutants in Umbilical Cord Blood of Inuit Infants

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Grant R01ES07902

Background: Indigenous people living in Nunavik, a region of Northern Quebec, Canada, consume large amounts of marine foods and are therefore exposed to high levels of biopersistent and bioaccumulating food chain contaminants. This research study measured persistent organic pollutants, mercury, and lead in umbilical cord blood samples from infants from three communities on the east coast of Hudson Bay in Nunavik. The researchers analyzed 251 samples collected from 1994 through 2001 for polychlorinated biphenyls (PCBs), dichlorodiphenyl trichloroethane (DDT), dichlorodiphenyl dichloroethylene (DDE), hexachlorobenzene (HCB), chlordanes, lead and mercury. All of these compounds are known to have adverse health outcomes.

Advance: The investigators found significantly decreasing trends for PCBs, DDT, DDE, and HCB ranging from 6.6% to 9.1% per year. No significant trend was noted for chlordane. Lead and mercury each declined by approximately 50% during the period of sample collection; however, there was no clear linear trend.

Implications: Since the 1970s, many restrictions and regulations have helped drastically reduce the input of persistent organic chemicals and heavy metals in the environment, and exposure through food contamination decreased accordingly. In this study, the investigators attribute the decline mainly to a diminution of food contamination and, to a lesser extent, dietary changes. Although questions remain as to the exact causes of the decline, it is encouraging to observe such an improvement in prenatal exposure for this highly exposed population. These researchers suggest that international efforts to further reduce environmental contamination should be continued.

Citation: Dallaire F, Dewailly E, Muckle G, Ayotte P. Time trends of persistent organic pollutants and heavy metals in umbilical cord blood of Inuit infants born in Nunavik (Quebec, Canada) between 1994 and 2001. Environ Health Perspect. 2003 Oct; 111(13):1660-4.

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History of Infection and Antibiotic Use and Risk of Non-Hodgkin's Lymphoma
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P30ES00260

Background: A growing body of research suggests that a variety of infectious agents may play roles in the development of several human cancers. Malignant lymphoma is the first human tumor for which an association with infectious agents was established. Since the discovery of the involvement of Epstein Barr virus in Burkitt's lymphoma, multiple viruses and bacteria, including HIV, hepatitis C virus and *helicobacter pylori*, have been linked with several types of malignant lymphoma. Although some viruses are known to stimulate lymphocytes directly, leading to monoclonal growth, other mechanisms have been proposed for an association of infectious agents with lymphoma. These observations suggest that infections that cause chronic inflammatory conditions potentially increase the risk of lymphoma.

To investigate the possibility that certain infections and antibiotic use are associated with risk of non-Hodgkin's lymphoma, these investigators conducted a population-based case-control study among women in upstate New York.

Advance: The results of the study showed a progressive increase in the risk of non-Hodgkin's lymphoma with increasing frequency and duration of systemic antibiotic use over the 2-20 year period prior to the beginning of the study. For the highest exposure group, consisting of more than 35 episodes or more than

1 year of use, the risk was 2.5 times higher than in controls. These associations were primarily due to antibiotic use for respiratory infections and dental conditions. Analyses by class of antibiotic use did not suggest a general cytotoxic effect of antibiotics was responsible for the increased risks.

Implications: The results of this study are generally consistent with the hypothesis that chronic infection and/or inflammation may predispose individuals to the development of non-Hodgkin's lymphoma. A direct role of antibiotic use in the development of non-Hodgkin's lymphoma could not be ruled out. The authors conclude that if the non-Hodgkin's lymphoma-antibiotic association is due to frequent/prolonged infections, the proper use of appropriate antibiotics might actually contribute to reducing the risk of the disease.

Citation: Kato I, Koenig KL, Baptiste MS, Lillquist PP, Frizzera G, Burke JS, Watanabe H, Shore RE. History of antibiotic use and risk of non-Hodgkin's lymphoma (NHL). Int J Cancer. 2003 Oct 20;107(1):99-105.

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Semen Quality Lower in Men from Rural Areas—Part II
Shanna H. Swan, Ph.D.University of Missouri-Columbia School of MedicineR01ES09916

Background: In a study published in April 2003, NIEHS-supported researchers reported that semen quality was found to be lower in a cohort of men living in an agrarian area in Missouri as compared to men from more urban locations. The authors speculated that a possible reason for these differences could be higher exposure to agricultural chemicals in the more rural Missouri population. Fifty-seven percent of the land in the Columbia, MO area is used for farming which far exceeds that of the other areas. The authors have conducted a follow-up study to determine whether exposure to eight commonly used pesticides is associated with changes in semen quality in two groups of men from Missouri and Minnesota.

Advance: Pesticide metabolites were measured in the urine of all men participating in the study. Pesticide metabolite levels were elevated in Missouri men, compared with controls, for the herbicides alachlor and atrazine, and for the pesticide diazinon. Men from Missouri with high levels of alachlor or diazinon were 30 and 16.7 times more likely to have poor semen quality. There were no associations for any pesticide exposure in the group of men from Minnesota where agricultural pesticides were low or for the commonly used mosquito repellant DEET or the insecticide Malathion.

Implications: The reported associations between pesticide exposure, confirmed by urine analysis, and poor semen quality in the Missouri men suggest that agricultural chemicals may be the cause of these effects. The researchers report, "This is the first population-based study to demonstrate links between specific biomarkers of environmental exposures and biomarkers of male reproduction in humans." They go on to conclude, "Given the current wisespread use of these pesticides, if further study confirms these findings, the implications for public health and agricultural practice could be considerable."

Citation: Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, Wang C, Brazil C, Overstreet JW; Study for Future Families Research Group. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect. 2003 Sep;111(12):1478-84.

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Receptor Polymorphisms and Predisposition to Heart Failure
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P30ES06096

Background: Despite advances in treating heart disease, mortality from heart failure is approximately 50% within 5 years. Beta adrenergic receptors are the predominant cardiac receptors for the catecholamines norepinephrine and epinephrine. These receptors represent the major mechanism whereby cardiac output is increased by the sympathetic nervous system. However, prolonged activation of the receptors ultimately worsens heart function regardless of the initial cause of failure. This is the basis for the therapeutic efficacy of beta-blockers in heart failure.

Advance: Beta-1 adrenergic receptors have been shown to be polymorphic, or to have genetic variants that affect the heart's contractility. This team of investigators created a transgenic mouse model of the human heart failure genotype thus enabling controlled laboratory studies that mimic the human condition. Their studies found that the hearts from the transgenic mice behaved similarly to human hearts.

Implications: These studies show that the human variant genotype predisposes individuals for heart failure by causing hyperactive signaling programs leading to depressed receptor binding and ventricular dysfunction. It also influences the response to therapeutic beta-receptor blockers. The authors conclude that if these phenotypic associations are confirmed in additional studies, early genotyping of all heart failure patients could be indicated for assessing risk or prognosis, or for tailoring therapy for individual patients.

Citation: Mialet Perez J, Rathz DA, Petrashevskaya NN, Hahn HS, Wagoner LE, Schwartz A, Dorn GW, Liggett SB. Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. Nat Med. 2003 Oct;9(10):1300-5. Epub 2003 Sep 14.

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Obesity and Asthma Risk

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P01ES09581 and P30ES07048

Background: Both asthma and obesity in children have been increasing in incidence rapidly in the past 20 years. Health care providers have noticed this association, which has been explained as evidence that children with asthma are less likely to engage in physical activity and therefore are more prone to gaining weight. However, this interpretation has been challenged in recent studies. To determine the relationship between obesity and newly diagnosed asthma among school-age children, this NIEHS-supported research team examined data from participants in the Southern California Children's Health Study.

Advance: The data reveal that new-onset asthma was about 1.5 times higher among overweight children. Boys had a slightly higher risk of about two-fold. Interestingly, the effect of being overweight was higher in non-allergic children than in children with documented allergies.

Implications: These findings may have important public health implications in the battle to control both epidemics of asthma and obesity in children. During the last decade, the incidence of overweight increased by 40%. If obesity is indeed contributing to the asthma epidemic, public health professionals may need to target obesity prevention in efforts to control asthma. Further longitudinal epidemiologic and mechanistic studies are necessary to confirm these results and to identify all causes of the childhood asthma epidemic.

Citation: Gilliland FD, Berhane K, Islan T, McConnell R, Gauderman WJ, Gilliland SS, Avol E, and Peters JM. Obesity and the Risk of Newly Diagnosed Asthma in School-age Children. Am J Epidemiol 2003; 158:406-415.

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Mold Exposure in First Year of Life May Lead to Asthma Development
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NIEHS Grants R01ES7456 and R01ES05410

Background: Asthma clinicians and researchers have reported a substantial rise in the prevalence and severity of asthma in children over the past decade. Genetic predisposition and exposure to various environmental agents, such as environmental tobacco smoke, endotoxin, and indoor allergens especially during early childhood, have been reported as risk factors for the development of sensitivities to inhaled allergens and the development and exacerbation of asthma. Suspect allergens include those from cockroaches, cats, dust mites, molds, and environmental tobacco smoke. Additional studies have shown a link between risk of a child developing asthma and maternal asthma history, however there have been very studies that have related allergen sensitization and asthma development to maternal history of asthma.

Advance: In a birth cohort study conducted by an NIEHS grantee at the Yale University Department of Medicine and colleagues at the University of Rochester, Harvard Medical School, Brigham and Women's Hospital, and the University of Virginia Medical Center, the issue of mold exposure and asthma development was addressed. The investigative team measured a number of indoor exposures early in life, including mold exposure, using questionnaires and by measuring airborne cultural spores. The association between these exposures and the development of wheeze and cough by twelve months of age was studied. A strong association was found for mold exposure, whether assessed by questionnaire or measured exposure, in children whose mothers had asthma.

Implications: This finding suggests potential differences in susceptibility to these exposures for children with and without asthmatic mothers. It also suggests that the differences in susceptibility are genetically based making some children more sensitive to specific environmental agents. The overall results of the study suggest that early mold exposure may increase the risk of asthma. These findings should be interpreted carefully because of the poor predictability of early wheeze and cough in asthma development. Continued research into specific gene-environment interactions may help to elucidate the cause of these differences.

Citation: Belanger K, Beckett W, Triche E, Bracken MB, Holdford T, Red, P, McSharry J, Gold DR, Platts-Mills TAE, and Leaderer BP. Symptoms of Wheeze and Persistent Cough in the First Year of Life: Associations with Indoor Allergens, Air Contaminants, and Maternal History of Asthma. Am J Epidemol 2003; 158:195-202.

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Gene Expression Analysis for Asbestos-Induced Lung Cancer
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R01ES09213

Background: Asbestos, the naturally occurring group of mineral fibers once used extensively as an insulator in many domestic and industrial settings, has been known for decades to cause a rare form of lung cancer in exposed workers. The cancer originates in the mesothelial lung cells and is therefore known as mesothelioma. Mesothelioma is difficult to treat and is generally known to have a poor prognosis. Even though the carcinogenic potential for the crocidolite form of the fiber is well known, the molecular and cellular mechanisms influenced by exposure and leading to malignancy have not been well characterized. In many different cell culture systems, asbestos fibers have been shown to have a variety of effects in the multistage process of tumorigenesis including DNA damage by causing oxidative lesions and base deletions, hyperplasia, and changes in normal gene expression.

Advance: Using the increasingly popular tool of microarray gene expression analysis, NIEHS-supported researchers at the University of Vermont sought to better characterize subsets of genes that were either "turned on" or "turned off" in rat mesothelial cells after exposure to acute asbestos and also in active mesothelioma tumors. These studies were the first of their kind and demonstrated that increased expression of a gene leading to the development of cancer, a proto-oncogene, known as *fra1* was linked to the expression of two other genes, *cmet* and *cd44*, which have been linked to migration and invasiveness of tumor cells

Implications: Even though asbestos has been banned in the United States, cases of malignant mesothelioma have increased at an alarming rate over the years. Currently there are over 3,000 recorded cases of persons that are diagnosed with malignant mesothelioma each year in the United States alone. The studies highlighted here suggest that inhibition of *fra-1* signaling pathways may be an effective strategy for treating malignant mesothelioma. The ability to modify the expression of critical genes involved in the spreading of tumors by inhibiting *fra1*expression could be used as a therapeutic approach to stop the chain of events in tumor progression. *Citation:* Ramos-Nino ME, Scapoli L, Martinelli M, Land S, Mossman BT. Microarray analysis and RNA silencing link fra-1 to cd44 and c-met expression in mesothelioma. Cancer Res. 2003 Jul 1;63(13):3539-45.

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Pregnancies at Risk from September 11th Debris
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P42ES07384

Background: Low birth weight is a recognized risk factor for some developmental problems. Heavy smoking by pregnant women and exposure to extreme air pollution have been linked to low birth weight. To see if pollution from the destruction of the World Trade Center produced similar effects, NIEHS-supported researchers at the Mt. Sinai School of Medicine and Bronx Veterans Affairs Medical Center tracked pregnant women who were living near the World Trade Center at the time of the attacks.

Advance: The team recruited 187 women who were pregnant and in the area of the World Trade Center on September 11 or during the 3 weeks following. For comparison, the researchers tracked 2,300 pregnant women from elsewhere in New York City who delivered babies at the same time. There were few differences between the two groups, but the most striking was that 8.2% of babies in the World Trade Center group were in the lowest 10% of birth weights for their gestational ages, compare to only 3.8% in the control group.

Implications: This study shows a strong effect even with a small number of participants. The research team speculates the cause could be exposure to particulate matter or polycyclic aromatic hydrocarbons. Possible long-term effects on the development of these children are unclear and will require continuous follow-up.

Citation: Berkowitz GS, Wolff MS, Janevic TM, Holzman IR, Yehuda R, and Landrigan PJ. The World Trade Center Disaster and Intrauterine Growth Restriction. JAMA. 290(5): 595-596.

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Common Nutrients Fed to Pregnant Mice Alter Offspring Coat Color and Disease Susceptibility
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R01ES08823

Background: We've all heard the saying "You are what you eat," but recent research from Duke University scientists suggests "You are what your mother ate" too. In a study of nutritional effects on development, this team showed they could change coat color of baby mice simply by feeding their mothers four common nutritional supplements before and during pregnancy and lactation. These four supplements also lowered the susceptibility of obesity, diabetes, and cancer in the offspring.

Advance: Pregnant laboratory mice that were fed vitamin B12, folic acid, choline, and betaine gave birth to babies predominantly with brown coats. Offspring from pregnant mice not given the supplements had yellow coats. The non-supplemented mothers were not deficient in these nutrients—they received normal levels from their food. Molecular biology techniques demonstrated that the reason for the difference in coat color was a change in the expression of a specific gene called Agouti. The nutritional supplements were shown to methylate the gene and prevent its expression. Mice that over-express the Agouti gene tend to obese and susceptible to diabetes because the protein it encodes binds to a receptor in the brain and interferes with the signal to stop eating.

Implications: Although the animals with the altered gene expression were healthier than the non-supplemented mice, this may not always be true. Methylation of genes, and subsequent reduced expression, could also produce deleterious effects depending on the specific gene altered. For example, methylation that occurs near or within a tumor suppressor gene can reduce its expression and therefore inhibit its anti-cancer activity. Further research is needed to understand the molecular effects of nutrients on cells, not just the obvious manifestations.

Citation: Waterland RA and Jirtle RL. Transposalbe elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol. 23(15):5293-5300.

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Tamoxifen Induced DNA Adduct Formation
Shinya Shibutani, Ph.D.
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R01ES09418

Background: Tamoxifen is widely used as an antiestrogen therapy for breast cancer patients and as a chemopreventive agent for healthy women at high risk for breast cancer. However, tamoxifen use has been associated with increased incidence of endometrial cancer. It has been characterized as a human carcinogen by the International Agency for Research on Cancer.

Oral dosing of tamoxifen causes liver cancer in laboratory animals. Analysis of liver tumors identified DNA adduct formation induced by the activated metabolites of the drug. Other researchers have tried to detect DNA adduct formation in breast cancer patients receiving tamoxifen; however, results have been mixed and inconclusive.

Advance: Using a newly developed modification of a high performance liquid chromatography laboratory analysis, these investigators report the presence of significant quantities of tamoxifen-induced DNA adducts in the livers, uteri, ovaries, and brains of cynomolgus monkeys orally treated with six times the human equivalent dose of tamoxifen for thirty days.

Implications: These results, though preliminary, suggest that women receiving tamoxifen may form DNA damage in many organs including the uterus and ovary. Additional studies are necessary to determine the genotoxic risk of tamoxifen in humans. These results could have important implications in the use of

tamoxifen in breast cancer patients and especially in healthy women taking the drug as a chemopreventive agent.

Citation: Shibutani S, Susuki N, Laxmi YR, Schild LJ, Divi RL, Grollman AP, and Poirier MC. Identification of tamoxifen-DNA adducts in monkeys treated with tamoxifen. Cancer Res. 2003 Aug 1; 63(15):4402-6.

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Peroxiredoxin's Role in Erythrocyte Antioxidant Defense and Tumor Suppression
Carola A. Neumann, MD
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T32ES07155

Background: Hydrogen peroxide, known mostly as a common antiseptic, is also a product of aerobic metabolism. As an organism consumes oxygen, small amounts of hydrogen peroxide and other similar reactive oxygen compounds are formed as by-products. All aerobic organisms have evolved systems to control the concentrations of reactive oxygen compounds so that they don't accumulate in quantities sufficient to kill or damage cells. One such mechanism is the enzyme peroxiredoxin. Peroxiredoxin and other enzymes, such as catalase, act to destroy reactive oxygen compounds. The story might end there, but there is a growing body of evidence that reactive oxygen compounds are important for cell signaling and communication and have also been implicated in cancer development and aging.

Advance: This publication by an NIEHS-supported post-doctoral fellow demonstrates that transgenic mice with targeted inactivation of the peroxiredoxin gene, *Prdx1,* are viable and fertile but have a shortened life-span from development of severe hemolytic anemia and several cancers beginning at about nine months of age. These effects are also seen in heterozygotes. The anemia is characterized by an increase in red blood cell reactive oxygen species, which lead to protein oxidation, hemoglobin instability, and decreased red blood cell life. The cancers include lymphomas, sarcomas and carcinomas, and are frequently associated with loss of Prdx1 expression in heterozygotes, which suggests that this enzyme functions as a tumor suppressor.

Implications: These results indicate that Prdx1 as an important defense against the actions of reactive oxygen compounds in red blood cells and tumor progression in aging mice and presumably in humans as well. Establishing the mechanisms underlying the cancer susceptibility of *Prdx1* mutant mice will require further studies. These mice should provide a valuable tool for understanding the role of antioxidant pathways in aging, carcinogenesis, and other processes.

Citation: Neumann CA, Krause DS, Carman CV, Das S, Dubey DP, Abraham JL, Bronson RT, Fujiwara Y, Orkin SH, and Van Etten RA. Essential role for the peroxiredoxin Prdx1 in erythrocyte antioxidant defence and tumour suppression. Nature. 2003 July 31;424:561-5.

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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 23, 2004

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Anne P. Sassaman, Ph.D. 02/12/2004
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 information details the procedure for early Council concurrence:**

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 **September/October Council meeting for the next calendar year.**

At least 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 **the** subgroup electronically through the Electronic Council Book.

Council **subgroup** members will be notified electronically of the existence of the panel of applications and a "due date" for their action will be identified. **Subgroup** members may concur en bloc or may remove any or all applications from concurrence. Any application removed from the early concurrence process by **subgroup** 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 23, 2004

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Anne P. Sassaman, Ph.D. 02/12/2004
Director, DERT, NIEHS

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Division of Extramural Research and Training
Susceptibility and Population Health Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

February 23-24, 2004

CONCEPT CLEARANCE

for

BUILT ENVIRONMENT AND HUMAN HEALTH

Introduction and Background

The built environment is our most important habitat, since 80% of North Americans live in towns and cities and spend 90% of their time indoors. The built environment can be conceptualized as "part of the overall ecosystem of our earth. It includes land-use planning and policies that impact our communities in urban, rural and suburban areas. It encompasses all buildings, spaces and products that are created, or modified, by people. It includes our homes, schools, workplaces, parks/recreation areas, business areas and roads. It extends overhead in the form of electric transmission lines, underground in the form of waste disposal sites and subway trains, and across the country in the form of highways" (Adapted from Health Canada). To date, much of the discussion on the built environment has focused on the challenges of providing adequate transportation (roads, highways, infrastructure, public transportation), urban sprawl, air pollution due to increased traffic, and the diminishing natural environment. New evidence, however, increasingly recognizes that even the places we live and work in clearly affect our health. Recent research explores the effect of improved built environments on physical activity, asthma, obesity, cardiovascular disease, lung cancer mortality, and mental health. However, a pressing need remains for more concerted research to identify mechanisms by which the built environment adversely and positively impacts health and to develop appropriate interventions to reduce or eliminate harmful health effects. Such research efforts are required because of the growing health burden and attendant economic costs associated with higher chronic disease incidence (e.g., obesity, asthma, cardiovascular disease, cancer). These complex diseases are attributable to an interaction of genetic and environmental influences, and many of the latter can be directly traced to the built environment.

Research on the connections between the built environment and health has largely focused on housing, transportation, and neighborhood characteristics and has pointed out that the burden of illness has been greater on lower socioeconomic strata and minority populations. This section reviews some of the literature in these areas.

Housing

The association between substandard housing and health has long been recognized. However, only recently has a growing body of evidence emerged suggesting that physical and mental

health problems—anxiety, depression, attention deficit disorder, substance abuse, aggressive behavior, asthma, heart disease, and obesity—relate to the built environment, particularly to poor urban planning and inadequate housing. Inadequate and dilapidated housing, for example, may indicate that inhabitants are under significant physical and mental stress. Housing disrepair among the poor exposes them disproportionately to lead, pests, air pollutants, contaminants, and greater social risks. Likewise, pesticide use in dilapidated structures may jeopardize the health of inhabitants.

Transportation

In recent decades, U.S. residents have had a greater reliance on cars and trucks, which burn fossil fuels, for transportation needs. Increased vehicle use and the methods employed in energy generation contribute to air pollution that negatively impacts health. In sprawling communities, cars and trucks pollute the atmosphere with ground-level ozone and particulate matter, contributing to human health problems such as lung disease. People most affected by air pollution include older adults with preexisting respiratory disease, children, especially those with asthma, persons with inadequate health care, and even healthy individuals who work and exercise outdoors. Higher dependence on motor vehicles, apart from resulting in higher levels of congestion, has increased motor and pedestrian injuries and deaths. Lack of safe sidewalks in growing urban areas has resulted in a reduction in the number of children walking or biking to schools. Today, only 10% of children walk or bicycle to school — a 40% reduction over the last 20 years.

Isolated Communities and Sedentary Lifestyles

Inadequate urban planning, including a dearth of bike paths and sidewalks, has contributed to an increasingly sedentary lifestyle for children, possibly factoring into the growing rates of childhood obesity. Mounting evidence suggests that there are social, health, and economic consequences to isolated and sedentary lifestyles. Further, the physical and social construct of the urban environment promotes isolation. Higher rates of television viewing, increased computer use, concern about crime, little contact with neighbors, and geographic isolation have created communities that are not interconnected. People who live in such isolated communities are often unable to effect changes or deal with crises or public health challenges. Studies suggest that a reduction in childhood and adolescent obesity, for example, through various intervention and prevention programs, would also yield long-term economic and social benefits.

Health Disparities

In exploring the impact of the built environment on public health, research indicates that the burden of illness is greater among minorities and low-income communities. Lower socioeconomic status communities usually have limited access to quality housing stock and live in neighborhoods that do not facilitate outdoor activities or provide many healthy food options. Inequities in construction and maintenance of low income housing, especially for African Americans, older persons, persons with disabilities, and immigrants, have resulted in insufficient housing, poor quality housing, overcrowding, and higher levels of population density and health problems. Consequently, these communities may experience greater rates of respiratory disease,

developmental disorders, obesity, chronic illnesses, and mental illness. Also, studies have consistently shown an association between a deteriorated physical environment and higher rates of crime, making neighborhoods less safe for walking and, in some cases, resulting in greater social isolation. Understanding linkages between socioeconomic inequity and health is essential to reducing exposures to environmental hazards as well as disparities in health.

Sustainable Communities

While some research indicates the negative health impact of the built environment, there is very limited research on the health benefits of promoting sustainable communities. The President's Council in 1993 offered a working definition for sustainable communities as "healthy communities where natural and historic resources are preserved, jobs are available, sprawl is contained, neighborhoods are secure, education is lifelong, transportation and health care are accessible, and all citizens have opportunities to improve the quality of their lives." The sparse research on sustainable communities suggests that diligent planning is needed to create an environment that is conducive to the mental and physical well being of humans as well as the natural environment.

Built Environment and Obesity

An important area of health that is related to the built environment is the issue of obesity. In the United States, obesity has risen at an epidemic rate during the past 20 years. Research indicates that the situation is worsening rather than improving. In fact, one of the national health objectives for the year 2010 is to reduce the prevalence of obesity among adults to less than 15%. Obesity-associated health care costs account for approximately 7% of national expenditures, approximately $75 billion. While obesity is an enormous public health threat for Americans of all ages, it is a far more serious problem for children and minorities.

Obesity, like most chronic health problems, is caused by complex interactions between genetic, environmental and behavioral factors. Basic research is needed to untangle these interactions and develop molecular intervention strategies. A practical approach at this time would be to modify the environmental contributors which are responsible for the obesity epidemic, such as eating behavior (excess calories), sedentary lifestyle, and the built environment (e.g., sidewalks and transportation systems).

Given the rapid progression of the problem of obesity in the United States and the resultant health care cost, the proposed program at National Institute of Environmental Health Sciences (NIEHS) will focus, as a first step, on developing a research initiative on the built environment and obesity and other co-morbid factors.

To address issues relating to the built environment and human health NIEHS convened a conference in 2002, a retreat in 2003, and is planning another conference later this year. Additionally, NIH established the Obesity Task Force in 2003.

Built Environment and Health Conference:

The first conference on the built environment and human health entitled "Built Environment—Healthy Communities, Healthy Homes, Healthy People: Multilevel, Interdisciplinary Research Approaches," was convened in July 2002 in Research Triangle Park, North Carolina. The conference was co-sponsored by National Institutes of Health's Office of Rare Diseases and Office of Behavioral and Social Science Research. As its objective, the conference sought to delineate areas of research to better understand the connection between specific illnesses and health challenges in the built environment. A broad spectrum of people representing community organizations, state and local departments of health, academic researchers, and federal agencies participated. Speakers described current research, discussed the state of the science, explored future directions and challenges in developing sustainable communities that seek to balance the social, economic, cultural, and ecological infrastructure with human health and development.

NIEHS Leadership Retreat

NIEHS organized a Leadership Retreat on May 19-21, 2003. One theme was "Urban Planning and Environmental Health". Recognizing that obesity is escalating as a public health problem, the focus of this session was to delineate environmental factors that affect obesity, such as housing, transportation, limited physical environments for physical activity, etc.

The NIH Obesity Research Task Force

Subsequent to the above meetings, a number of Institutes, Centers, and Offices (ICs) of the NIH have recently taken new actions to augment their obesity research portfolios, supporting extramural research at academic and medical institutions throughout the U.S., and intramural studies on the NIH campus and satellite facilities. The complexity of the problem of obesity dictated that the NIH takes a more collaborative and multi-disciplinary approach. Thus, in the spring of 2003 the NIH Director created the "NIH Obesity Research Task Force" as a new effort to facilitate progress in obesity research across the NIH, enhancing and synergizing the efforts of individual ICs.

The aim of the Task Force includes developing an NIH Strategic Plan for Obesity Research (to be released in February/March 2004), monitoring implementation of the plan and reporting progress to the NIH Director and IC Directors, and serving as a point of contact between the NIH and relevant external agencies. A key element in framing the Strategic Plan for Obesity Research is input from extramural scientists and the public. The strategic plan is based on the identification of areas of greatest scientific opportunity and need, and seeks to maximize collaboration among the ICs and to capitalize on their expertise in developing initiatives. A component of the planning process includes the development of a coordinated Intramural obesity research program. The agenda on Built Environment and Obesity is an initiative that has been adopted by this Task Force.

Future Conference

To further explore research avenues on the theme of the built environment and obesity, a conference is being planned on the topic in May 24-26, 2004. Details of the conference can be found at: http://www.niehs.nih.gov/drcpt/beoconf/.

Program Strategy

The studies in this program on Built Environment and Obesity will delineate the significance and impact of urban design and development on individual and population health by understanding the roles played by planning, housing structure, transportation issues, and the availability of public and green spaces as determinants of physical activity, nutrition, and access to healthy foods. The outcome of this program is to improve public health and impact policy by developing urban models that would promote environmentally healthful lifestyles. These models would identify and create index variables of healthful environments. While the goal is to improve the health of the community, it is also important to develop and evaluate new cost-effective interventions that promote healthful environments. This program will support studies that seek to understand mechanisms by which the built environment influences obesity.

Awareness of environmental health consequences requires not only collaborative partnerships but also the adoption of multidisciplinary research approaches to environmental health, such as studies that include public health researchers, health professionals, architects, builders, planners, and transportation officials. Such multidisciplinary coalitions with an interdisciplinary perspective would be better equipped to develop indicators and measures of sustainable communities and to elucidate their association with environmental health.

From previous meetings and conferences held on the built environment and health the following are some of the research recommendations that emerged:

- Develop effective environmental measures and indicators for understanding sustainable communities.

- Identify and quantify risk factors and variables that mediate and moderate built environment health effects for public health interventions and outcomes, e.g., measures of nutrition and dietary intake, physical activity.

- Assess and further develop existing models that will enhance our ability to study how and when environmental factors (such as sidewalks, accessibility to grocery stores and nutritious foods, green spaces) affect human health, specifically obesity.

- Conduct multidisciplinary research on the positive health impacts of sustainable and planned communities.

- Develop models to incorporate cost-effectiveness of developing sustainable communities that promote health and weight loss.

- Examine the role of the social environment (including but not limited to social capital, issues surrounding isolated communities) and its interaction with the physical environment in impacting weight loss.

- Develop multilevel techniques of measurement and longitudinal models of analysis for assessing the impact of the built environment/sustainable communities on health promotion. These measures and models should account for individual, community, and systemic variables including biological factors, socioeconomic factors, and neighborhood and physical environment variables.

- Incorporate community based participatory research processes to understand the relationship between the built environment and healthful lifestyles leading to a reduction in obesity.

The projects under this program would also incorporate methods and channels to translate research findings into policy and to the community-at-large to improve public health.

Management Plan

In collaboration with several institutes and centers at NIH (National Institute of Child Health and Human Development, Office of Behavioral and Social Sciences), other federal agencies (such as HUD and CDC), NIEHS seeks to develop an inter-agency, interdisciplinary research and intervention program. The plan is to announce a collaborative request for application (RFA). The RFA will be announced in Spring-Summer 2004 with a council review in mid 2005 and funding later the same year. The plan is to announce a request for application (RFA) with funding of $3 million from NIEHS, including $1 million from the NIH Director's Fund. Additional funding may be forthcoming from NICHD, OBSSR, other NIH Institutes, and other federal agencies such as DOT or HUD.