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 September 15-16, 2003

The National Advisory Environmental Health Sciences Council was convened for its one hundred tenth regular meeting on September 15, at 8:30 a.m., in Rodbell Auditorium, Building 101, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The meeting was open to the public from 8:30 a.m. until 5:30 p.m.. The meeting was closed for consideration of grant applications on September 16, 8:30 a.m. - 12:30 p.m. Dr. Kenneth Olden presided as Chair on September 15-16, 2003.

Members Present:

Dan Baden, Ph.D.
Joan Cranmer, Ph.D., ATS
Dale Eastman
George Friedman-Jimenez, M.D.
Michael Gallo, Ph.D.
Bernard Goldstein, M.D., Ph.D.
Frederick P. Guengerich, Ph.D.
Daniel W. Nebert, M.D.
Peggy Shepard
Frank Talamantes, Ph.D.
Peter Thorne, Ph.D.
James G. Townsel, Ph.D.

Members Absent:

Martyn T. Smith, Ph.D.
Charli Coon, J.D.
George Gray, Ph.D.
Deborah Brooks
Deeohn Ferris, J.D.

Ex Officio Members Present:

Eric L. Stephens

Ex Officio Members Absent:

Kelly Brix, M.D., M.P.H.

Liaison Members Present:

Drue Barrett, Ph.D. - CDC

Members of the Public Present:

Not Applicable

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
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dorothy Duke
Sally Eckert-Tilotta, Ph.D.
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
Edith Lee
Francine Little
Elizabeth Maull, Ph.D.
Carolyn Mason
Patrick Mastin, Ph.D.
Liam O'Fallon
Michelle Owens
Joan Packenham, Ph.D.
Jerry Phelps

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

Other Federal Staff:

Peggy Jones - FDA
Bradley Glasscock, FDA
Patricia Greenwel, Ph.D.- CSR

I. CALL TO ORDER AND OPENING REMARKS

The one hundred tenth 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 May 19, 2003, MEETING

Council accepted the minutes without change.

FUTURE COUNCIL MEETING DATES

February 23-24, 2004 NIH (Bethesda)
May 17-19, 2004 NIEHS with Leadership retreat
September 13-14, 2004 NIEHS

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

Dr. Olden began his report by commenting on the budget for NIH. The House and Senate have proposed a mark for FY04 but no appropriation has yet been passed. The House proposed an increase of 2.7% to $630 million and the Senate, had an increase of 3.7% to $637 million for NIEHS. These increases are not as large as the increases in the past and will not likely be in the next few years. The VA/HUD appropriation was increased 3.38% by which is also lower than previous years.

Dr. Olden noted the Institute of Medicine Report on the organization of NIH, a summary of which was provided. This report was requested by Congress and discussed at the NIH Leadership retreat to begin preparing a response for reauthorization hearings. Dr. Olden discussed each point of the report and the perspective of NIH.

Dr. Olden commented on the Roadmap initiatives under consideration for FY04 and FY05. Funding for these initiatives will come from the Office of the Director and proportional contributions from each Institute or Center (IC). These funds will be identified as "Roadmap" and will not go into the base for the lead institute. One of the initiatives deals with nanotechnology, and the National Toxicology Program is beginning a related effort to review nominations for toxicity testing of nanoparticles.

Dr. Olden sees the importance of expanding translation beyond clinical implications to public health and hopes that this will be incorporated into Roadmap goals. He reminded Council that funding of trans-NIH issues, while important, will have impact on IC budgets, since the bottom line of budget is the same and there is no additional money from Congress.

The NIH reauthorization hearings will be held soon. Congress will hear from a number of NIH constituencies. These will have impact on subsequent appropriation language, even if NIH is not reauthorized.

There is a trans-NIH Obesity Research Task Force. The built environment is where the NIEHS will take the lead on this initiative. This has been discussed at the Council meetings and retreat as part of our planning process.

Dr. Olden stated that NIEHS employs a 3-prong approach to prevention of human illness: identification of risk factors or causes of disease; development of measures to eliminate or reduce risk; and translation of knowledge and technology gained into practice. The various programs that have been put into place in this approach include the Environmental Genome Project, the National Center for Toxicogenomics, consortia and multi-disciplinary centers, and community outreach and public education programs. These have grown over the years, as the NIEHS budget growth has been in line with those of most institutes since 1993, as opposed to negative growth in the 1983-1991 period, based on real dollars.

In concluding his report, Dr. Olden mentioned the status of some other programs as well as recent conferences and publications. He specifically reported on the recent meeting of the Public Interest Liaison Group in New York City, at which Senator Hilary Rodham Clinton spoke.

Dr. Olden then announced to the Council his resignation plans and thanked the Council for its support.

The Council had questions about the search process for the new institute director. An announcement will be widely distributed through journals and other means, and there will be a search committee chaired by Dr. Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases and Dr. Tom Insel, Director, National Institute of Mental Health. The committee will be typical of the NIH process, with members chosen on the basis of scientific credentials and with input from Dr. Zerhouni.

The Council also had concerns about the appropriation language. Dr. Olden explained that the language referring to ALS but no other neurodegenerative disease was the result of the impact of public interest groups. The Council's concerns about prevention in reauthorization language could be made known to Congress through individuals or professional societies. Council members also expressed some concern that prevention is not apparent in the Roadmap initiatives.

V. "Parkinson's Consortium Center Directors Update on Progress" Dr. Cindy Lawler, Dr. Donato Di Monte, Dr. MarieFrancoise Chesselet and Dr. Timothy Greenamyre (Attachment B)

Dr. Cindy Lawler introduced the program by telling about the administrative structure of the NIEHS Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Program and the programmatic highlights.

Dr. Di Monte discussed the four integrated multi-disciplinary projects that are being carried out by the investigators at the Parkinson's Institute. The first project involves the epidemiological assessment of occupational and avocational risk factors for Parkinson's disease (PD) in four different populations. Dr. Caroline M. Tanner in collaboration with Dr. Kathleen Giacomini will also determine if PD risk is affected in individuals carrying polymorphic variants of genes encoding xenobiotic-specific transporters. The second project is led by Dr. Di Monte and the purpose is to evaluate interactions between a-synuclein and neuroteoxicants in animal models and to test the hypothesis that such interactions could explain how environmental agents contirbute to the pathogenesis of PD. The third study will assess the role of oxidative stress in toxicant-induced PD-like pathology. The fourth project is aimed at elucidating the mechanistic basis by which cigarette smoking may prevent neurodegeneration in PD.

Dr. Chesselet commented on the value of the pilot grants used for the first year to develop new models. The central hypothesis of the proposed UCLA-CGEP is that the gene and environmental toxins combine to increase the risk for PD in susceptible individuals through an interplay between pesticides and mechanisms regulating dopamine homeostasis.

Dr. Greenamyre commented on the purpose of the Emory CCPDER which is to perform collaborative research on PD pathogenesis, with a focus on gene-environment interactions. With the aging of the U.S. population, the prevalence and importance of these disorders is growing and there is overwhelming evidence that environmental factors are important in PD pathogenesis. This is an area where NIEHS is uniquely positioned to make a huge impact. New developments of the center are an established external advisory committee, monthly meetings

with Pis or principal investigators, postdocs, students and Pilot PIs. In 2002-03 there were six pilot project applications and in 2003-04 there will be twelve pilot project applications.

VI. The Fogarty Program - Dr. Gerald Keusch

The Fogarty International Center (FIC) was established in 1968 and today one hundred percent of Fogarty International Center activities are dedicated to reducing disparities in global health and advancing health research in low and middle-income countries. There have been successes in the 20th Century such as: receptors and cell signaling mechanisms, immunology, imaging, genetics, genomics, and gene-environment, proteomics and designer drugs. However, there have also been disappointments of the 20th Century: increasing discrepancies in health between rich and poor; the 90/10 disparity in research allocations; neglected diseases; and failure to use available technology are just a few.

Health status is not determined only by services or science, moreover it is determined by factors such as political stability, population growth and healthcare delivery systems. Without new and significant interventions the expectations for the 21st Century are more old, poor and hungry; more crowding; more risk of communicable disease; more pollution and environmental degradation; and more political instability, violence and terrorism. The Strategic Plans of Fogarty International Center include some of the following: concentrating resources on developing countries; research and training on communicable diseases; and building capacity for research from basic to applied.

The FIC-NIEHS Partnerships include: International Training and Research Program in Environmental and Occupational Health; International Collaborative Genetics Research Training Program and Ecology of Infectious Diseases. There are also FIC-NIEHS Initiatives that include: career paths for women in science and in developing countries and gene and environment linkages - public health genetics. Dr. Keusch emphasized the importance of investing in people, to have infrastructure and people "on the ground" in developing countries to do research.

VII. Comparative Toxicogenomics Database - Dr. Carolyn Mattingly (Attachment C)

The Mount Desert Island Biological Laboratory (MDIBL) is developing the Comparative Toxicogenomics Database (CTD) to promote understanding about gene-environment interactions. The CTD will be the first publicly available, curated database devoted to genes and proteins of human toxicological significance. The goals of the CTD include: toxicological curation of genes, proteins and sequences; platform for comparative studies of toxicologically significant genes; representation of diverse organisms; and the integration of molecular and toxicology resources. The researchers are curating toxicologically significant genes based on those identified as environmentally responsive by the NIEHS Environmental Genome Project.

Dr. Mattingly discussed the next steps planned by the group. These include ongoing curation, gene sets, sequence-gene-toxicant associations, and integration of comparative analysis results. Eventually, this will include integration of expression data, toxicologic curation, and a platform for comparative studies of toxiocologically significant genes.

VIII. Environmental Health Perspectives - Dr. Tom Goehl (Attachment D)

Dr. Goehl provided a historical perspective of the Environmental Health Perspectives (EHP's) growth and also presented plans for the future growth. EHP is the journal of the NIEHS and is an important vehicle for the dissemination of environmental health information and research findings. EHP was first published in 1972 with 12 regular monthly issues. In 1993, EHP transformed into a monthly publication plus a series of supplements. There are special sections devoted to children's environmental health and environmental medicine. EHP also publishes an annual review issue as a separate issue, and four quarterly Toxicogenomics section issues. Other publications include special monograph issues and a Chinese-language edition.

The journal provides many value added services. There is an ehponline web site that includes EHP archives and a search by topic option. There is an Environews section, Science Selection, Book Reviews, Calendar of Events, Position Announcements, and Extramural Updates.

The journal is the second most cited environmental science journal and has an international outreach program that includes complimentary subscriptions to readers in developing countries and a Chinese-language edition published quarterly and distributed to 35,000 readers. The journal's "In This Issue" section, which encapsulates each issue's news and research content, is available on the EHP website in five languages: Chinese, French, Japanese, Russian, and Spanish.

The journal's circulation includes a print distribution of 7,000 copies, and the electronic subscriptions comprise 25,000 users from more than 145 countries. More than 85,000 individual users visit the site each month.

IX. Update on Agricultural Health Study and Prostate Cancer Risk - Dr. Dale Sandler (Attachment E)

The Agricultural Health Study (AHS) is a long-term prospective study of potential health effects associated with pesticides and other agricultural exposures. Farmers have been reported to be at increased risk for some cancers, including cancers of the hematopoeitic system, connective tissue, skin, brain, prostrate, stomach and lip. The study is a collaboration of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the US Environmental Protection Agency. Between 1993 and 1997, more than 57,000 licensed applicators, representing 82% of the eligible private pesticide applicators (largely farmers) in Iowa and North Carolina and 43% of commercial applicators from Iowa were enrolled. More than 32,000 spouses of farmer applicators were also enrolled. The first wave of follow-up interviews with participants began in 1999 and will be completed this year.

Between enrollment and December 31, 2000, a total of 2504 new cases of cancer were diagnosed among applicators. There was a small but significantly increased risk of prostate cancer in the private applicators. Other cancers previously to linked to pesticides or farming were elevated, including lip cancer among applicators and melanoma among spouses.

The interactions between family history and pesticide exposure suggests the possibility of shared genes or other exposures that increase susceptibility to adverse effects of these pesticides. The study will continue to identify new cases of prostate cancer among applicators.

Future activities include a re-analysis or prostate cancer-pesticide relationships next year when about 500 additional prostate cancers will be available. A nested case-control study is being planned to evaluate gen-pesticide interactions in the development of prostate cancer.

X. Obesity and the Environment - Dr. Allen Dearry (Attachment F)

Dr. Dearry commented on the article in the American Journal of Public Health, September 2003, Vol 93, that he co-authored with Dr. Shobha Srinivasan and Liam R. O'Fallon, MA, "Initiating a Research Agenda on the Built Environment and Public Health." The National Health and Nutrition Survey data from 1999-2000 show that about 65% of the adult population in the United States are overweight and that 31% are obese. If the weight gain continues at this rate, the obesity rate will approach 40% within the next five years.

The built environment and physical activity are influenced by zoning, planning and architectural issues, building designs that mitigate the use of stairs, and city planning and zoning that often ignore pedestrian traffic. NIEHS plans to address the built environment and obesity in the following ways:

- Education
- Research
- Collaborations

The RW Johnson Foundation (RWJF) has 25 communities which implement active living programs, policies, and communication strategies. There is a special emphasis on low and mixed income communities. The NIEHS partnership with RWJF is to provide an evaluation of the program.

There is also the NIH Obesity Research Task Force that was established in April 2003 to facilitate progress in obesity research. It is developing an NIH strategic plan for obesity research based on identification of areas of greatest scientific opportunity and need. The FY2005 Obesity Initiative Concept Proposals are:

- The Built Environment and Obesity
- Genetics and Genomics of Obesity and Progression to Comorbidities
- Neurobiologic Basis of Human Obesity
- Prevention and Treatment of Pediatric Obesity in Primary Care Settings

XI. Superfund Basic Research Program External Advisory Group Report - Dr. Dan Baden (Attachment G)

Dr. Baden reported on the Superfund Basic Research Program (SBRP) which was created under the 1986 Superfund Amendments and Reauthorization Act to establish a university-based

research program to help address the wide array of scientific uncertainties facing the Environmental Protection Agency's Superfund program.

The SBRP is preparing to release annual Requests for Applications (RFA), beginning in Fall 2003. In February 2003 the NIEHS established an ad hoc External Advisory Group (EAG) as a working group of the National Advisory Environmental Health Sciences Council.

The EAG recommended that the SBRP continue the integrated science approach in its funded research programs while working to develop additional mechanisms to identify and address unmet needs and emerging issues. The EAG's view of the overal quality of SBRP-funded research and results is very favorable. The EAG found the Program to be strong, relevant, and well-focused to address its mandates.

XII. Report of the Deputy Director, NIEHS - Dr. Samuel Wilson

Dr. Wilson presented some information about the distribution of the NIEHS grants portfolio in relation to disease burden, which will be useful in long-range planning. His conclusion was that our portfolio is widely distributed among the areas within our mission and responsive to needs and priorities.

He also then challenged the Council regarding new thoughts on approaches to exposure assessment, particularly in relation to the broader definition of environmental factors and greater precision due to "omics" and other new technologies and animal models. New approaches might include health-oriented exposure assessment, which would use diseases incidence and mortality, which can be measured precisely; or indicator-oriented exposure assessment, employing multiple domains, including, for example, fate and trasport/bioavailabity, regional modeling, and general environmental sampling. Both of these approaches could be viewed as hypothesis-generating research to grow this field as a research enterprise. He suggested that a focus on early biological response/stress might be a new way of approaching exposure assessment.

XIII. Report of the Director, DERT - Dr. Anne Sassaman (Attachment H)

Dr. Sassaman referred the Council to the Featured Activities of the Division of Extramural Research and Training (DERT) in the agenda book for information on the many workshops and conferences in which NIEHS staff have been leaders. She introduced Dr. David Balshaw, a new program administrator in the Center for Risk and Ingrated Science, and announced the selection of Dr. Gwen Collman as Chief, Susceptibility and Population Health Branch and Dr. Pat Mastin as Chief, Cellular, Organ, and Systems Toxicology Branch. Dr. Mastin replaces Dr. Michael McClure, who retired September 1 after many years of service to NIH.

She then gave a brief summary of the NIH Botanicals Research Centers Program in which NIEHS participates, presented the recommendations from a recent review by an expert panel regarding future solicitations and management, and a concept for Council review for a readvertisement of the program. Council unanimously approved the concept.

Next Dr. Sassaman reviewed with Council the results of the FY03 Extramural Loan Repayment Program, which includes a clinical research program and a pediatric research program. The NIEHS budget for this program was $446,000, which funded 12 investigators, 3 in the clinical program and 9 in the pediatrics program.

She concluded her remarks with comments on the status of FY03 funding for Research Project Grants and the extent of NIEHS participation in activities with other institutes via co-funding.

XIV. Report of the Director, DIR - Dr. Lutz Birnbaumer (Attachment I)

Dr. Birnbaumer gave the Council and update on the staff of the Davison of Intramural Research in various categories of Principal Investigators, staff scientists, and others, and described current recruitments. He spoke of hopes of establishing a "clinical center south," for which NIEHS has submitted a business plan to NIH. Space on campus is filled at present with the staff on board and planned recruitments. There is no room for programmatic expansion, and new space would be required. Funds for construction are difficult to obtain and funding is very competitive.

He closed his report by acknowledging the changes ahead with Dr. Olden's departure and his desire that the new director would find a strong intramural program when he or she arrives.

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).

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

XV. REVIEW OF APPLICATIONS

The Council considered 341 applications requesting $117,127,112 in total cost. The Council recommended 197 applications with the total cost of $68,725,545.

XVI. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 12:30 pm on September 16, 2003.

ATTACHMENTS:

To view some of these documents you will need to have Adobe Reader. You may download a copy at *Adobe Reader*.

A. Council Roster

B. Parkinson's Disease Consortium Update

- Environmental Risk Factors and Gene-Environment Interactions in Parkinson's Disease: Investigations at the Parkinson's Institute as Part of the CCPDER by Donato A. Di Monte
- The Center for Gene-Environment Studies in Parkinson Disease at UCLA by Dr. Marie-Francoise Chesselet
- Emory CCPDER by Dr. Greenamyre

C. Comparative Toxicogenomics Database

D. Environmental Health Perspectives

E. Update on Agricultural Health Study and Prostate Cancer Risk

F. Obesity and the Environment

G. Superfund Basic Research Program External Advisory Group Report

H. Report of the Director, DERT

I. Report of the Director, DIR

Environmental Risk Factors and Gene-Environment Interactions in Parkinson's Disease: Investigations at the Parkinson's Institute as Part of the CCPDER
by Donato A. Di Monte

As part of the Collaborative Center for Parkinson's Disease Environmental Research (CCPDER), four integrated multi-disciplinary projects are being carried out by investigators at the Parkinson's Institute. The first project, entitled "Genes, Environment and Parkinson's Disease," is led by Dr. Caroline M. Tanner and involves the epidemiological assessment of occupational and avocational risk factors for Parkinson's disease (PD) in four different populations. In collaboration with Dr. Kathleen Giacomini at UCSF, Dr. Tanner will also determine if PD risk is affected in individuals carrying polymorphic variants of genes encoding xenobiotic-specific transporters. The second project is entitled "Neurotoxicants, Oxidative Stress and α-Synuclein in PD" and is led by Dr. Donato A. Di Monte. The protein α-synuclein has recently been implicated in the pathological process underlying PD. The purpose of these studies is to evaluate interactions between α-synuclein and neurotoxicants in animal models and to test the hypothesis that such interactions could explain how environmental agents contribute to the pathogenesis of PD. Dr. Di Monte's work is closely related to the work of Dr. Julie K. Andersen (at the Buck Institute), who leads the third project entitled "Iron, Oxidative Stress and Pesticides in PD". Both these projects will assess the role of oxidative stress in toxicant-induced PD-like pathology. Dr. Andersen will focus on the effects of increased iron level as a risk factor for neuronal injury in the substantia nigra (the area of the brain that is targeted by the neurodegenerative process in PD) and will determine how iron levels, toxicant exposures and oxidative stress may be affected by aging (PD is an age-related disease). Epidemiological studies have identified potential adverse risk factors for PD (e.g. exposure to pesticides) as well as one relatively undisputed protective association, i.e. the inverse correlation between PD and cigarette smoking. The fourth project is aimed at elucidating the mechanistic basis by which cigarette smoking may prevent neurodegeneration in PD. It is entitled "Nicotine and Neuroprotection in Non-Human Primates" and is led by Drs. Maryka Quik and J. William Langston. It will test the hypotheses that a specific subunit of the nicotinic receptor (the α6*) mediates the neuroprotective action of nicotine (and hence cigarette smoking) and that this neuroprotection involves a receptor-dependent increase in neurotrophic factors (bFGF and BDNF). These studies could lead to the development of new therapeutic strategies. In particular, specific nicotinic receptor agonists could reproduce the beneficial effects of smoking against PD. Overall, the integrated effort of investigators involved in these four projects should yield valuable insights into mutations and polymorphisms in relevant PD genes, environmental risk factors for PD, the role of oxidative stress and protein aggregation in PD pathogenesis, mechanisms of neuroprotection and the development of new animal models of PD (all critical research opportunities identified by the original RFA for the CCPDER). Furthermore, scientific achievements in these fields will undoubtedly be fostered by collaborations among the three Institutions that comprise the CCPDER, the Parkinson's Institute, Emory University and UCLA.

The Center for Gene-Environment Studies in Parkinson Disease at UCLA

Dr. Marie-Francoise Chesselet

The Center for Gene-Environment studies in Parkinson disease at UCLA (UCLA-CGEP) bridges three major NIH and VA-supported awards in Parkinson's disease (PD) and one NIH-sponsored study of Huntington's disease. The central hypothesis of the proposed UCLA-CGEP is that gene and environmental toxins combine to increase the risk for PD in susceptible individuals through an interplay between pesticides and mechanisms regulating dopamine homeostasis. We postulate that critical factors in this interaction are oxidative stress and resulting alterations in proteasomal function. Project I "Environmental toxins and genes that influence dopamine in Drosophila and humans" will examine interindividual variability of dopamine vesicular transporter (VMAT) expression due to promoter variants in two human populations in parallel with a reporter gene assay. These populations will be genotyped for functional VMAT2 variants and association analyses of
gene-environment interactions and pesticide exposures collected in the parent grant will be conducted. In addition, Drosophila genetics will be used to determine how the expression of VMAT affects dopamine-mediated toxicity and identify genes that modulate VMAT function, which will then be examined in the human population for their relevance to increased risk of PD. Project II "Interaction between pesticides and genetic alterations in dopamine homeostasis in mice" will test the hypothesis that pesticides and genetic variations in combination increase the vulnerability of dopaminergic neurons, and that one of the mechanisms involved is oxidative stress. Genetically engineered mice with a reduction in expression of VMAT or the cytoplasmic dopamine transporters, and mice with altered expression of alpha-synuclein and parkin, two proteins known to cause familial PD, will be examined. Behavior and quantitative anatomy will be used to assess the
effect of pesticides on dopaminergic neurons in these genetically altered mice. Histology, gene expression profiling, in vivo neurochemistry and slice electrophysiology will be used to examine the role of oxidative stress in this interaction. Project III, "Pesticides and Proteasomal Dysfunction:

genetic susceptibility in cellular models" will test the hypothesis that proteasomal dysfunction is central to the deleterious effects of the combined environmental and genetic insults. Cell lines, primary neuronal cultures from genetically altered mice, and human lymphoblasts will be
examined.

Emory CCPDER Center
Dr. Timothy Greenamyre

The purpose of the Emory CCPDER is to perform cutting-edge collaborative research on PD pathogenesis, with a focus on gene-environment interactions. The CCPDER brings together 3 established investigators - Drs. Greenamyre, Levey and Miller - who are each individually interested in the pathogenesis of PD and the roles that gene-environment interactions play in this disorder. Drs. Greenamyre and Levey bring both clinical and basic research perspectives to the Center. Dr. Miller brings an environmental toxicologist's point of view to the group. The proposed research will take place under the auspices of the new Center for Neurodegenerative Diseases (CND) in the recently completed Whitehead Research Building, where the investigators will share contiguous lab space and core equipment and facilities. The Emory CCPDER will capitalize on the expertise of each individual project leader in a truly collaborative, multidisciplinary endeavor in which the investigators will literally interact on a daily basis. The CCPDER consists of 3 integrative research projects supported by a Research Development Core. There are no Scientific Cores because the CND was conceived as a facility that would contain most necessary core facilities within its walls, with free access to all facilities by all CND investigators. Project 1 expands the rotenone model of PD into mice and organotypic slice cultures in order to examine gene-environment interactions in this model. It will also screen other similar pesticides for their ability to cause PD, and it will screen neuro-protective strategies. Project 2 examines the vesicular monoamine transporter (VMAT2) as a target of environmental toxicants, such as organochlorines. Genetic approaches will be used to manipulate VMAT2 and examine its interactions with genes important in PD pathogenesis, such as alpha-synuclein. Project 3 is a genetic and pathological study of a new genetic linkage to PD, PARK10, which has been associated with increased risk of 'sporadic' PD in Iceland. Sporadic PD patients will be evaluated at Emory and high-density genome scans will be performed. Candidate genes have been identified and antibodies raised to the gene products. These will be assessed in human postmortem brain specimens and in experimental models of PD. The projects and administrative core involve molecular neurobiology, human genetics, clinical research, education, and collaboration with a PD epidemiologist. Common themes of the interactive projects include pesticides, gene-environment interactions, the ubiquitin/proteasome system, and dopamine. Each of the projects capitalizes on one or more existing funded projects. This fact, together with the core facilities of the CND allows us to leverage the requested funds for maximal effect.

The Comparative Toxicogenomics Database (CTD): New Perspectives Through Data Integration and Curation

Carolyn J. Mattingly[1], Glenn T. Colby[1], Michael C. Rosenstein[1], John N. Forrest[2], and James L. Boyer[2]
[1] Mount Desert Island Biological Laboratory, Salisbury Cove, ME 04672; [2]Department of Medicine, Yale University School of Medicine, New Haven, CT 06520

The Mount Desert Island Biological Laboratory (MDIBL) is developing the Comparative Toxicogenomics Database (CTD) to promote understanding about gene-environment interactions. Since 1898, investigators at MDIBL have exploited the power of comparative biology using marine and freshwater models in physiology, molecular biology and toxicology research. In this tradition, CTD will facilitate comparative studies of toxicologically significant genes in evolutionarily diverse organisms. The goal is that these comparisons will provide important insights into molecular evolution, the significance of conserved sequences and the genetic basis of variable sensitivity to environmental agents.

CTD will be the first publicly available, curated database devoted to genes and proteins of human toxicological significance. Major goals of this resource include: 1) curating and integrating sequence, reference and toxicant data for toxicologically important genes and proteins; 2) promoting comparative studies of these genes and proteins in divergent species; and 3) integrating information from existing molecular and toxicology resources. We are developing CTD using a phased implementation approach in which the content, functionality and level of data integration are enhanced incrementally.

The core data in CTD include nucleotide and amino acid sequences from vertebrates and invertebrates and references from the published literature. Within this comprehensive data set, we are curating toxicologically significant genes based on those identified as environmentally responsive by the NIEHS Environmental Genome Project. Currently, CTD curation includes creating explicit associations between sequences, references and toxicants, as well as between sequences and genes through the novel concept of a Gene Set. Whereas many molecular databases present sequences in isolation, Gene Sets present them in a comparative context by grouping all sequences from diverse species for a gene or related genes. Curated Gene Sets also consist of text descriptions and an inclusive collection of synonyms, references and toxicants associated with member genes. This format provides users with a comprehensive and comparative perspective of available sequences for toxicologically relevant genes and proteins and a foundation on which they may analyze sequences across species. Data in CTD is highly integrated with information from many other biological resources and several controlled vocabularies. Continued curation and integration of toxicology resources (eg, TOXNET) are current priorities for CTD development. We continue to evaluate the needs of the biological and toxicological communities and will expand our curation efforts accordingly. This expansion may include enhancing the scope of manual curation, integrating results from comparative sequence analyses with curated data in CTD and including toxicological microarray data from aquatic organisms.

Environmental Health Perspectives

Overview and Future Plans

Thomas J. Goehl, Ph.D.
Editor-in-Chief

Environmental Health Perspectives, the journal of the NIEHS, is an important vehicle for the dissemination of environmental health information and research findings. With an impact factor of 3.45, *EHP* ranks second of the 132 environmental sciences journals and sixth of the 90 public, environmental, and occupational health journals. *EHP* is read in every country of the world.

EHP publishes12 regular monthly issues with sections devoted to children's environmental health and environmental medicine. Mini-monographs are published frequently throughout the year. *EHP* also publishes an annual review issue and, as a separate issue, a quarterly Toxicogenomics section.

Electronic submission and review are the norm for the more than 800 manuscripts that *EHP* receives each year. All articles are published within 24 hours of acceptance on our website as *EHP*-in-Press articles. These articles are completely citable using the CrossRef DOI system.

The journal provides many value added services. The journal's Environews section provides analysis of topical issues. Science Selections summarizes selected research papers appearing in the same issue, putting current *EHP* research findings into perspective. Other services include book reviews of important current publications, a calendar of events, position announcements, and updates on the latest news from the NIEHS Division of Extramural Research and Training. Our website (http://www.ehponline.org), contains archived *EHP* issues and provides a search-by-topic feature.

EHP has an international outreach program that includes complimentary subscriptions to readers in developing countries and a Chinese-language edition published quarterly and distributed to 35,000 readers. In addition, the journal's "In This Issue" section, which encapsulates each issue's news and research content, is available on the *EHP* website in five languages: Chinese, French, Japanese, Russian, and Spanish.

Our circulation includes a print distribution of 7,000 copies, and our electronic subscriptions comprise 25,000 users from more 145 countries. More than 85,000 individual users visit the site each month, and 1,000,000 files are served.

Future plans call for a separate children's health section to be published quarterly, an expanded environmental medicine section, and an audio web segment ("*EHP* Speaks"). We also plan to become an Open Access journal and participate in the Fogarty International Center's African journal partnership.

The Agricultural Health Study
Prostate Cancer Risk

Farmers have been reported to be at increased risk for some cancers, including cancers of the hematopoeitic system, connective tissue, skin, brain, prostate, stomach and lip. Farmers are exposed to pesticides, solvents, fuels and oils, engine exhaust, dust, animals and other hazards, but previous studies generally have not been large enough or have not included enough detailed information about specific exposures, making it difficult to interpret results.

We are examining cancer incidence and other health endpoints in licensed pesticide applicators and spouses from North Carolina and Iowa. The Agricultural Health Study (AHS) is a long-term prospective study of potential health effects associated with pesticides and other agricultural exposures. The study is a collaboration of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the US Environmental Protection Agency. Between 1993 and 1997, we enrolled more than 57,000 licensed applicators, representing 82% of eligible private pesticide applicators (largely farmers) in Iowa and North Carolina and 43% of commercial applicators from Iowa. More than 32,000 spouses of farmer applicators also enrolled. A first wave of follow-up interviews with participants began in 1999 and will be completed this year. Cohort members are matched annually to vital statistics and population-based cancer registries in each state to determine mortality and cancer incidence.

Between enrollment and December 31, 2000, a total of 2,504 new cases of cancer were diagnosed among applicators. In an initial evaluation of cancer incidence, rates among applicators were compared to the expected rates in each state, adjusted for age- and calendar year[1]. After an average 5.3 years of follow-up, the overall cancer incidence among the private applicators and their spouses was lower than expected, with standardized incidence ratios (SIR) of 0.80 and 0.83. The cancer incidence among commercial applicators was similar to that expected (SIR = 1.01). Private applicators had a small but significantly increased risk of prostate cancer (SIR = 1.16, 95% CI 1.07-1.25). Although not significantly increased, some other cancers previously linked to pesticides or farming were elevated, including lip cancer among applicators and melanoma among spouses. Female applicators had significantly more ovarian cancer, but results were based on a small number of observed cases. Commercial applicators who are on average 9 years younger than private applicators also had increased risk for prostate cancer compared to the rates of similarly aged men in Iowa (SIR =1.29), although this risk was not statistically significant.

Farming and working with pesticides have previously been associated with prostate cancer. Potential farm-related risk factors include exposure to insecticides, fertilizers, herbicides, and other chemicals, although the role of specific chemicals has not been firmly established. In more detailed evaluation of the role of agricultural factors in the development of prostate cancer, internal analyses were used to compare exposed with unexposed cohort members.

Through December 31, 1999, 566 new cases of prostate cancer had been diagnosed among 55,332 male private and commercial pesticide applicators with no history of prostate cancer at enrollment, This was by far the most common type of cancer occurring in the cohort, with a standardized incidence ratio of 1.14 (95% CI = 1.05-1.24). To explore this risk further, we

compared applicators who developed prostate cancer to the remaining cohort members to identify potential risk factors[2].

Prostate cancer risk increased with age and with family history of prostate cancer. Risk also tended to be higher for nonwhites, smokers, and those with more than a high school education. Other potential life style risk factors and non-farm occupational exposures were not associated with prostate cancer in this population.

We evaluated risk associated with a total of 50 specific pesticides – 18 herbicides, 22 insecticides, 6 fungicides, and 4 fumigants. For 22 of these, we had detailed information from the enrollment questionnaire for all applicators. For the remaining 28 pesticides, details such as frequency and duration of use were available only for the subset of applicators who had completed a comprehensive take-home questionnaire. We carried out a factor analysis to identify patterns of pesticide use, and computed several measures of pesticide exposure including ever use, application days per year, total years of exposure, an exposure intensity index which takes into account application method, use of protective equipment, and whether the applicator repaired application equipment which would tend to increase exposure, and a cumulative pesticide exposure score which multiplied together application days, years of exposure, and exposure intensity. A second exposure intensity index took into account additional details concerning mixing and application methods, and other factors and behaviors that could modify exposure available for those who completed the take-home questionnaire.

Prostate cancer risk was associated with a pesticide use pattern characterized by older age, and use of chlorinated pesticides including aldrin, chlordane, dieldrin, DDT, heptachlor, and toxaphene as well as two chlorinated phenoxy herbicides, 2,4,5-T and 2,4,5-TP. Ever use of several of these individual pesticides was associated with increased prostate cancer risk, but no clear dose response trends were seen. Ever use of the fumigant methyl bromide was associated with a slight but not significant increase in risk (odds ratio (OR) = 1.10, 95% CI=0.77-1.36) but the odds of prostate cancer increased significantly with increasing cumulative exposure. Compared with no exposure, the risk of prostate cancer for applicators at the highest level of exposure was increased 3.5-fold.

A family history of prostate cancer appeared to modify risks associated with several chemicals. Whereas little or no risk was observed among persons without a family history of prostate cancer, among those with a family history, prostate cancer risk was significantly associated with exposure to butylate, aldicarb, carbofuran, coumaphos, 2,2-dichloroethenyl, fonofos, permethrin, and phorate, and odds ratios were suggestively increased for several additional chemicals. In many instances, the differences between those with and without a family history represented significant interactions.

While the results linking a pattern of organochlorine pesticide use and prostate cancer are intriguing, the fact that no individual chemical was associated with an exposure–response relationship suggests that the relationship between prostate cancer and chlorinated pesticides could be due to other factors that are correlated with this pesticide use pattern. The only statistically significant dose-response trend we observed was for methyl bromide. This could be a chance observation, but other factors suggest the association should be further evaluated.

Methyl bromide was significantly associated with prostate cancer in both states and in both private and commercial applicators. The association was seen with more than one exposure metric, and the inclusion of other pesticides in the statistical models did not alter results. Methyl bromide is an alkylating agent considered by NIOSH to be a potential occupational carcinogen. Small experimental studies provide evidence of genotoxicity, and industrial hygiene studies demonstrate high concentrations of methyl bromide in the breathing zone of agricultural workers performing soil fumigation under tarps. Even so, if methyl bromide is responsible for an elevated prostate cancer risk, it may be only among the most highly exposed. This could also be a chance finding as there was no prior evidence for an association with prostate cancer risk.

Family history of prostate cancer was associated with a nearly 2-fold increase in prostate cancer risk in this cohort. The interactions between family history and pesticide exposure suggest the possibility of shared genes or other exposures that increase susceptibility to adverse effects of these pesticides. We will continue to identify new cases of prostate cancer among applicators. As part of our follow-up efforts, we are collecting buccal cells to obtain DNA for genetic analyses. The role of specific gene polymorphisms that may play a role will be explored in the future as more cases accrue.

Future activities planned include a re-analysis of prostate cancer – pesticide relationships next year when about 500 additional prostate cancers will be available. A nested case-control study is being planned to evaluate gene – pesticide interactions in the development of prostate cancer.

1. Alavanja MCR, Sandler DP, Lynch C, Knott C, Lubin JH, Tarone R, Thomas K, Dosemeci M. Barker J, Hoppin J. Blair A. Cancer incidence in the Agricultural Health Study. In press, Scand J Work, Env, Health.

2. Alavanja MCR, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA. Barker J. Cobel J, Sandler DP, Blair A. Use of Agricultural pesticides and prostate cancer risk in the Agricultural Health Study Cohort. Amer J Epidemiol 2003;257:800-814.

Executive Summary

Report of the 2003 SBRP External Advisory Group
A Working Group of the National Advisory Environmental Health Council
August 2003

The National Institute of Environmental Health Sciences' (NIEHS) Superfund Basic Research Program (SBRP) was created under the 1986 Superfund Amendments and Reauthorization Act (SARA) to establish a university-based research program to help address the wide array of scientific uncertainties facing the Environmental Protection Agency's (EPA) Superfund program. Until 2001, when Congress chose to provide the Program funds directly to NIEHS, the SBRP received its funds as pass through dollars from EPA. This change in funding strategy expands the research opportunities for the Program as it strives to address its mandates and allows for the use of additional funding mechanisms as well as changes to the grant award cycle.

The SBRP is preparing to release annual Requests for Applications (RFA), beginning in Fall 2003. As the Program plans for the future, NIEHS considered an external review of the SBRP essential. In February of 2003, the NIEHS established an ad hoc External Advisory Group (EAG) as a subcommittee of the National Advisory Environmental Health Sciences Council. The EAG, which consisted of sixteen individuals representing academia, industry, and federal and state agencies, served to identify the strengths and areas of productivity of the Program and assess the efforts undertaken to communicate the science emanating from the Program. In addition, the group provided insights on potential future directions for the Program. The EAG did not evaluate specific SBRP programs or individual projects within the programs, this having been conducted via competitive application and independent peer review processes.

Research and Programmatic Issues

The EAG review of the current status of the Program focused on the scope of the science funded, internal and external communication efforts, and programmatic management. The EAG believes that the SBRP is an active, vibrant, and significant program, citing the overall historical quality and relevance of SBRP-funded research and results. The EAG determined that SBRP-funded research remains highly relevant to the EPA Superfund goals, noting that the SBRP has been successful at enhancing investigations and remediation work at many hazardous waste sites across the country.

Research: The SBRP is the only NIEHS or NIH program to fund both biomedical and nonbiomedical research within the structure of a multi-project grant. The SBRP strives to assemble researchers from diverse disciplines to focus on a unifying theme. This cross-cutting focus and multidisciplinary nature enable the SBRP to address the range of environmental problems that exist at hazardous waste sites. The resultant synergy between biomedical and nonbiomedical projects research projects is crucial to the development of holistic evaluations of hazardous waste sites.

The SBRP has always emphasized the importance of a firm public health foundation and is well positioned to meet the challenge of translating research findings into public health practice. The multidisciplinary structure of the Program places it in a in a strong position to address complex public health issues that cannot be adequately resolved through the contributions of a single scientific discipline. The Programmatic goal that basic research should lead to application is an important feature of the SBRP and supporting an effective integrated research approach maximizes the likelihood of achieving this goal.

The EAG recommended that the SBRP continue the integrated science approach in its funded research programs while working to develop additional mechanisms to identify and address unmet needs and emerging issues.

Communication: Without question, technology transfer, in the broadest sense, is the SBRP's raison d'etre. Because of the ultimate goals of the SBRP -- that is, enhancing decision making -- the research results must be freely communicated at several levels, from the scientific community, to other agencies and to those affected. The Program views information and technology transfer activities to be a shared responsibility with efforts required by both the Program staff and the grantees. The grantees address this responsibility through technology and information transfer, community outreach and training.

Clearly technology and information transfer must be concerned with converting research results into practical applications. Grantees have selected several approaches to foster this exchange:

- SPRP grantees have an impressive record of peer-reviewed publications, with over 6,500 publications in the scientific literature. The existing SBRP web-accessible database containing all publications resulting from SBRP sponsorship is excellent. Suggested further refinements to the web search features will enhance the ability to access this rich data set.
- SBRP researchers communicate their findings at local, national and international scientific meetings, resulting in a successful transfer of science and technology both within and external to the scientific community. The EAG considered this activity to be laudable.
- A significant amount of SBRP-funded science has been converted to patents, suggesting current and future commercialization to field or other laboratory applications; however, the EAG recognized that it is difficult to assess other areas that have not progressed to the same extent.
- SBRP grantees have conducted research at more than 100 hazardous waste sites, which demonstrates the successful reduction of SBRP research to practice.
- In 2002, the Program established Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Initiatives designed to foster development of field applications of science and technology in the private sector. This mechanism appears to be a potentially valuable mechanism to promote the movement of science into commercial or other field use.

The EAG recognized that Outreach has become a natural extension and an integral part of the Program; however, the EAG recommended that Outreach should be more effectively presented in future RFAs by more explicitly identifying overall outreach goals, priorities and audiences.

The concept of a multidisciplinary approach is also an integral aspect of SBRP-funded training and has a major impact on graduate and post-graduate students. The SBRP provides an environment that fosters the development of multi-faceted investigators within the interdisciplinary framework required to meet complex human and environmental health challenges. The EAG recommendations to enhance the SBRP's training efforts included increased involvement of students in Outreach activities and formal post-graduation tracking of students for documentation and evaluation purposes.

Management: There is a clear sense of commitment to the mission of the SBRP by the Program staff who actively works to promote the Program and continually seeks ways to assist individual SBRP-funded programs in getting their message out. The SBRP staff has reached out to EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and state agencies with the intent of promoting the use of the Program's research results and identifying potential future research needs. The EAG recommended that SBRP staff should continue to build upon its communication with EPA regions when SBRP-funded research involves investigations and applied technology at specific Superfund sites.

The SBRP staff has established several programmatic tools and information transfer mechanisms that serve as important common resources to the SBRP. These resources, which include the SBRP

web site, the monthly Research Briefs, web-base seminars and support for scientific meetings and lectures, provide an important foundation for facilitating and tracking the efficacy of technology transfer within, across, and outside of institutional SBRP grantees. With respect to the existing resources, the EAG recommended (1) restructuring of the web site to emphasize the overall science and technology output and value of the SBRP; (2) increasing the distribution of the Research Briefs to additional industry sectors; and (3) using the Research Briefs to illustrate science/technology transfers between investigators within, across or external to their funded institution.

To ensure the growth and continued relevance of the SBRP, clearly defined program assessment plans such as metrics need to be incorporated into planning activities. The Program currently uses a variety of data to evaluate program successes; these include numbers of publications, patents, and students trained. The EAG recommended that additional qualitative metrics be incorporated to evaluate synergy, publication impact, graduate student success or career relevance, and success of technology transfer. The EAG noted that approaches to collecting and evaluating these, or other, measures are not yet developed.

Future Directions

Since its inception, the SBRP has been on the forefront of health and environmental research -- the SBRP's proactive, interdisciplinary approach is clearly exemplified by its early recognition of and involvement in research related to arsenic contamination, children's environmental health, and the value of use of wildlife as indicators of public health. The SBRP continues to look to the future and strives to maintain the cutting-edge nature of the Program. The EAG attempted to provide guidance in future directions for SBRP, placing particular emphasis on two aspects: utilization of existing and emerging cutting-edge science tools and approaches; and encouraging innovative, cross-cutting, systems level interdisciplinary approaches. EAG discussion led to observations on particular research areas where members see the opportunity for innovative research that will be relevant to the SBRP mission. Many of these concepts build upon current Program elements and activities.

The EAG was encouraged to note that several current research projects utilize new tools and methods that are being developed through basic research in biomolecular sciences, especially those that relate to gene-environment relationships. To remain relevant and cutting-edge, the EAG recommended that the SBRP consider new research avenues including:

- development and application of scientific approaches and methods that will advance the integration of human and ecological risk assessment;
- utilization of a dynamic systems level approach to site characterization;
- development and application of methods to examine the theoretical and empirical connectivity between human health and ecological condition;
- design and implementation of studies to examine strategies for information transfer to communities and the resulting impacts on community attitudes and actions; and
- inclusion of researchers from a wider breadth of academic disciplines such as sociology, economics, ethnology, anthropology, psychology/behavioral medicine, and bioethics and philosophy to add additional insight to research design, interpretation, and communication.

In addition, the EAG recommended that the SBRP increase its emphasis on:

- development and application of advanced sensor systems to enhance site characterization;
- development and application of scientific approaches and methods that will advance the integration of biological systems and chemical-physical processes in mechanistic studies of environmental processes;
- development and application of new analysis and visualization methods to interpret environmental information;
- development and application of more vigorous mathematical methods to model environmental data;

- application of “omics” technologies to investigate the human and ecosystem health impacts of exposure-dose levels representative of real-world conditions at hazardous waste sites;
- development and application of increasingly sophisticated and innovative remediation approaches that rely on cooperative efforts of researchers from multiple disciplines;
- development and application of creative approaches to examine remediation and risk management such as those that involve theoretical approaches based on computational and statistically-based biological models;
- design and implementation of studies related to specific community groups who may be especially affected, such as the aged, children, and minorities or low-income populations; and
- development of interdisciplinary approaches to the study of Superfund events, sites, and chemicals to serve as a mechanism to further the synergistic goals of the SBRP.

To be positioned to most effectively address interdisciplinary research, the EAG felt that the SBRP should encourage the sharing of expertise among the SBRP community. Accordingly, mechanisms should be developed and applied that decrease impediments to inter-program collaboration. The goal would be to foster the sharing of resources, expertise, and to include increased scientific and logistical interchange amongst program directors. The committee also recommended the broadening of SBRP grant mechanisms beyond the “P” series to include a variety of types of “R” series grants to fulfill the Program mandates.

The EAG acknowledges several limitations to its evaluation and recommendations for future direction of the SBRP:

- The list of observations and opportunities for the future is by no means comprehensive nor can it be, given the pace of innovation in contemporary science;
- The EAG recognizes that the NIEHS does not direct the research envisioned and that the Program will consist of funded grant applications, approved on the basis of scientific quality; and
- While acknowledging resource restrictions faced by the Program, the EAG did not consider the resource issues generated by its observations and recommendations.

The EAG’s view of the overall quality of SBRP-funded research and results is very favorable. The EAG believes that over the past 16 years the SBRP has established a remarkable record of research and outreach through its support of over 60 programs. The EAG found the Program to be strong, relevant, and well-focused to address its mandates. With respect to the future direction of the Program, the EAG believes that the SBPR has built a firm foundation to increase opportunities to merge cutting-edge technologies with hypothesis-driven research. The EAG supports the SBRP’s aim to apply systems approaches using innovative technologies to address environmental health issues. The EAG regards the SBRP strategy of annual competition as a valuable opportunity for the Program to become increasingly responsive to emerging issues.

The EAG believes that this review of the SBRP accurately reflects our perceptions and study of the present status of the Program. Recommendations for future directions or improvement of the Program represent our best efforts, based on the information supplied and acquired. The EAG would like to acknowledge the assistance received during this process. The SBRP staff provided extensive background materials and was available to provide additional information as needed. Mr. Larry Reed, EPA, served as Executive Secretary, functioning as liaison between the EAG and SBRP staff. Mr. Reed provided invaluable support to Dr. Daniel Baden and the entire EAG. We are also appreciative of the editorial support provided by Ms. Kerry Murray and Ms. Maureen Avakian of MDB, Inc.

FEATURED ACTIVITIES of DERT
October 2003

MEETINGS

Genes, Environment & Disease
June 7-9, 2003
Harvard School of Public Health and the Seaport Hotel
Boston, Massachusetts

Drs. Joan Packenham, Kimberly Gray, and Elizabeth Maull, SPHB, in conjunction with the Harvard Comparative Mouse Genomics Center, organized and convened a scientific symposium under the auspices of the Environmental Genome Project titled"Genes, Environment and Disease." This meeting was held on June 7-9 in Boston, Massachusetts, at the Harvard School of Public Health and Seaport Hotel. The scientific symposium was designed to examine the role of genetic variation in gene-environment interactions, emerging technologies used in the study of genetic variation, and to examine issues of ethics and social consequences related to the discovery of environmentally responsive genes in human populations.

Symposium Goals
The mission of the Environmental Genome Project is"to improve the understanding of human genetic susceptibility to environmental exposures." The goals of the year meeting were:

1. To review the state-of-the-art research relevant to gene-environment interactions and human genetic susceptibility, with a focus on the impact of these factors on human health and disease,

2. To foster dialog and discussion that may lead to new directions for the Environmental Genome Project,

3. To encourage and facilitate multidisciplinary discussion about issues related to studying genetic susceptibility of environmentally induced diseases in the laboratory setting and within human populations, and

4. To educate and inform scientists in all Environmental Genome Project-related disciplines about programs, resources, and future needs in order to facilitate new research initiatives.

Following the symposium on June 9, EGP scientists, invited experts and NIEHS program staff participated in a Roundtable Discussion, moderated by Drs. Packenham and Gray. The goals of this discussion session were:

1. To initiate and facilitate discussion between EGP scientists who study genetic susceptibility to environmentally-induced disease in mouse models and EGP molecular epidemiologists who study genetic susceptibility in human populations; and
2. To enhance current and plan future activities of the EGP.

Highlights and Summary:

The following four themes emerged during the roundtable discussion:

1. The size of the DNA sample set and number of candidate genes targeted for EGP resequencing;

2. The need for an ethnically defined DNA sample set;

3. The interface between human population-based molecular epidemiology and animal model-based molecular genetics;

4. Mechanisms to enhance progress in functional analysis of SNPs and/or molecular epidemiology.

    - Although consensus was not reached during this discussion, the majority of participants supported increasing the size of the sample set for EGP resequencing and to determine if the samples could be ethnically defined.

    - The discussants emphasized the importance of SNP validation and functional characterization of SNPs in the current set of candidate genes.

    - Methods development is the most prevalent concern in order to enhance the interface between molecular epidemiology in human populations and molecular genetics in animal models.

    - Mechanisms that promote data sharing and sample sharing, as well as high throughput inexpensive genotyping and resequencing technology would facilitate progress in molecular epidemiology.

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Eighth International Congress on Toxic Combustion By-Products
June 16-19
Umea, Sweden

The goal of the Eighth International Congress on Toxic Combustion By-Products was to provide an international forum to discuss topics on the origins, fate, and health effects of combustion. This field has gained significant relevance to worldwide environmental policy, as risk-based programs increasingly rely on the ability of advanced scientific research to provide mechanistic, diagnostic, and analytical answers to complex problems concerning air toxic exposure. The meeting brought together industrial, governmental, and academic researchers involved in basic and applied

engineering technologies and in health-related research in order to both identify and resolve key issues.

Congress sessions included Organic Pollutants, Metals in Combustion, Thermal Waste Treatment, Ash Treatment, By-product Monitoring and Emission Control.

Meeting Highlights

The meeting (1) critically examined the impact of mechanistic/toxicological knowledge of combustion by-products on human and ecological systems; (2) identified processes and principles related to the exposure to combustion by-products; and (3) discussed the development and application of innovative engineering technologies to reduce the amount and/or toxicity of combustion by-products.

Research on toxic combustion by-products may be characterized by its complexity – that is the complexity of the number of agents, complexity of their interactions, complexity of their sources and origins, and complexity of their environmental fates. A number of recommendations have come from these international congresses, among them are:

- Advanced methods are needed for characterization of the bioavailability of particle-associated pollutants. Fine particles can act as effective delivery systems for toxic chemicals, but the bioavailability of the toxins depends upon the nature of their interaction with the particles. Advanced methods for characterizing the nature of association and binding of stable molecular as well as radical species with various types of particles are essential.

- Improved computational methods for modeling gas and particle properties are needed. Detailed reaction kinetic mechanisms of pollutant formation and fate require accurate thermochemical and reaction rate parameters.

- Rapid microarray techniques should be applied for assessing potential health impacts of individual pollutants and mixtures. The varied and complex products formed in combustion systems can potentially induce a variety of health impacts alone or in combination in a manner that has previously defied characterization. Application of the rapidly advancing field of microarray technology to screening for various biological endpoints of individual pollutants and mixtures should be used to address this poorly understood but critical component of environmental health

- Additional research should be conducted to increase our understanding of the composition, sources, and health impacts of ultrafine particles and nano-particles. Atmospheric studies should determine the composition of ultrafine particles, as well as nano-particles; determine the ratios of elemental carbon (EC) to organic carbon (OC) in airborne particulate matter; identify the main sources for ultrafine and nano-particles; and identify alterations of ultrafine and nano-particles by time and by location.

- Research in toxicology should be advanced to determine the fate of ultrafine particles and nanoparticles during inhalation and after deposition (dosimetry); determine translocation rates to other extrapulmonary tissues and influence of particle chemistry on such translocation; evaluate specific cellular and molecular mechanisms via both animal and *in vitro* studies; develop and use compromised animal models; and to apply toxicogenomics and proteomics in mechanistic studies.

- Concerted and focused efforts should be made to fulfill the potential of biomarkers to significantly reduce the burden of exposure and disease and to protect individuals from the uncertainty of risk, specifically in the area of exposure and effects of combustion by-products.

Dr. William Suk, CRIS, served on the organizing committee for the 8th International Congress. The 8th International Congress is directly related to ongoing research of NIEHS, primarily in the area of assessing and evaluating risk in humans and in research issues germane to chemical exposure from hazardous substances. It was supported, in part, by the Superfund Basic Research Program. Other co-sponsors included the U.S. Environmental Protection Agency, the Coalition for Responsible Waste Incineration, Louisiana State University, University of California, Berkeley, Umea University, and the United Nations Environment Programme.

The 9th International Congress on Combustion By-Products is scheduled for June, 2005, at the University of Arizona.

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Metabolic Profiling: Application to Toxicology and Risk Reduction
An International Conference
May 14-15, 2003
Research Triangle Park, North Carolina

The NIEHS/NIH/DHHS cosponsored an international conference on "Metabolic Profiling: Application to Toxicology and Risk Reduction" with the Office of Rare Diseases/NIH/DHHS, Food and Drug Administration, Paradigm Genetics and Waters Corporation. The meeting, held May 14-15 in Research Triangle Park, North Carolina, convened a multidisciplinary group of research and computational scientists from academia, industry and government to define the state of the science for the emerging area of metabolic profiling, also called metabonomics or metabolomics, and its application in basic and applied health research.The conference agenda and selected presentations can be found at http://www.niehs.nih.gov/dert/metabol.htm. A summary of the science of metabolomics as well as future research directions and challenges are summarized here. A full meeting report will be published later this year*Dr. Brenda Weis, CRIS*, was the lead organizer of this meeting.

Metabolites are the end products of cellular processes and their levels reflect the integrated response of biological systems to genetic and environmental influences.Metabolic profiling is defined as a high throughput approach to measuring and interpreting the complex, time-related

concentration, activity and flux of endogenous metabolites in biosamples (urine, blood, tissues, cells).

- Metabolomics is a new word but not a new science. Studies aimed at measuring metabolites in biological systems have been ongoing for over 50 years with a long history of studies on intermediary metabolism. What is new is the ability to measure and quantify the full complement of metabolites in biosamples, thus, greatly enhancing our capability for scientific discovery. Integration of old and new studies is needed.

- The metabolome is an integral part of biological pathways and networks,"downstream" of the genome and the proteome and more directly influenced by external agents such as diet, drugs, disease, and chemicals. Integrated studies involving these complementary datasets are needed to construct models of how biological pathways, networks and systems function in producing toxicity and delivering health. This challenging task will require new databases and computational tools.

- The metabolome is complex, involving a range of small molecules (peptides, lipids, amino acids) with varying size, structure, polarity and function. There are several metabolomics technologies in use, including LC-MS/MS, NMR, FT-MS. More work is needed to evaluate and improve the sensitivity and specificity of these technologies for a variety of applications (blood, urine, cells, cellular compartments).

- There are ongoing efforts to link changes in metabolite profiles to histological changes in target organs and tissues. These studies should be expanded to include multiple time points and species, and to address normal variations in metabolites, in order to validate the use of metabolomics in predictive toxicology and risk assessment. Specific emphasis should be placed on describing the dynamics of metabolite activity and flux in biological systems.

- Metabolomics approaches are being applied to drug development, detection of adverse responses and disease diagnosis. Defining metabolite profiles in blood and urine samples has been used to classify the status and progression of metabolic disorders, diabetes, and neurodegenerative, renal and cardiovascular diseases. Additional studies are needed to define the underlying biological mechanisms in order to personalize clinical diagnosis, treatment and prevention.

- The field of metabonomics offers tremendous opportunities for environmental health research; however, relatively little work has been devoted to environmental or occupational exposures. NIEHS should take the lead and foster partnerships among federal agencies, academia and industry to advance the application to toxicology and disease risk reduction.

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Embryonic Stem Cell Biomedicine: The Journey from Mice to Patients

May 15-17, 2003
University of Pittsburgh, Pittsburgh, Pennsylvania

Human Stem Cells (HSCs) and Human Embryonic Stem Cells (hESCs) have burst upon the biomedical/medical research scene like no other"breakthrough" advance in the health sciences in the last thirty years save one – whole animal cloning. The NIEHS has moved quickly to explore the potential of human stem cells for environmental health sciences research and environmental medicine applications. Unlike cloning, human HSCs bear a more immediate promise of new tools for research and new medical treatments for previously intractable human diseases and disorders.

Background

Dr. McClure, former Chief COSPB, organized a brainstorming session on November 18, 2002, to explore the potential in environmental health sciences research of embryonic stem cell research. Nearly two-thirds of the investigators leading major stem cell research programs attended. As an outcome, the NIEHS sponsored this international human embryonic stem cell research symposium. Dr. McClure co-organized the symposium with Dr. Gerald Schatten, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Dr. McClure introduced and moderated a session in the symposium, which also involved a number of NIEHS scientists. The symposium was held contiguous with the 1st Annual Human Embryonic Stem Cell Research Training Course funded by the OD, NIH. Dr. McClure served on the faculty for the training course. He also served on the organizing committee for the June 12, 2003 NIH Director's conference entitled "NIH Research: Recent Progress and Future Promise of Human Embryonic Stem Cells and moderated the introductory session on "stem cell plasticity." This conference followed contiguously with the First Annual meeting of the International Society for Stem Cell Research in Washington, D.C. as coordinated with the NIH Stem Cell Research Implementation Committee.

Research Recommendations

A number of research recommendations have come from the May 15-17 meeting, together with the other stem cell research meetings convened by or with the assistance of the NIEHS:

- The development of advanced methods for characterizing and validating HSCs and hESCs identities and potency is needed.

- Improved *in vitro* culture methods for HSCs or hESCs that will maintain their initial state of potency are needed. Additionally, reliable culture methods are needed that do not rely on animal/human cell feeder layers (prevent disease transmission risk) and predictably allow expansion of the parent cell populations.

- Research should be conducted to increase our understanding of the signaling molecules and mechanisms that communicate instructions guiding HSCs or hESCs into and through defined differentiation pathways leading to tissue-specific cell types.In particular, the role of genomic imprinting in regulating genomic gene networks associated with the progressive restriction of cell potential needs to be aggressively explored.

- The metabonomics and metabalonomics of stem cells differentiating into cell lineages needs to be actively studied *in vitro* to establish paradigms for translation to the *in vivo* circumstance of the progeny cell growth, regulation and life potential.

- Engraftment research must be aggressively pursued to identify and characterize the host individual's acceptance parameters that are required to ensure the integration of stem cell progeny into the target tissue or organ. The pathobiology of engraftment failure must be explored deeply due to the risk of adding morbidity or mortality factors instead of ameliorating existing ones.

- hESCs from donors bearing defined genetic mutation(s), single nucleotide polymorphisms (SNPs), or complex genetic disease traits offer huge potential for modeling the human health consequences of such inborn traits. Studies of these knock-outs, knock-ins, knock-downs, knock-ups, or silenced genes or gene networks) could be translated to knowledge of the human condition with the highest degree of direct relevance.

    a. Comparative *in vitro* and *in vivo* effects of the allelic variations of the expression of such traits and how they contribute to genetic/epigenetic susceptibility to environmental toxicant or toxin exposure(s) should be thoroughly studied in *in vitro* stem cell models. This includes life-span animal model studies of host recipients derived from or bearing stem cell originated tissue/organ cell populations exposed to environmental agent or factor insult(s). Such studies of exposures to a toxicant or mixtures of toxicants could elucidate the consequences or predicted consequences of the related acute and chronic pathobiology to morbidity and mortality over the full lifespan of exposed individuals.

    b. Engraftment integrates animal or human stem cells of defined function and lifespan parameters into the tissues or organs of recipient animal models. This offers the potential to study "built-in" susceptibilities to environmental agent or factor exposures in animals of defined genetic backgrounds or to "build-in" resistance to same. Such research could lead to high efficiency "alternative models" for research on the effects of toxicant exposures in environmental health and risk assessment. Further, such research could lead to regenerative medicine treatments using stem cell based tissue engineering for the treatment of individuals injured by incidental, occupational or military tissue/organ environmental agent toxicities.

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DERT PAPERS OF NOTE

Uracil Positioning Affects Efficiency of Base Excision Repair Enzymes
Michael Smerdon, Ph.D., Washington State University and

Samuel Wilson, NIEHS
R01ES04106

Background: DNA damage can occur from a wide variety of environmental agents including UV and other sources of ionizing radiation and cancer-causing chemicals. As a major defense against environmental damage to cells, DNA repair systems are present in organisms as diverse as bacteria, yeast, fruit flies, fish, amphibians, rodents and humans. DNA repair is involved in processes that minimize cell killing, mutations, DNA copying errors, and genomic instability. Abnormalities in repair processes have been implicated in cancer and aging.

Advance: Researchers at the University of Washington and the National Institute of Environmental Health Sciences report here that DNA repair enzymes do a much better job of repairing damaged DNA depending on whether the orientation of repair enzymes is toward or away from nucleosomes. Nucleosomes are complexes of chromatin material and chromosomal protein structures known as histones. Histones act as spools around which DNA winds, thus facilitating its compaction so that the large genomes of advanced animals will fit into every cell nucleus.

Implications: This novel finding represents a new model for studying DNA repair and opens new insights into the efficiency of repair processes. It also has implications in possible therapeutic treatments aimed at improving repair mechanisms to prevent and treat serious diseases associated with DNA repair abnormalities such as cancer and Alzheimer's.

Citation: Beard BC, Wilson SH, Smerdon MJ. Suppressed catalytic activity of base excision repair enzymes on rotationally positioned uracil in nucleosomes. Proc Natl Acad Sci U S A. 2003 Jun 24;100(13):7465-70. Epub 2003 Jun 10.

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Sperm Abnormalities in Men Exposed to PCBs and PCDFs
George H. Lambert, MD
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R01ES11256

Background: Polychlorinated biphenyls (PCBs) were used in transformers and other industrial applications because of their superior insulating properties and stability. When the adverse health effects of this class of compounds were discovered in the 1970s, they were banned by much of the world. However, because of their persistence, they are among the most ubiquitous man-made environmental contaminants and are detectable in most human beings worldwide. Polychlorinated dibenzofurans (PCDFs) are produced when PCBs are burned and are equally persistent and toxic.

There are many instances of accidental poisonings from exposure to PCBs. One such incident occurred during a six-month period in Taiwan in 1978-1979. The poisoning was traced back to contaminated cooking oil. PCBs had leaked from heat exchangers into the finished oil product. The PCBs were partially degraded by the heat, which produced PCDFs and other chlorinated multi-ring compounds. Approximately 2,000 people consumed the contaminated oil in what became known as the Yucheng or "poison oil" incident. A registry of those exposed was created to track adverse health outcomes.

A previous study of prenatally exposed young men born to Yucheng women showed increased abnormal sperm morphology, reduced motility, and reduced fertility; however effects of post-natal exposures to PCBs/PCDFs are less well documented. The study described below assessed the sperm quality of men directly exposed to PCBs and PCDFs in the Yucheng incident.

Advance: As in the previous study, directly exposed men exhibited higher abnormal sperm morphology than controls. A standard measure of fertility, the ability of sperm to penetrate hamster oocytes, was also lower in the directly exposed men, just as it was in the earlier study. Other semen characteristics were similar between exposed and control subjects.

Implications: This is the first study to show adverse effects in sperm from men directly exposed to PCBs and PCDFs. These findings are compatible with a previous study of prenatally exposed men and also with animal studies investigating similar compounds. The male-to-female offspring ratio was reduced in Yucheng men exposed before age 20 years. The current data suggest that the reduced capability of oocyte penetration found in this study may be specific to Y chromosome-bearing sperm, but this has not been confirmed and warrants further investigation.

Citation: Hsu PC, Huang W, Yao WJ, Wu MH, Guo YL, Lambert GH. Sperm changes in men exposed to polychlorinated biphenyls and dibenzofurans. JAMA. 2003 Jun 11;289(22):2943-4.

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Birth Outcomes of Women Exposed to Dioxin in Seveso Italy

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R01ES07171 and P30ES01896

Background: On July 10, 1976, an explosion occurred at an chemical manufacturing facility in Seveso, Italy. Approximately 30 kg of dioxin were released into the environment resulting in the highest exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) known in human residential populations. Eleven communities in the densely populated area between Milan and Lake Como were contaminated. Researchers at the University of California Berkeley, along with colleagues in Italy at the University Milano-Bicocca, initiated the Seveso Women's Health Study to determine whether there was an association between TCDD exposure and adverse reproductive health outcomes.

TCDD is considered to be one of, if not the most toxic man-made substance. It has been shown to cause cancer and disrupt multiple endocrine functions. TCDD is a by-product of several manufacturing processes such as paper production and pesticide formulation. Among its varied effects, TCDD has been shown to cause increased fetal loss and reduced birth weight in animal studies.
Advance: In the current study, the pregnancy outcomes of 510 women representing 888 total pregnancies were examined in relation to TCDD in serum samples collected from these women shortly after the explosion. Ninety-seven of the pregnancies ended in spontaneous abortions. There were no significant associations between TCDD exposure and spontaneous abortion, birth weight, or births that were small for gestational age. However, although not statistically significant, there were stronger associations for birth weight and small for gestational age among pregnancies that occurred within the first eight years after exposure.

Implications: This study reports the lack of a statistically significant association between maternal serum levels of TCDD and adverse birth outcomes in this cohort of women. However, the authors state "It remains possible that the effects of TCDD on birth outcomes are yet to be observed, because the most heavily exposed women were the youngest at follow-up and therefore are less likely to have yet had a post-explosion pregnancy." Additional epidemiologic studies are planned to further investigate this exposure.

Citation: Eskenazi B, Mocarelli P, Warner M, Chee WY, Gerthoux PM, Samuels S, Needham LL, Patterson DG Jr. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. Environ Health Perspect. 2003 Jun;111(7):947-53.

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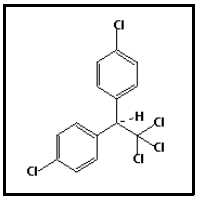
DDT and DDE: Second Generation Time to Pregnancy Effects
Barbara A. Cohn, Ph.D., MPH, MCP, NIEHS
Public Health Insittute, Berkeley, California
R01ES08345



Background: DDT was originally prepared in 1873, but it was not until 1939 that Paul Muller discovered the effectiveness of DDT as an insecticide. He was awarded the Nobel Prize in medicine and physiology in 1948 for this discovery.

The use of DDT increased enormously worldwide after World War II, primarily because of its effectiveness against the mosquito and lice. The World Health Organization estimates that during the period of its use approximately 25 million lives were saved predominantly from malaria and typhus. However, many species of insects developed resistance to DDT; it proved to have a high toxicity toward fish; and it was responsible for the near extinction of several bird species because of its interference with the formation of egg shells. For these reasons and because of its environmental persistence, the use of DDT was banned in the United States in 1972. However, It is still in use in some other parts of the world.

In mammals, DDT is of relatively low toxicity, but it does have troubling effects. DDT and its major metabolite, known as DDE, are persistent and are stored in fat tissue. DDT is know to have weak estrogenic activity and DDE has considerable anti-androgenic activity. They cross the placenta potentially interfering with fetal development. To further investigate possible effects on the human reproductive system, this team of investigators measured DDT and DDE levels in maternal serum samples collected from 1960-1963 in the Child Health and Development Studies. They compared these levels to the time to pregnancy in 289 daughters around 30 years later.

Advance: This is the first report to link DDT exposure in early life to human reproductive problems 30 years later. There was a clear association between increased DDT concentrations in maternal blood with a decreased chance of pregnancy in the daughters. For every 10 mg/L of DDT in maternal serum, the probability of pregnancy dropped 32%. However, quite unexpectedly, the chance of pregnancy increased 16% with each increase of 10 mg/L of DDE. The opposing effects of DDT and DDE may explain why large changes in reproductive performance have not been noticed in humans since the introduction of DDT.

Implications: Although the decreased fertility associated with *in utero* exposure to DDT remains unexplained, the authors speculate that the "antiandrogenic effects of DDE may mitigate harmful androgenic effects on the ovary during gestation and early life." This study demonstrates the long delay from exposure to noticeable effect. The findings support both the establishment of new long-term human studies that can monitor effects of environmental exposures on reproduction as well as continued support of existing studies where multigenerational follow-up is in progress.

Citation: Cohn BA, Cirillo PM, Wolff MS, Schwingl PJ, Cohen RD, Sholtz RI, Ferrara A, Christianson RE, van den Berg BJ, Siiteri PK. DDT and DDE exposure in mothers and time to pregnancy in daughters. Lancet. 2003 Jun 28;361(9376):2205-6.

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The Form of Vitamin E in Food Reduces Inflammation Triggers

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P01ES01896

Background: Chronic inflammation not only causes pain as in rheumatoid arthritis, it is also an important factor in fatal and disabling conditions such as asthma, hepatitis, diabetes, cancer, neurodegenerative disorders, cardiovascular disease, etc. Inflammatory responses are mediated by the production of compounds known as eicosanoids, which are derived from arachidonic acid. Prostaglandin E_2 (PGE_2), an eicosanoid produced by a cyclooxygenase-catalyzed oxidation reaction of arachidonic acid, is believed to cause pain and fever. PGE_2 and another oxidatively produced compound, leukotriene B_4 (LTB_4), and the enzymes that catalyze their production have been recognized as key targets for drug therapies in inflammation-associated diseases.

These researchers recently reported that g-tocopherol (gT), the major form of vitamin-E found in the U.S. diet, and its major metabolite inhibit the production of PGE_2. However, a-tocopherol (aT), the major form of vitamin-E found in tissues and in most vitamin supplements proved to be much less effective in this regard. The current study was performed to further investigate these effects in a mammalian model as opposed to an*in vitro* system.

Advance: Administration of gT, but not aT, to laboratory rats significantly reduced PGE_2 and LTB_4 synthesis. gT also significantly reduced the inflammation-mediated increase in a biomarker for lipid peroxidation. The inflammatory cytokine, tumor necrosis factor-a, was also reduced by gT.

Implication: This study shows the importance of gT in reducing the production of pro-inflammatory products and attenuated inflammation-mediated damage in a rat model.This observation, along with previous studies from this laboratory, strongly suggests that gT is important to human health and deserves further study. It also suggests that people suffering from inflammatory diseases might respond well to additional gT in their diet or from gT-containing supplements.

Citation: Jiang Q, Ames BN. Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats.FASEB J. 2003 May;17(8):816-22.

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Methylmercury Exposure from Ocean Fish Consumption and Neurodevelopment

Thomas Clarkson and Christopher Cox
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R01ES10219, R01ES08442, P30ES01247, and T32ES07371

Background: Exposure to methylmercury before birth has been shown to cause disruptions in neurobehavioral and cognitive development in children. The most common route of exposure is through maternal consumption of mercury-contaminated seafood products, but there have been conflicting reports on whether this level of exposure is harmful. NIEHS has funded to long-term studies on distinct populations of children in the Faeroe Islands and the Republic of Seychelles with distinctly different dietary exposures. The Faeroe Islanders consume whale meat while the Seychelle populations consumes only fish. The overriding question addressed by these studies is whether seafood consumption by pregnant and nursing women results in mercury exposures in their children at levels high enough to cause harm.

Advance: The study highlighted here was carried out in a population cohort, which consisted 779 mother-infant pairs residing in the Republic of Seychelles. The mothers reported consuming 12 meals of fish per week. These fish contained about the same concentrations of methylmercury as commercial ocean fish found elsewhere. Only two endpoints were associated with prenatal methylmercury exposure. Increased exposure was associated with decreased performance in a standardized motor control test and improved scores in the hyperactivity index of the Conner's teacher rating scale.

Implication: These data do not support the hypothesis that there is a neurodevelopmental risk from prenatal methylmercury exposure resulting solely from maternal ocean fish consumption. An accompanying editorial by Dr. Constantine G Lyketsos of the Division of Geriatric Psychiatry and Neuropsychiatry at Johns Hopkins Hospital reaches the same conclusion. "On balance, the existing evidence suggests that methylmercury exposure from fish consumption during pregnancy, of the level seen in most parts of the world, does not have measurable cognitive or behavioral effects in later childhood." The editorial goes on to state that "the positive findings from the Faeroe Islands and New Zealand studies may be related to the fact that pilotwhale blubber and shark muscle contain 5–7 times the concentrations of methylmercury than the fish consumed in the Seychelles." Dr. Lyketsos final conclusion is that "there is no reason for pregnant women to reduce fish consumption below current levels, which are probably safe."

Citation: Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding GE, Kost J, Huang LS, Clarkson TW. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet. 2003 May 17;361(9370):1686-92.

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Exposure to Second-Hand Tobacco Smoke Increases School Absenteeism in Children

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P01ES09581 and P30ES07048

Background: Research has shown that exposure to environmental tobacco smoke (ETS) is responsible for respiratory illnesses among young children; however, the ETS-associated morbidity for school-age children is less well defined.Previous research by this team has shown that asthma-related school absenteeism is a major problem in southern California accounting for a large portion of all absences. To determine the extent to which ETS exposure might be implicated in school absenteeism, the team investigated the relations between ETS exposure, asthma status, and illness-related school absences in 1,932 fourth-grade schoolchildren from 12 southern California communities.

Advance: Overall, ETS exposure was associated with a 27% increased risk of respiratory-illness-related school absences. Children living in a household with two or more smokers were at a substantially higher risk (75%) of such absences. Children with asthma were at increased risk of respiratory-illness-related school absences. When exposed to one smoker, the risk was 2.35 times higher and when exposed to two or more smokers, the risk increased to 4.45.

Implications: This study demonstrates that ETS exposure is associated with increased respiratory-related school absenteeism among children with much higher risks for children with asthma. Approximately 9 million children in the U.S. suffer from asthma, which causes millions of lost work hours for parents who must stay home from work to care for them. This research shows that ETS plays a major part in some of these absences and points out the need for smoking cessation programs, especially for the parents of children with asthma.

Citation: Gilliland FD, Berhane K, Islam T, Wenten M, Rappaport E, Avol E, Gauderman WJ, McConnell R, Peters JM. Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren. Am J Epidemiol. 2003 May 15;157(10):861-9.

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Triplet Repeats in the Myotonic Dystrophy Gene

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R01ES11347

Background: A recent report by Richard Sinden of Texas A&M University (J Mol Biol. 326(4):1095-11) described an unusual trinucleotide repeat sequence in the gene for spinocerebellar ataxia type 10. Genes in normal individuals contain short lengths of trinucleotide repeats in which a combination of nucleotides, the building blocks of DNA, are repeated a number of times, usually less than 30. Eighteen human genetic diseases have been associated with expansion of the number of these repeats, sometimes numbering in the thousands. These diseases

often become increasingly severe and have earlier onsets in successive generations.

A new study, from a different research team at Texas A&M, sheds light on repeat expansions in the gene for Myotonic Dystrophy (DM). DM is the most common inherited neuromuscular disease in humans affecting one in 8,000 people worldwide.

Advance: This paper describes a model system in which repeats of the trinucleotide sequence CTG from the DM gene are deposited into an intron in one copy of a tandemly duplicated pair of *APRT* genes. Selecting for homologous recombination between the duplicated copies of the gene enables the examination of changes to the inserted CTG repeats in cells located nearby a recombination event. Long CTG repeats experienced large contractions and generated a high frequency of rearrangements. Replicating cells displayed a high frequency of expansions and contractions that usually involve a small number of triplets. The results demonstrate that homologous recombination destabilizes long CTG repeats in this cell system.

Implication: The roles of contraction and rearrangements of trinucleotide repeat sequences, along with other aspects of DNA metabolism, in the development of triplet repeat diseases is unclear. This model offers insights on the mechanism of repeat expansion and may lead to further discoveries on how to prevent or repair these genetic defects. Scientists have theorized that if the cause of the repeat expansion can be discovered, there is hope in preventing them from occurring.

Citation: Meservy JL, Sargent RG, Iyer RR, Chan F, McKenzie GJ, Wells RD, Wilson JH. Long CTG tracts from the myotonic dystrophy gene induce deletions and rearrangements during recombination at the APRT locus in CHO cells. Mol Cell Biol. 2003 May;23(9):3152-62.

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Hydrogen Peroxide: A Messenger Important in Cancer Cell Survival

P. Andrew Karplus, Ph.D., Department of Biochemistry and Biophysics, Oregon State University
P30ES00210 (Joseph Beckman, Ph.D., Director)

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 are formed as a by-product. All aerobic organisms have evolved systems to control this simple molecule so that it doesn'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 hydrogen peroxide. The story might end there, but there is a growing body of evidence that hydrogen peroxide is important for cell signaling and communication. A team of researchers, using support from the NIEHS Center at Oregon State University, has discovered that differences in the bacterial and human forms of peroxiredoxin affect how well it functions. These findings suggest that the enzyme plays a role in cancer development.

Advance: The team showed that the human enzyme is over 100 times more sensitive to damage by hydrogen peroxide than is the bacterial enzyme, and they revealed the structural explanation of this difference. They postulated that this must have evolutionary value; that perhaps the human peroxiredoxin acts like a "floodgate" keeping resting levels in control, but allowing higher levels to signal the cell to undergo programmed cell death.

Implication: What started as a basic research investigation into the function of the enzyme turned out to have implications for cancer therapy. Some cancer drugs, such as cisplatin used in testicular cancer, cause an increase in the production of hydrogen peroxide killing the cells from the inside out. Cancer cells that are resistant to cisplatin or other cancer therapies such as radiation, seem to be making larger amounts of peroxiredoxin which degrades the hydrogen peroxide before it has a chance to kill the cell.

Citation: Wood ZA, Poole LB, Karplus PA. Peroxiredoxin evolution and the regulation of hydrogen peroxide signaling. Science. 2003 Apr 25;300(5619):650-3.

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Semen Quality Lower in Men from Rural Areas

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R01ES09916

Background: Many studies conducted over the last decade have reported large differences in semen quality parameters in men from different areas of the U.S. and in international studies as well. Comparisons of these studies are difficult because semen analyses are highly sensitive to the methods of semen collection and analysis. There are also indications that sperm concentrations declined dramatically during the 20th century; however, analytical differences again may be at least partially responsible for the decline.

In 1998, NIEHS funded the Study for Future Families, a multi-center study similar in design to multi-center studies being conducted collaboratively in Europe and Japan. The study's goal is to estimate the geographic variability of semen parameters in men in the U.S. and to compare the results to those from other centers worldwide. A NIEHS-supported researcher at the University of Missouri, Columbia, the coordinating center for the U.S. study, recently reported the results of analyses from men in four distinct geographic areas.

Advance: The team studied 512 men in four areas: Columbia, Missouri; Los Angeles, California; New York, New York; and Minneapolis, Minnesota. Sperm concentration and the total number of motile sperm were significantly lower for men from Columbia, Missouri than the other three centers. Total motile sperm was 58% lower in the Missouri men than the men from Minnesota. Although some of the men had low semen quality, it was not low enough to cause infertility, since the men were partners of pregnant women.

Implication: A possible reason for these differences could be higher exposure to pesticides in the more rural Missouri population than the other areas. Fifty-seven percent of the land in the Columbia area is used for farming which far exceeds that of the other areas. Many animal studies have shown that pesticides affect fertility; however, more research is needed to determine if this is the cause for the differences seen in this study. Additional research is being planned in Iowa City, Iowa, an area with even higher exposure to pesticides than Columbia.

Citation: Swan SH, Brazil C, Drobnis EZ, Liu F, Kruse RL, Hatch M, Redmon JB, Wang C, Overstreet JW, The Study For Future Families Research Group. Geographic differences in semen quality of fertile U.S. Males. Environ Health Perspect. 2003 Apr;111(4):414-20.

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Inhibition of IKK and NF-kB Prevents Inflammation but Increases Local Injury
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University of California San Diego
P42ES10337

Background: NFkB is a transcription factor that is a major regulator of immune responses stimulated by pro-inflammatory agents such as tumor necrosis factor, viruses, interleukin-1, and bacteria. NFkB normally resides in the cytoplasm bound by an inhibitory protein known as IkB. Phosphorylation of IkB by IkB kinase-b (IKK-b) releases NFkB, which then moves into the nucleus where it acts in the induction of numerous regulatory genes of the immune system. The products of these genes are pro-inflammatory factors.

This paper describes the role of NFkB in severe systemic inflammation and multiple organ dysfunction syndrome (MODS). MODS, a serious and often fatal condition, occurs in patients with septic and toxic shock and other systemic inflammatory response syndromes. Since activated nuclear NFkB is often found at sites of inflammation and infection, it is thought to be a key mediator of both acute and chronic inflammatory diseases such as septic shock and asthma. In MODS, activated neutrophils infiltrate tissues resulting in the release of proteases, reactive oxygen species and various cytokines and inflammatory mediators that contribute to tissue injury and failure. NFkB has been proposed as an important contributor in amplifying this response, but it is unclear whether it is crucial for initiating the inflammatory response.

Advance: Using a classic model to induce severe inflammation called gut ischemia-reperfusion in which the blood supply is cut off to the gastrointestinal tract for 30 minutes and then restored, these investigators determined that mice whose intestinal cells lacked IKK-b did not produce the predicted systemic inflammatory response. IKK-b works as a complex with two other proteins to allow activation of NFkB following infection. However, the lack of IKK-b caused severe damage to the reperfused intestinal mucosa in these mice because of apoptosis or programmed cell death. Therefore, therapeutically blocking the activity of IKK-b in humans would likely block the inflammatory response, preventing MODS. However, this would occur at the cost of severe tissue injury caused by programmed cell death. These results show the dual roles for the NFkB

system in both tissue protection and systemic inflammation.

Implication: This paper identifies two points that are important regarding future development and possible therapeutic use of IKK and NFkB inhibitors as anti-inflammatory agents.First, it provides "unequivocal and direct proof that NFkB is not just a marker of inflammation, but is the driving force for initiation and spread of acute and systemic inflammation". Second is " a primary role for NFkB activation in response to physical and chemical stressors is to protect the challenged cells or tissues from apoptosis." Although IKK-b and NFkB inhibitors are likely to be potent anti-inflammatory agents, this study underscores the potential danger of using them during severe inflammatory episodes caused by shock, trauma, and other critical illnesses.

Citation: Chen LW, Egan L, Li ZW, Greten FR, Kagnoff MF, Karin M. The two faces of IKK and NF-kappaB inhibition: prevention of systemic inflammation but increased local injury following intestinal ischemia-reperfusion. Nat Med. 2003 Apr 7.

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Low Levels of Lead and IQ Deficits
Bruce Lanphear, M.D., M.P.H., Cincinnati-Children's Hospital Medical Center and
Deborah A. Cory-Slechta, Ph.D., University of Rochester Medical Center
R01ES08388 and P30ES01247

Background: Among environmental hazards, lead is one of the most prevalent and dangerous to children. Lead poisoning was first recognized and describes as a distinct entity 100 years ago. Since then, numerous studies have shown that blood lead concentrations above 10 micrograms/deciliter (mg/dl) are associated with adverse outcomes on intellectual development, functioning and behavior. Much of this work was supported by NIEHS and led the Centers for Disease Control and Prevention (CDC) in 1991 to set the "level of concern" for lead at 10 mg/dl. Very little data exists documenting adverse effects at concentrations below this level; however, the CDC and the World Health Organization do not recognize a threshold for lead associated deficits.

Advance: In a 5-year study of 172 children, a team of NIEHS-supported researchers from the University of Rochester, Cincinnati Children's Hospital Medical Center, and Cornell University found that lead does cause intellectual impairment at low levels. The researchers found that IQ scores for children with blood lead levels at 10 mg/dl were about 7.4 points lower than for children at 1 mg/dl. Surprisingly, the study also concluded that as blood lead increased from 10 to 30 mg/dl, there was a more modest decline in IQ scores indicating that more damage occurs at lower levels for any given exposure.

Implication: The average blood lead level of children in the U.S. has been declining steadily since the removal of lead from gasoline and household paint. However, this study suggests that many more children--perhaps more than 1 out of 10--are affected by lead than previously

estimated. These data emphasize the importance of prevention and add further evidence that there is indeed no safe level of lead exposure.

Citation: Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N Engl J Med. 2003 Apr 17;348(16):1517-26.

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GRANTEE HONORS and AWARDS

James M. Tiedje, PhD., Michigan State University, has been elected to the National Academy of Sciences (NAS) in the scientific discipline of Environmental Sciences and Ecology. Dr. Tiedje is a current grantee of the Superfund Basic Research Program (SBRP) within Michigan State University's Project. His research is focused on understanding the ecology, physiology and molecular biology of microbial processes important in nature, including those that degrade environmental pollutants. According to the NAS, "In addition to fundamental contributions to the microbial ecology of biodegradation of anthropogenic compounds and of the nitrogen cycle, Tiedje has pioneered the use of molecular techniques to understand the nature and significance of microbial diversity in soils and sediments. He is the world's leading environmental microbiologist." Dr. Tiedje has also been elected as the incoming American Society for Microbiology's (ASM) President-Elect. He has been active in the ASM for many years, including service as Editor-in-Chief of *Applied and Environmental Microbiology* and was the recipient of its Environmental and Distinguished Service Awards. The ASM originated in 1899, and is considered the "oldest and largest life science membership organization in the world" with over 42,000 members. The ASM promotes the study of microbiological research and science and "their applications to the common good."

Bruce Weir, Ph.D., William Neal Reynolds Professor of statistics and genetics at North Carolina State University and one of the world's foremost researchers on statistical analysis of DNA for forensic, human health, and agricultural applications, was honored May 9 with the O. Max Gardner Award, the highest faculty award presented by the Board of Governors of the University of North Carolina.

STAFF HONORS and AWARDS

Dr. William Suk, was honored by the University of Cincinnati, with the *Roy E. Albert Memorial Award for Translational Research in Environmental Health.* The award was conferred at a workshop entitled "State Environmental and Health Agencies: Surviving in the Post 9/11 World", which was held at the Kingsgate Conference Center in Cincinnati, June 9. This award recognizes the efforts of those who have made major contributions to the advancement of science at the

interface between basic research in environmental health and practical applications to preventive medicine and/or public policy. An awardee may have had an outstanding career in research at this interface, or may have worked in an academic or governmental institution to promote outstanding research at this interface. The award was given to Dr. Suk for his work "fostering outstanding research at the interface of basic science, remediation of environmental contaminants, and public policy."

The following awards were made at the Grants Management Awards Ceremony, held Friday, June 6 in Gaithersburg, Maryland.

Ms. Dorothy Duke, GMB, received an Excellence in Leadership Award for her commitment and leadership as co-chair of the GMAC Vision Steering Committee (VCS) for the second, one year term. In this capacity she has served as organizer and facilitator of the monthly VSC meetings and has continuously provided leadership and direction to the Committee as a whole as well as its individual members. She maintained the VSC membership and GM Infonet database based on the new membership structure adopted August 2001 She initiated and organized a Principals only GMAC and VSC combined meeting on December18, 2002. This meeting was devoted to the review and evaluation of the missions and functions of the VSC and its's subcommittees. The meeting was productive and brought new insights and recommendations for future directions to the VSC.

Ms. Carolyn Mason, GMB, received from the Vision Steering Committee a Special Recognition Award for outstanding contributions to the IMPAC II GM Lead Users Group and the Grants Management community for participation in the GM Module Edit Checks Working Group. The Edit Checks Working Group analyzed every GM Module edit check/business rule, recommended deletion of outdated edit checks/business rules and edited the wording of all warnings and errors. The efforts of the Edit Checks Working Group will simplify the use of the GM Module for all staff and will eliminate the need to analyze the edit checks/business rules when the GM Module is redesigned in FY2004.

Ms. Jackie Russell, retired from GMB, has received a Letter of Appreciation from the Vision Steering Committee for significant contributions to Compliance Education & Review Team activities and participation in the majority of subcommittee meetings during the past year.

Ms. Lerlita Garcia, GMB, has received a Letter of Appreciation from the Vision Steering Committee for significant contributions to Grant Expert Subcommittee activities and participation in the majority of subcommittee meetings during the past year.

STAFF ACTIVITIES

Dr. Van Houten, PAB, was a co-chair and invited speaker at the Gordon Research Conference on Genetic Toxicology, held in Oxford, United Kingdom, August 10-15. The title of his talk was "Oxidative Stress-Induced Mitochondrial DNA Damage: Sorting Out Life and Death Decisions."

Mr. Outwater, OD/WETB, assisted the U.S. Department of HUD as a reviewer for their 2003 Healthy Homes Demonstration Project awards through a series of a training period and conference calls. The final review meeting was held on August 6. *Dr. Srinivasan, SPHB*, worked in collaboration with Mr. Outwater.

Ms. Beard, OD/WETB, presented at the U.S. EPA Superfund Community Involvement Coordinators Conference on July 21 in Philadelphia, PA. The presentation was entitled "Keeping it Local: Engaging Community Based Organizations in Workforce Development Programs." WETP grantees Mark Holdbrooks and Kiameesha Evans from the University of Medicine & Dentistry of New Jersey and Donna McDaniels of the Laborers-AGC Education & Training Program also presented the accomplishments of our Superfund Jobs Training Initiatives as well as Brownfields and Minority Worker Training Programs to the coordinators.

Dr. McClure, COSPB, participated in the organizing of the 36th annual program for the Society for the Study of Reproduction (SSR) held July 19-22 in Cincinnati, OH. The meeting was supported in part by NIEHS funding for the theme of "Reproduction and the Environment," which included sponsored sessions for the President's Symposium (Reproduction and the Environment), a State of the Art Lectureship, three mini-symposia (Endangered Species and Reproduction, Endocrine Disruptors, Fetal Basis of Adult Disease) and the Trainee and Minority Affairs Forum on Career Development and Networking. At this meeting, the Board of Directors of the SSR formally approved the recommendation of the membership to establish the SSR Committee on Reproduction and the Environment (CoRE) populated by SSR members from the community of private sector, USDA, EPA, NIEHS, and NIOSH scientists. The CoRE sponsored an information booth at this meeting which was both well-visited and exhausted of hand-out materials within its first four hours. The purpose of the CoRE is to bring together reproductive and developmental biologists, toxicologists, and ecologists and promote greater collaborative, multi-disciplinary environmental health sciences research to improve the public health.

NIEHS hosted a Roundtable on Preparation and Protection of Site Disaster Responders in Beckley, WV on July 9. *Dr. Olden, Director, Mr. Hughes, Ms. Beard, and Mr. Outwater, OD/WETB* joined approximately 25 other participants from unions, universities, and other federal agencies to discuss further steps that are needed to adequately train workers who respond to disasters. The Roundtable included a demonstration of the coordinated efforts of emergency medical personnel, police, hazmat experts, and heavy equipment operators to deal with a simulated leak of a chemical from a tank truck and recovery of a victim incapacitated by the leak. Participants concluded that more detailed action plans are needed to determine the specific roles

and activation of emergency responders including skilled support personnel when responding to disasters. In addition, a pilot should be developed to test the use of a registry of responders.

Dr. Reinlib, SPHB, was an invited speaker to the "Workshop on Breast Cancer and the Environment" organized by the DHHS Office of Women's Health in Washington, DC on June 26. His presentation was entitled, "Breast Cancer Research Opportunities at NIEHS." The Workshop discussed the findings of major international studies on breast cancer and made recommendations for future directions for research that would better include stakeholders and for utilization of the resources of the Department's Centers of Excellence.

Dr. Van Houten, PAB, was a discussion leader for the "Introduction to Toxicogenomics" session at the Gordon Research Conference on Toxicogenomics, which was held June 22-27 in Lewiston, Maine.

Mr. Outwater, OD/WETB, gave an overview of the NIEHS Worker Education and Training Program to the Knight Journalism/CDC Boot Camp participants in Atlanta, GA on June 21. This was part of a collaborative activity with the Center for Disease Control and the International Association of Firefighters, an outstanding NIEHS awardee, to provide "awareness level" training for professional journalists designed to assist them in protecting themselves during hazardous materials and weapons of mass destruction incidents.

Dr. McClure, COSPB, served on the organizing committee for the June 12 NIH Director's conference entitled "NIH Research: Recent Progress and Future Promise of Human Embryonic Stem Cells," which was held at the main NIH campus in Bethesda, Maryland. The audience exceeded 800; the meeting was also televised live to two satellite sites at NIH and presented live on the NIH web-cast resource. Dr. McClure moderated the introductory session on "stem cell plasticity." This conference followed contiguously with the First Annual meeting of the International Society for Stem Cell Research in Washington, D.C. coordinated by the NIH Stem Cell Research Implementation Committee, upon which Dr. McClure serves by appointment of the OD, NIH.

Dr. Van Houten, PAB, was an invited speaker June 3 at the University of New York, Pharmacological Sciences Department, Stony Brook, New York where he gave a talk was entitled, "Arsenic, Oxidative Stress and Mitochondrial Damage: Sorting out Life and Death Decisions."

Dr. Mastin, COSPB, was an invited speaker at a sessions at the meeting of the American Thoracic Society, entitled, "Air Pollution as a Cause of Childhood Asthma and Chronic Airway Disease" on May 21. The purpose of the session was to present and discuss evidence for causative link between air pollution and childhood lung disease, primarily asthma, and to discuss areas for future research.

Ms. Beard, OD/WETB, hosted a Brownfields Focus Meeting in Research Triangle Park, North Carolina on May 20. This meeting focused on strengthening and promoting our strategic plan for Brownfields issues in 2003. All NIEHS/WETP Brownfields Minority Worker Training Awardees participated in this meeting. Staff attending and participating in the meeting included *Mr. Hughes, Mr. Outwater, and Ms. Thompson, OD/WETB*.

Dr. McClure, COSPB, delivered the introductory lecture to the class of 2003-2004 on May 17th and served on the faculty of the 6th Annual Frontiers in Reproduction (FIR) training course at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. He received an award acknowledging his leadership in founding and developing the FIR course. The course includes environmental health sciences faculty investigators and topics related to reproductive and developmental toxicology. From the international competition for the sixteen trainee positions available each year, one to two are awarded to young environmental sciences investigators actively engaged in developing a research career. Many of the environmental sciences investigator faculty and graduate trainees of FIR have become active members of other professional societies reproductive and developmental committees/activities promoting greater collaboration amongst the toxicology and biology community of scientists.

Dr. McClure, COSPB, served on the organizing committee for the 51st Annual Meeting of the Society for Gynecologic Investigation (SGI), which has the theme of "Genes, Cells and the Environment: Implications for Women's Health" and a post-graduate Course on "Epigenetic Regulation of Reproductive Development and Function: More than Just Genes. A substantial representation of speakers on these themes are NIEHS funded investigators. The meeting and post-graduate course will be held in Houston, Texas on March 24-27, 2004.

Drs. Sassaman (OD) and Suk (CRIS) hosted a delegation from the Vietnamese National Center for Science and Technology at NIEHS on September 2 and Dr. Sassaman with EPA in Washington, DC on September 3. The purpose of the visit was to continue to develop collaborations under a Memorandum of Understanding between the US and Vietnamese governments and to plan for a workshop to be held in Hanoi on remediation and exposure measurements November 3-5.

UPCOMING MEETINGS and WORKSHOPS

Mr. Hughes, OD/WETB, will address a study tour group from South Africa on the NIEHS Worker Education and Training Program. Hazardous in Washington, DC on September 20. The Development Associates, Inc. has been awarded a contract by the U.S. Agency for International Development (USAID) to provide technical services to the South African Department of Labour (DOL) and supporting government institutions. This major effort revolves around the passage of the Skills Development Act in 1998, which introduced a new approach to the promotion and development of work-related skills in South Africa.

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

Ms. Beard and Mr. Outwater, OD/WETB, will attend the Brownfields 2003: Growing a Greener America Conference in Portland, Oregon on October 26. This national conference will build upon past successes and continue to offer up-to-date and stimulating information for brownfields practitioners from throughout the United States and overseas. The NIEHS WETP is a co-sponsor for this conference and several sessions will focus on brownfields job training, public health and environmental justice efforts of our grantee community. During this meeting, Ms. Beard and Mr. Outwater are also planning to conduct 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 is a collaborative effort between the WETP and Lenny Siegel of the Center for Public Environmental Oversight, who has conduced these very successful caucuses since 1996 at each Brownfields National Conference.

The conference "Emerging Scientific Issues for Superfund" will be held October 8 - 10 at the University of California, Berkeley. This conference will bring four current west coast Superfund Basic Research Program grantees together with their EPA Region 9 colleagues to examine emerging scientific issues for the Superfund Program including "Emerging Contaminants - New Threats," "Emerging Issues in Transport and Detection," and "Emerging Issues in Remediation and Treatment."

The Serono Symposia International (SSI) Workshop entitled "The Role of Environmental Factors on the Onset and Progression of Puberty" to be held November 6-8, 2003 at the Hyatt Regency O'Hare in Rosemont, Illinois. The workshop, sponsored by the SSI with the assistance of NIEHS, CDC and EPA will explore the extant body of knowledge to determine if a consensus can be reached with regard to the sufficiency of the data to support a secular trend in the age of puberty onset and progression in boys and girls and a role of the environment in influencing any such trend. *Dr. McClure, COSPB*, participated in the organizational planning of the workshop.

The annual meeting of the Superfund Basic Research Program (SBRP) grantees will be held November 9-12 at Dartmouth College in Hanover, New Hampshire. Throughout the three-day conference, technical sessions and presentations will highlight a broad spectrum of research, providing a greater understanding of the work currently being performed by the program's researchers. In addition to the conference's technical and student poster sessions, Administrators and Outreach Core staff from each SBRP university program will meet concurrently in their own meetings to review information relevant to their roles and responsibilities.

Mr. Hughes, OD/WETB, and staff will host 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 is to take 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 will include *Ms. Beard, Mr. Outwater, Ms. Thompson, OD/WETP, and Ms. Mason, GMB*.

STAFF CHANGES

Recruitments:
Dr. Gwen Collman became Chief of the Susceptibility and Population Health Branch in July. She earned a B.S. in Biology from State University of New York at Binghamton, an M.P.H. in Epidemiology from the University of Michigan, and a Ph.D. in Environmental Epidemiology, from the University of North Carolina School of Public Health. She has worked at the National Institute of Environmental Health Sciences since 1984, first as a member of the Epidemiology Branch in the Division of Intramural Research, and since 1992 as a member of the Chemical Exposures and Molecular Biology Branch, DERT. As a Scientific Program Administrator she was responsible for the grant portfolio in Environmental and Molecular Epidemiology. She was also responsible for developing and managing the NIEHS Breast Cancer and the Environment Research Program and the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention. In her new capacity, Dr. Collman is also the Program Director for the NIEHS Environmental Health Sciences Centers program.

Dr. J. Patrick Mastin has been named Chief of the Cellular, Organ and Systems Pathophysiology Branch. He received a B.S. degree in Biochemistry and Molecular Biology from Centre College in Kentucky and a Ph.D. in Pathology from Duke University. Prior to joining the NIEHS, Dr. Mastin was a Research Biologist and then Chief of the Immunochemistry Research Section at NIOSH. He joined DERT in July 1998, as a Scientific Review Administrator in the Scientific Review Branch. On May 16, 2001, he transferred to the Cellular, Organs & Systems Pathobiology Branch (Formerly OSTB) as a Program Administrator for the extramural Pulmonary, Cardiovascular Immunotoxicology, and Renal programs.

Dr. David Balshaw has recently joined The Center for Risk and Integrated Sciences as a Program Administrator, where he will be responsible for developing a portfolio in proteomics and systems biology. He comes to the Institute from the NHLBI where he served for two years as a program administrator, overseeing portfolios in ischemic heart disease and traumatic injury, and developing initiatives intended to facilitate the translation of basic research findings into clinical investigation and application. He was also one of the principal players in developing the NHLBI's Proteomics Initiative, a significant investment in technology development geared towards biological application. Dr. Balshaw earned his Ph.D. in the Department of Pharmacology and Cellular Biophysics at the University of Cincinnati where he focused on kinetic modeling of ion transport processes. Following his doctoral work, he took a fellowship at the University of North Carolina at Chapel Hill investigating the regulation of intracellular calcium release. His expertise includes protein biochemistry, molecular biology, and computational approaches to modeling biological phenomenon.

Ms. Lisa Archer has moved within DERT to a Grants Management Specialist position within the Grants Management Branch. Lisa has worked in DERT for all but three of her 12-year government career, most recently serving as an Extramural Information Specialist in the OD's office.

Ms. Pam Evans has joined the DERT as a Grants Management Specialist. Prior to joining DERT, she worked for three years as a Contract Specialist in the NIEHS Aquisitions Management

Branch. She has been employed with the government for more than 22 years. Prior to coming to NIEHS, she worked in procurement for the Departments of Defense and Veterans Affairs.

Dr. Ethel Jackson, who served as Chief of the Scientific Review Branch for many years, has relocated to the Office of the Director, where she is a Special Assistant to Dr. Sassaman and will direct staff training efforts, among other projects.

Dr. Dennis Lang, Deputy Director DERT, has been named Acting Chief of the Scientific Review Branch. Recruitment for a permanent branch chief will take place this fall.

Departures:

Dr. Michael McClure, Chief of the Cellular, Organ and Systems Pathobiology Branch retired on August 30, 2003 after 24 years of government service. Dr. McClure had been active in developing programs in reproduction at the National Institute of Child Health and Human Development before coming to NIEHS as branch chief with primary responsibility for program development in female reproductive toxicology. He was active in many trans-NIH issues and was instrumental in developing the first non-governmental joint program, that between the NIEHS and the American Chemistry Council on developmental toxicology.

Ms. Jackie Russell retired from GMB on May 31 after more than 30 years of government service.

Dr. Larry Reed, an EPA employee who has served as a guest researcher with the Superfund Basic Research Program for the past year, has departed from CRIS. He chose to remain in North Carolina, accepting a position at the EPA.

Mr. Rodney Winchel, a Presidential Management Intern (PMI) appointed to the Office of the Director/ National Institutes of Health (OD/NIH), has left the NIEHS Worker Education and Training Program to continue his PMI rotation with the Intramural Administrative Management Branch for the Division of Intramural Research at the National Institute of Allergy and Infectious Disease.

Division of Intramural Research

NAEHS Council Update

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DIR RECRUITMENTS

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. Dr. Robert Maronpot, Chief of the Laboratory of Experimental Pathology, is the Chair of the search committee.

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

Tenure-track Immunologist
The Laboratory of Pulmonary Pathobiology is conducting a national search for a cellular/molecular immunologist. The candidate will be expected to establish a high-quality independent research program in pulmonary immunology in a laboratory with diverse research interests and backgrounds. The successful candidate will have research strengths in, but not necessarily limited to, pulmonary biology (such as mechanisms of tolerance, allergy, adaptive and/or innate immune response to respiratory infections, etc). A search committee chaired by Dr. John Drake, Chief or the Laboratory of Molecular Genetics has recommended a candidate and negotiations are underway.

Tenure-track Environmental Epidemiologist
The Epidemiology Branch has conducting a national search for an environmental epidemiologist. This person will be expected to develop an outstanding research program on the effects of environmental exposures and risks of chronic disease. Applicants with

demonstrated research interests in biological mechanisms and etiology of (not limited to) neurodegenerative diseases, diabetes, multiple sclerosis, renal disease, cardio-respiratory diseases; and such exposures as pesticides, metals, and/or solvents are most welcome. A search committee chaired by Dr. Steven Kleeberger, Chief of the Laboratory of Pulmonary Pathobiology is interviewing candidates.

Tenure-track or Tenured Biostatistician--Statistical Genetics
The Biostatistics Branch has conducted an international search for a tenure-track or tenured statistician to conduct independent research on methods development in statistical genetics. 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.

Staff Scientist--Toxicologic Pathologist
The Laboratory of Experimental Pathology is conducting 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. A search committee chaired by Dr. Rick Hailey, Toxicology Operations Branch, is interviewing candidates.

Staff Scientist—Pathologist/Laboratory Animal Veterinarian
The Laboratory of Experimental Pathology is conducting 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. A search committee chaired by Dr. Joseph Roycroft, Toxicology Operations Branch, is interviewing candidates.

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. A search committee is being 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. Stephanie London, Epidemiology Branch, has been formed and the position has been advertised.

DIR RECRUITS

Dr. Grace Kissling
Staff Scientist—Biostatistics Branch
Dr. Kissling has recently joined the NIEHS from a faculty position at the University of North Carolina-Greensboro. She will be analyzing data from NTP studies, providing statistical consulting services to researchers across the institute, and developing new statistical methodology where needed. Dr. Kissling has experience collaborating as a statistical consultant in research projects from a wide range of disciplines, including anthropology, biology, cardiology, education research, history, internal medicine, pharmacy, physical therapy, psychology, music, nursing, nutrition, sport science, and textiles.

Dr. Kissling's statistical research involves developing methods for assessing spatial association of measurements whose geographic locations are known. Several spatial autocorrelation measures have been proposed in the past. She has extended one of these measures, Moran's I statistic, in two ways--first, she developed a spatial autocorrelation coefficient for multivariate data so that a spatial "autocovariance" might shed light on how two or more continuous variables co-vary over space; second, for categorical measurements, she developed a measure of the degree of agreement of categories, taking into account the spatial proximity of the observations.

Selected publications

Brodie, B.R., T. D. Stuckey, C. Hansen, G. Kissling, and D. Muncy. Influence of vessel size on early and late outcomes after primary angioplasty for acute myocardial infarction, J. Invas. Cardiol. 12:13-19, (2000).

C. G. Gegick, M. D. Altheimer, G. E. and Kissling. "Benefits of outcome analysis in diabetes management, Endocrin. Pract., 6:253-259 (2000).

S. A. Beeson and G. E. Kissling. Predicting success for baccalaureate graduates on the NCLEX-RN#2, J. Prof. Nurs., 17: 121-127, (2001).

C. K. Miller, L. Edwards, G. Kissling, and L. Sanville. Evaluation of a theory-based nutrition intervention for older adults with diabetes mellitus, J. Amer. Diet. Assoc. 102:1069-1081, (2002).

M. K. Sandford, G. Bogdan, and G. E. Kissling. Biological adaptation in the prehistoric Caribbean: Osteology and bioarchaeology of the Tutu site, in E. Righter (ed.) Human Adaptations at the Tutu Archaeological Village Site: A Multidisciplinary Case Study, Gordon and Breach Science Publishers, New York, 209-229 (2002).

DIR SCIENTIFIC ACCOMPLISHMENTS
2003

DDT Might Increase Infant Mortality When Used To Control Malaria
Sub-Saharan African countries have sought exemptions from the worldwide ban on DDT to spray houses for malaria control. DDT is not acutely toxic to humans, but data from NIEHS epidemiology studies have shown that DDT may increase low birthweight and interfere with prolonged breastfeeding, both of which would increase infant mortality. NIEHS epidemiologists have shown that the cost in increased infant mortality from DDT toxicity was of the same order of magnitude as the benefit from infant malaria deaths prevented, if the associations are causal and of the same strength in Africa as seen in North America. Thus programs that propose to use DDT should have sufficient research capability to see if they are having the hoped-for effect, and alternative treatments, such as insecticide treated bed nets, should be reconsidered in the light of these findings.

Chen, A. and Rogan, W.J.: Nonmalarial Infant Deaths and DDT Use for Malaria Control. Emerg. Infect. Dis. 9: in press, 2003.

A New Way To Cause Mutations and Cancer by Environmental Factors.
Cadmium, which is a known human carcinogen, was found to cause extreme hypermutability in yeast following chronic exposure to low amounts that are similar to those that accumulate in the human body and can be found in the environment. Genetic analysis in yeast and direct biochemical testing in human cell extracts demonstrated that cadmium is a new kind of mutagen that acts by inhibiting the DNA mismatch repair system rather than via direct DNA damage. It was believed for many years that environmental mutagens may have their effects not only through directly damaging DNA, but also by altering the physiology of genome stability maintenance, but there has never been a clear identification of the biological targets. Environmental alteration of key DNA damage response pathways may prove as important as direct DNA damage by mutagens.

Jin Y.H., Clark A.B., Slebos R.J., Al-Refai H., Taylor J.A., Kunkel T.A., Resnick M.A. and Gordenin D.A.: Cadmium is a mutagen that acts by inhibiting mismatch repair. Nature Genet., 34: 326-329, 2003.

Grandparents Have a Lot to Tell Us About Genetic Contributions to Early-onset Disease.
Diseases with onset early in life, such as birth defects, insulin-dependent diabetes, and schizophrenia, are known to depend on both genetic and environmental factors. The genetic variations that confer increased susceptibility to such "complex" diseases have been difficult
to identify. NIEHS statisticians developed a method to locate risk-related genes by studying the transmission of genes from grandparents through the parents to affected grandchildren. Each copy of a gene that we carry represents a random choice from

among the 8 copies that were present in our 4 grandparents. However, if a variant form of the gene is related to increased risk of the disease under study, then that variant will have been inherited by diseased grandchildren with a likelihood higher than chance. We developed powerful statistical methods to identify such apparent transmission distortions and estimate the relative risks associated with the variant alleles.

Weinberg, C.R.: Studying parents and grandparents to assess genetic contributions to early-onset disease. Am. J. Hum. Gen. 72: 438-47, 2003.

The Insecticide DDT is a Reproductive Toxin In Humans.

DDT is still used for control of malaria in dozens of countries worldwide. Ongoing use of DDT is endorsed by the World Health Organization, based on the assumption that it has little or adverse effects on humans. New evidence, however, suggests that like birds and other animals, humans experience reproductive toxicity when exposed to the levels of DDT encountered in insect control programs. International policy regarding this persistent organic pollutant needs to be reconsidered.

Longnecker, M.P., Klebanoff, M.A., Dunson, D.B., Guo, X., Chen, Z., Zhou, H. and Brock, J.W.: Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies. Environ. Res., in press, 2003.

Elimination of Mercury and Methyl-mercury Accelerated by Kidney Transport Proteins.

Our bodies are protected from the toxic effects of mercury and methyl-mercury by their rapid reaction with endogenous sulfur-containing molecules or by antidotes including dimercapto-propane-sulfonate (DMPS). An important component of these protective effects was shown by NIEHS pharmacologists to be the rapid excretion of mercury-sulfhydryl compounds mediated by the kidney drug and xenobiotic transport protein known as organic anion transporter 1 (OAT1). Thanks to the action of this excretory protein the body burden of mercury, and thus its toxicity, is greatly reduced.

Koh, A.S., Simmons-Willis, T.A., Pritchard, J.B., Grassl, S.L. and Ballatori, N.: Identification of a mechanism by which the methylmercury antidotes N-acetylcysteine and dimercapto-propane-sulfonate enhance urinary metal excretion: Transport by the renal organic anion transporter-1, Oat1, but not by Oat3. Molec. Pharmacol. 62: 921-926, 2002.

Aslamkhan, A.G., Han, Y-H.. Yang, X-P, Zalups, R.K. and Pritchard, J.B.: Human renal organic anion transporter 1 (hOAT1) dependent uptake and toxicity of mercuric thiol-conjugates in MDCK cells. Molec. Pharmacol. 63: 590-596, 2003.

New Genetic Defects Identified in Human Drug Metabolizing Enzymes That Potentially Alter Dosage Requirements, Cure Rates and Toxicity for Prescription Drugs and Over-the-Counter Remedies.

NIEHS scientists have been identified genetic defects in two enzymes, CYP2C9 and CYP2C19, which metabolize approximately 16% of clinically used drugs including anticoagulents, anticonvulsant drugs used for epilepsy, antidiabetic drugs, drugs for high blood pressure, anti-inflammatory drugs such as celebrex and ibuprofen, the popular antiulcer agent omeprazole, and valium. These defects potentially cause variability in effective dosages, cure rates for ulcers, and drug toxicity in different individuals. Discovery of the majority of defective alleles opens the possibility of using genetic testing in the future to customize drug prescription to the patient to avoid toxicity and assure that drugs will be effective in the particular patient.

Blaisdell, J., Mohrenweiser, H., Jackson, J., Ferguson, S., Coulter, S., Chanas, B., Xi, Ti, Ghanayem, B. and Goldstein, J.A.: Identification and functional characterization of new potentially defective alleles of human CYP2C19. Pharmacogenetics 12: 703-711, 2002.

Goldstein, J.A.: Polymorphisms in the Human CYP2C Subfamily. Drug Metabolism Reviews 34: 5, 2002.

Lee, C.R., Goldstein, J.A. and Pieper, J.A.: Cytochrome P450 2C9 Genetic Polymorphisms: a Comprehensive Review of the In Vitro and Human data. Pharmacogenetics, 12: 251-263, 2002.

Lee, C.R., Pieper, J.A., Frye, R.F., Hinderliter, A.L., Blaisdell, J.A. and Goldstein, J.A.: Tolbutamide, Flurbiprofen and Losartan as probes of CYP2C9 activity in humans. J. Clin Pharm., 43: 84-91, 2003.

Fischer, T.L., Pieper, J.A., Graff, D.W., Rodgers, J.E., Fischer, J.D., Parnell, K.J., Goldstein, J.A., Greenwood, R. and Patterson, J.H.: Evaluation of potential losartin-phenytoin drug interactions in healthy volunteers. Clin Pharm. Ther. 72: 238-46, 2002.

Dust Mite Allergen Exposure is Common In U.S. Homes.

Dust mite allergen is perhaps one of the most studied indoor allergens but levels of exposures to dust mite allergen in U.S. homes had not been previously described. NIEHS scientists reported that 84% US homes have detectable levels of dust mite allergen in at least one bed. Levels previously associated with allergic sensitization and asthma morbidity are common in U.S. bedrooms. Independent predictors of higher dust mite allergen concentrations include older homes, regions other than the West, single-family homes, the absence of resident children, lower household income, a musty or mildew odor in the home, and higher bedroom humidity.

Arbes, S.J., Friedman, W., Vojta, P.J., Muilenberg, M.L., Burge, H.A., Yin, M., Cohn, R. and Zeldin, D.C.: House dust mite allergens in U.S. beds: results from the first national survey of lead and allergens in housing. J. Allergy Clin. Immunol. 111: 408-414, 2003.

Breastfeeding Protects Young Children Against Asthma and Recurrent Wheezing.
Using data from the third National Health and Nutrition Examination Survey, NIEHS researchers found evidence that breastfeeding may delay the onset of, or actively protect children less than 24 months of age against, asthma and recurrent wheeze. Compared to children who had never breastfed, breastfed children had significantly reduced chance of being diagnosed with asthma and of having recurrent wheeze before 24 months of age. Also, among children 2 to 71 months of age who had been exposed to environmental tobacco smoke, those who had ever been breastfed had significantly reduced risks of asthma and wheeze compared with those who had never been breastfed.

Chulada, P.C., Arbes, S.J., Dunson, D. and Zeldin, D.C.: Breastfeeding and the prevalence of asthma and wheeze in children: analysis from the third national health and nutrition examination survey (NHANES III), 1988-1994. J. Allergy Clinl. Immunol. 111: 328-336, 2003.

Hydrocephalus Gene Discovery.
NIEHS researchers identified a novel gene called RFX4 that is critical for normal brain development. Loss of a single copy of this gene in mice results in severe congenital hydrocephalus (brain swelling) due to stenosis of the aqueduct of Sylvius and failure of formation of the subcommissural organ. Loss of both copies of this gene results in a severe brain defects and death in the perinatal period. These studies raise the possibility that similar defects in the expression of this gene in man might lead to congenital hydrocephalus, a disease that is present in 0.5-1.8 per 1000 live births.

Blackshear, P.J., Graves, J., Stumpo, D.J., Cobos, I., Rubenstein, J.L., and Zeldin, D.C. Graded phenotypic response to partial and complete deficiency of a brain-specific isoform of the winged helix transcription factor RFX4. Development. In Press, 2003.

Mechanism of Glucocorticoid Resistance Described.
Glucocorticoids are a class of drugs used for treatment of many inflammatory and autoimmune diseases caused by environmental stimuli. Glucocorticoid resistance is a pathological state characterized by the inability of glucocorticoids to elicit a normal pharmacological or physiological response and is associated with poor therapeutic outcome. Overexpression of the beta isoform of the human glucocorticoid receptor is associated with glucocorticoid resistance. NIEHS scientists described a molecular mechanism that can explain the properties of glucocorticoid receptor beta and its potential role in glucocorticoid resistance. Using atomic scale, three-dimensional modeling and molecular biology techniques, they have characterized how two specific amino acids in glucocorticoid receptor beta are responsible for its dominant negative phenotype and its suspected role in glucocorticoid resistance. This work may lead to novel therapeutic targets of glucocorticoid receptor beta that may result in new therapies for overcoming glucocorticoid resistance.

Yudt, M.R., Jewell, C.M., Bienstock, R.J. and Cidlowski, J.A.: Molecular origins for the dominant negative function of human glucocorticoid receptor beta. Mol. Cell. Biol. 23:4319-4330, 2003.

New Method Reduces Exposure to Cockroach Allergen in Inner-City Homes.
Clinically relevant reductions in exposure to cockroach allergen, an important risk factor for asthma in inner-city households, have proven very difficult to achieve in intervention trials. Using a randomized study NIEHS researchers investigated new methods for the abatement of cockroach allergen in low-income, urban homes. Interventions consisted of occupant education, placement of insecticide bait, and professional cleaning. Substantial reductions in cockroach allergen levels were achieved. Allergen levels were reduced below the sensitization threshold in beds, arguably the most relevant site for exposure, and below the asthma morbidity threshold on bedroom floors and living room floors/sofas.

Arbes, S.J., Sever, M., Archer, J., Long, E.H., Gore, C., Schal, C., Walter, M., Neubler, B., Vaughn, B., Mitchell, H. Liu, E., Collette, N., Adler, P. and Zeldin, D.C.: Abatement of cockroach allergen (blag1) in low-income, urban housing – A randomized control trial. J. Allergy Clin. Immunol. In press, 2003.

Power Frequency Magnetic Fields Have No Effect on Breast Cancer Incidence
Some previously published data suggest that residential exposure to power frequency magnetic fields may increase risk of breast cancer. NIEHS epidemiologists have found in a subset of the Hawaii and Los Angeles Multiethnic Cohort that higher residential exposure to magnetic fields did not increase breast cancer risk.

London, S.J., Pogoda, J.M., Hwang, K.L., Langholz, B., Monroe, K.R., Kolonel, L.N., Kaune, W.T., Peters, J.M. and Henderson, B.: Residential magnetic field exposure and breast cancer risk in the Multiethnic Cohort Study. Amer. J. Epidemiol., in press, 2003.

Mice and Men: Gene Mutations Causing Male Infertility.
Men with a syndrome called dysplasia of the fibrous sheath (DSF) are infertile and have sperm with a short, rigid, and immotile tail. DSF occurs in several men in some families, evidence that it is caused by a genetic mutation. The fibrous sheath forms a skeletal framework for the sperm tail and it is under-developed and disorganized in DSF sperm. AKAP4 is a major protein of the fibrous sheath in mice and men. NIEHS researchers have shown that, when AKAP4 was mutated experimentally in mice, their sperm were remarkably similar to sperm in DSF patients. This study suggests that men with DSF should be screened for mutations in the AKAP4 gene and is one of the first to identify a candidate gene for a specific cause of male infertility.

Miki, K., Willis, W.D., Brown, P.R., Goulding, E.H., Fulcher, K.D. and Eddy, E.M.: Targeted disruption of the AKAP4 gene causes defects in sperm flagellum and motility. Devel. Biol. 248: 331-342, 2002.

New Mechanism Identified for a Critical Drug Transport Protein Found in Kidney and the Blood-Brain Barrier.

Human organic anion transporter 3 (hOAT3) is highly expressed in the kidney and the blood brain barriers. In expression systems, it was shown to be capable of transporting small (<500 Daltons) negatively charged drugs, foreign chemicals, and their metabolites. The mechanism used by this transport protein was poorly understood and thus, its importance in vivo for elimination of toxins from the brain or the body was not established. NIEHS researchers showed that transport was coupled to metabolic energy (via organic anion/dicarboxylate exchange) leading to markedly accelerated elimination of negatively charged chemicals or metabolites. In doing so, it demonstrated the critical importance of hOAT3 in protecting our bodies as a whole, and our brains in particular, from chemical toxicity.

Sweet, D.H., Chan, L.M.S., Walden, R., Yang, X-P., Miller, D.S. and Pritchard, J.B.: Renal organic anion transporter 3 (OAT3 [SLC22a8]) is a dicarboxylate exchanger indirectly coupled to the sodium gradient. Am. J. Physiol. 284: F763-F769, 2003.

Identification of a Marker for Progenitor Cell Population in Mouse Skin - Implications in Gene Therapy and Carcinogenesis Research.

Although it is a widely held belief that adult skin stem and progenitor cells reside in the bulge region of the hair follicle, no reliable marker has been identified to date that allows for direct isolation of this cell population. NIEHS scientists have recently demonstrated that the cell surface marker CD34 identifies this specific population of cells in mouse skin, and allows for the enrichment of living bulge cells, providing a unique opportunity for to study the behavior of these cells under experimental conditions. CD34-expressing hair follicles cells have characteristics unique to stem and progenitor cells--they are quiescent and have a high proliferative capacity--characteristics that are necessary for potential gene therapy and tissue engineering applications, as well as for the study of carcinogen target cells in the skin. This work represents the first use of a hair follicle bulge-specific marker that allows for positive selection of potential epidermal progenitor cells.

Trempus, C.S., Morris, R.J., Bortner, C.D., Cotsarelis, G., Faircloth, R.S., Reece, J.M. and Tennant, R.W.: Enrichment for living murine keratinocytes from the hair follicle bulge with the cell surface marker CD34. J. Invest. Dermatol. 120: 501-511, 2003.

Global Ultraviolet Light May Alter Autoimmune Muscle Disease
NIEHS clinical researchers coordinated a study that produced the first global findings from a group of international experts organized to utilize the natural genetic and environmental variations around the world to begin to understand differences in the clinical expression of, and genetic and environmental risk factors for, the autoimmune muscle disease, myositis. Myositis occurs in two major forms, dermatomyositis and polymyositis. Of the geoclimatic variables studied, surface ultraviolet radiation intensity most strongly predicted the relative proportion of dermatomyositis, and was strongly related to the proportion of the dermatomyositis autoantibodies at 15 locations on four continents. The striking differences in the proportion of dermatomyositis and dermatomyositis-specific autoantibodies observed around the world do not appear to be the result of inherent global variations in known genetic risk factors. These data suggest that ultraviolet light exposure modulates the expression of an autoimmune disease in different populations around the world. These findings have important preventative implications, may affect studies of other immune-mediated diseases, and suggest new avenues of investigation for such disorders.

Okada, S., Weatherhead, E. Targoff, I.N., Wesley, R. and Miller, F.W. for The International Myositis Collaborative Study Group: Global surface ultraviolet radiation intensity may modulate the clinical and immunologic expression of autoimmune muscle disease. Arthritis Rheum., in press, 2003.

Genetically Modified Mouse Models (GEMM) Shown to Have Great Potential as Screening Tools for Identifying Human Cancer Causing Chemicals.
GEMM have important advantages over conventional rodent bioassay screening paradigms including shorter duration and reduced animal requirements. However, uncertainties exist surrounding their sensitivity and predictiveness. In an extensive review of nearly 100 chemicals now tested in the three most studied GEMM, NIEHS scientists have shown that they identified a high percentage of the human carcinogens tested (80-90%) while maintaining a low background of "false positives" (non-carcinogens incorrectly identified as carcinogens). However, a number of "false negatives" (human carcinogens incorrectly identified as non-carcinogens) were seen. This analysis should provide the basis for further refinement of this important research and screening tool.

Pritchard, J.B., French, J.F., Davis, B.J. and Haseman, J.K.: Transgenic mouse models: Their role in carcinogen identification. Environ. Hlth. Perspectives 111: 444-454, 2003.

Analysis of Mutations of the P53 Tumor Suppressor has Implications for Evolution of Extensive Signaling Networks in Cells.
Alterations in the tumor suppressor and stress-responsive p53 gene are associated with many tumors. Since p53 regulates over 50 "downstream" genes, which are part of a vast network of cellular processes including programmed cell division and death, changes in

p53 can have dramatic effects on normal metabolism. NIEHS geneticists developed a unique system using yeast to assess the impact of human p53 mutations on regulation of many genes. Surprisingly, mutations with altered function can lead to a change in the spectrum and the level of genes activated by p53. This result suggests that there may be master genes of diversity such as p53 that provide rapid evolution of cellular regulatory networks, which helps explain how specific p53 mutations may be selected for tumor development.

Inga, A., Storici, F., Darden, T.A. and Resnick, M.A.: Differential transactivation by the p53 transcription factor is highly dependent on p53 level and promoter target sequence. Mol. Cell. Biol., 22: 8612-86125, 2002.

Resnick, M.A. and Inga, A.: Functional mutations in the sequence-specific transcription factor p53 and implications for master genes of diversity. Proc. Nat. Acad. Sci. USA in press, 2003.

Ion fluxes are Required for Apoptosis.

Cell shrinkage is a ubiquitous characteristic of apoptosis that discriminates it from other types of cell death such as necrosis. NIEHS scientists have shown for the first time that influx of sodum ions is required for cell shrinkage and a loss in intracellular potassium is actually the critical event that controls the progression of apoptosis, regardless of whether cells shrink or swell. This novel finding indicates that cell shrinkage can now be separated from other features of apoptosis. Such a basic science result can provide new avenues of therapy for many of the over 40 human apoptotic diseases.

Bortner, C.D. and Cidlowski, J.A.: Uncoupling cell shrinkage from apoptosis reveals that Na^+ influx is required for volume loss during programmed cell death. J. Biol. Chem., in press, 2003.

Ion Channel Regulation by Signal Transduction Pathways

NIEHS scientists have reported novel mechanisms for potassium channel regulation by signal transduction pathways. These mechanisms provide new targets for investigating the disruptive effects of environmental toxicants on cell function. In particular, potassium channel stimulation by thyroid hormone through the Rac GTPase provides a direct molecular mechanism to explain the human neurological deficits associated with disruption of thyroid hormone signaling during development by dietary iodine deficiency, organochlorine exposure, and inherited mutations in the thyroid hormone receptor. In addition the regulation of cardiac calcium channels by dihydropyridines, which are used to treat human cardiovascular disease was studied.

Storey, N., O'Bryan, J. and Armstrong, D.L.: Rac and Rho mediate opposing hormonal regulation of ether-a-go-go related potassium channels. Curr. Biol., 12: 27-33, 2002.

Erxleben, C., Everhart, A., Romeo, C., Florance, H., Bauer, M.B., Alcorta, D., Rossie, S., Shipston, M.J. and Armstrong, D.L.: Interacting effects of N-

terminal variation and strex-exon splicing on rSlo potassium channel modulation by calcium, phosphorylation and oxidation. J. Biol. Chem., 277: 27045-27052, 2002.

Tian, L., Coghill, L.S., MacDonald, H-F., Armstrong, D.L. and Shipston, M.J.: Leucine zipper domain targets PKA to mammalian BKca channels. J. Biol. Chem., 278: 8669-8677, 2003.

Storey, N.M, Gómez-Angelats, M., Bortner, C., Armstrong, D.L. and Cidlowski, J.A.: Stimulation of Kv1.3 potassium channels by death receptors in Jurkat T lymphocytes. J. Biol. Chem., in press, 2003

Erxleben, C. Allegria-Gomez, T. Darden, T., Mori, Y., Birnbaumer, L. and Armstrong, D.L.: Modulation of cardiac CaV1.2 channels by dihydropyridine and phosphatase inhibitor requires Ser-1142 in the domain III pore loop. Proc. Natl. Acad. Sci. USA, 100: 2929-2934, 2003.

Long Sought Understanding of Drug Transporter Function Achieved.

Organic anion transporter 1 (Oat1) was the first anionic drug transporter cloned, but its precise mechanism remained elusive. Using membranes isolated from both native rat kidneys and cell lines expressing human OAT1, NIEHS pharmacologists have shown that drug uptake was mediated by exchange for the Krebs cycle intermediate, α-ketoglutarate. Moreover, this exchange was 1 for 1, meaning that each transporter cycle results in net entry of one positive charge and providing a direct means of tapping the energy stored in the inside negative membrane potential present in the renal excretory cells. In this manner, the cell's energy is harnessed to drive the rapid and effective elimination of toxic foreign chemicals and their metabolites.

Aslamkhan, A.G., Han, Y-H., Walden, R., Sweet, D.H. and Pritchard, J.B.: Stoichiometry of renal organic anion/dicarboxylate exchange: Assessment in membrane vesicles from rat renal cortex isolated from rat kidney and human OAT1- expressing MDCK cells. Am. J. Physiol., in press, 2003.

Possible Cause of Progressive External Opthalmoplegia Identified.

NIEHS scientists have discovered an active site point mutation in the gene for the mitochondrial DNA polymerase gamma that is associated with the human genetic disease Progressive External Opthalmoplegia, which results from mitochondrial dysfunction. This mutated gene encodes a polymerase with reduced catalytic efficiency and reduced DNA replication fidelity, features that are implicated as causative for this disease.

Ponamarev, P., Longley, M.J., Nguyen, D., Kunkel, T.A. and Copeland, W.C.: Active site mutation in DNA polymerase gamma associated with Progressive External Ophthalmoplegia causes error-prone DNA synthesis. J. Biol. Chem. 277: 15225-15228, 2002.

Identification of Deleted In Split Hand/Split Foot 1 (Dss1) as a TPA-Responsive Gene Expressed in Keratinocyte Stem/Progenitor Cells and Possible Involvement in Early Skin Tumorigenesis.

The keratinocyte stem cells (KSCs) have become a major target for cutaneous carcinogens and skin tumorigenesis might be initiated by cellular transformation of KSCs. NIEHS scientists are identifying the specific promotion-relevant effector genes that might lead to neoplastic transformation in skin following treatment with tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) using genetically initiated Tg·AC mouse keratinocyte stem/progenitor cells. Dss1 was one of novel TPA-responsive genes in mouse skin KSCs and its expression was also shown to be elevated in skin papillomas relative to normal skins, and further increased in squamous cell malignancies. Functional studies by constitutive expression of Dss1 in JB6 Cl 41-5a preneoplastic epidermal cells strongly increased focus-formation and proliferation of these cells and enhanced efficiency of neoplastic transformation of the cells. Dss1 represents an attractive candidate mediator of TPA-induced tumor promotion. These results are of broad interests in the skin cancer fields as well as other related stem/progenitor cell biomedical research areas.

Wei, S.-J., Trempus, C.S., Cannon, R.E. Bortner, C.D. and Tennant, R.W.: Identification of Dss1 as a 12-O-tetradecanoylphorbol-13-acetate-responsive gene expressed in keratinocyte progenitor cells, with possible involvement in early skin tumorigenesis. J. Biol. Chem. 278: 1758-1768, 2003.

The Structural Mechanism of Anti-viral Induced Mitochondrial Toxicity.

AIDS patients undergoing antiviral therapy with nucleoside analogs such as AZT, D4T, and ddC, can develop mitochondrial toxicity due to the inhibition of the mitochondrial DNA polymerase. NIEHS scientists have determined how the human mitochondrial DNA polymerase selects and incorporates these nucleoside analogs into mitochondrial DNA to cause inhibition of mitochondrial function. A single amino acid in the active site of the DNA polymerase gamma provides for most of the selection of ddC and D4T and possible carbovir. This comprehensive study of inhibition by antiviral nucleotide analogs should be useful to the rational design of more effective anti-viral inhibitors that do not cause such deleterious effects on mitochondrial DNA replication.

Lim, S.E., Ponamarev, M.V., Longley, M.J. and Copeland W.C.: Structural determinants in DNA polymerase γ that account for mitochondrial toxicity from antiviral nucleotide analogs J. Mol. Biol. 329: 45-57, 2003.

Molecular Modeling of Human DNA Repair Protein Gives Insight into Three Human Diseases.

Structural studies of human proteins often give insights into disease processes. However, it is sometimes difficult or impossible to obtain sufficient human protein in high enough purity to obtain crystals that yield atomic resolution information. Therefore, molecular modeling is an extremely useful complementary approach when direct structural

information is lacking. Scientists at the NIEHS have built a detailed molecular model of a human DNA repair protein, XPD using the crystal structure of UvrB, a homologous repair protein from bacteria. Mutations in the XPD gene can lead to one of three human diseases: xeroderma pigmentosum, trichothiodystrophy, and Cockayne's Syndrome. XPD as part of a nine protein complex functions in a variety of cellular functions including, DNA repair, transcription and cell cycle control. The validity of the model was tested in two ways. First. mutations associated with these human diseases were introduced in the bacterial UvrB protein and these mutant proteins was tested in a series of biochemical DNA repair assays. Second, specific mutations were introduced into XPD and its activity tested in DNA repair and transcriptional assays. Mutations in specific regions of the protein were found to affect repair producing xeroderma pigmentosum, while other sites in the protein affect transcription, producing either trichothiodystrophy, or Cockayne's Syndrome.

Bienstock, R.J., Skorvaga, M., Mandavilli, B.S. and Van Houten, B.: Structural and functional characterization of the human DNA repair helicase XPD by comparative molecular modeling and site-directed mutagenesis of the bacterial repair protein UvrB. J. Biol. Chem., 278: 5309 – 5316, 2003.

Dubaele, S., Proietti de Santis, L., Bienstock, R.J., Keriel, A., Stefanini, M., Van Houten, B. and Egly, J.M.: Transcription activity of TFIIH derived from XPD patients discriminates between Xeroderma Pigmentosum and Trichothiodystrophy Molecular Cell 11: 1635-46, 2003.

Pharmacological Activation of an Oxygen Sensor in Cells Confers Protection by Upregulating Protective Genes.

Recently NIEHS scientists have identified an oxygen dependent prolyl hydroxylase domain-containing enzyme as an oxygen-sensing pathway. Hydroxylation of a specific proline in the hypoxic-inducible-factor by this enzyme results in an increased synthesis of a number of genes that protected the cell from additional stress.

Wright, G., Higgins, J.J., Raines, R.T., Steenbergen, C. and Murphy, E.: Activation of the Prolyl Hydroxylase Oxygen-sensor results in induction of GLUT1, heme oxygenase-1, and nitric-oxide synthase proteins and confers protection from metabolic inhibition to cardiomyocytes. J. Biol. Chem. 278: 20235-20239, 2003.

Discovery and Characterization of a Novel ABC Transporter Gene.

The Abca13 gene encodes an ATP-binding cassette (ABC) transporter with 12 transmembrane domains that is expressed at relatively high levels in the epididymis and salivary gland. Of the 48 members of the human ABC transporter gene superfamily, 14 are associated with human diseases (including cystic fibrosis, retinal degeneration, and sterol transport deficiencies) and 6 are associated with multidrug resistance (MDR). The orthologous human ABCA13 gene maps to a syntenic region on chromosome

7p12.3, containing a locus (INM7) associated with T-cell tumor invasion and metastasis, which is presently under investigation by NIEHS scientists.

Barros, S.A., Tennant, R.W. and Cannon RE.: Molecular structure and characterization of a novel murine ABC transporter, Abca13. Gene: 307:191-200, 2003

Development of a yeast system to determine fidelity of DNA replication.
NIEHS scientists have established an in vivo system using yeast cells to determine the fidelity of DNA replication by the leading and lagging strand DNA replication machinery and used the system to demonstrate that yeast origins establish a strand bias for replicational mutagenesis induced by two base analogs, one of which (8-oxo-guanine) is a major DNA lesion generated by oxidative stress.

Pavlov, Y.I., Newlon, C.S. and Kunkel, T.A.: Yeast origins establish a strand bias for replicational mutagenesis. Molec. Cell 10, 207-213, 2002.

Mechanism for Control of Antibody Affinity.
NIEHS scientists obtained evidence that DNA polymerase eta, a Y family enzyme, likely participates in somatic hypermutation of immunoglobulin genes, a process responsible for development of high affinity antibodies.

Pavlov, Y.I., Rogozin, I.B., Galkin, A.P., Aksenova, A.Y., Hanaoka, F., Rada, C. and Kunkel, T.A.: Evidence for participation of DNA polymerase eta in somatic hypermutation of an immunoglobulin κ light chain transgene. Proc. Natl. Acad. Sci. USA 99, 9954-9959, 2002.

A Mathematical Model Indicates that Current Risk Assessment Procedures May Not be Adequate for Environmental Agents that Mimic Natural Hormones.
NIEHS scientists created mathematical model to examine how environmental agents that bind to nuclear receptor proteins may affect the expression of hormone-regulated genes. The model indicates that a non-monotonic response is a plausible outcome for environmental agents that activate nuclear receptors (e.g., estrogen receptor) in the same manner as the natural hormone (e.g., estrogen). These results imply that such agents can have important consequences on human health even at low, environmental exposure levels

Kohn, M.C. and Melnick, R.L.: Biochemical origins of the non-monotonic receptor-mediated dose-response. J. Mol. Endocrinol. 29: 113-123, 2002.

Genetic Mutations in Mice Offer Clues About Cancer-Causing Pathways Following Chemical Exposure.

Over 30 million pounds of o-nitrotoluene are produced in the United States each year because of its use in synthesizing a wide variety of industrial products including pesticides, pharmaceuticals, dyes, and rubber chemicals. Researchers at the NIEHS report that a diet containing o-nitrotoluene caused hemangiosarcomas, a cancer originating from blood vessels at multiple sites (skeletal muscle, mesentery, subcutaneous tissues), in mice. The significance of the study is the different genetic mutations found between the hemangiosarcomas caused by exposure to the o-nitrotoluene and similar tumors that occurred spontaneously, without chemical induction. The researchers examined the genetic mutations in three genes for which mutations are thought to be important in the development of human cancers. These findings offer important clues to how cancer may occur in people when exposed to this or other potentially toxic substances.

Hong, H.L, Ton, T.V., Devereux, T.R., Moomaw, C, Clayton, N., Chan, P., Dunnick, J.K. and Sills, R.C.: Chemical-specific alterations in ras, p53, and B-catenin genes in hemangiosarcomas from B6C3F1 mice exposed to o-nitrotoluene or reddelliine for 2 years. Tox. Appl. Pharmacol., in press, 2003.

A Biological Model Characterizes Methemoglobinemia in Animals and Humans.
NIEHS scientists created biologically based mathematical model to characterize the induction of methemoglobinemia due to exposure to nitrite. Elevated levels of methemoglobin can lead to anemia hypoxia, a condition in which there is inadequate supply of oxygen to tissues. The model predicts the rate and extent of oxidation of hemoglobin by nitrite in rats given oral doses of sodium nitrite. The model also predicts the induction and recovery of methemogobinemia in humans

Kohn, M.C., Melnick, R.L., Ye, F. and Portier, C.J.: Pharmacokinetics of sodium nitrite-induced methemoglobinemia in the rat. Drug Metab Dispos. 30: 676-683, 2002.

Direct Comparison of Results From Human Studies of PCB Exposure in Relation to Neurodevelopment Made Possible.
Everyone in developed countries is exposed before birth to the man-made environmental contaminant, PCB, which is known to adversely effect neurodevelopment in animals. Whether exposure to low levels of PCB is harmful to humans is controversial and affects regulatory decisions, hazardous waste cleanup policy, and dietary recommendations. NIEHS researchers have facilitated risk assessment and data interpretation by making direct comparison of results across studies possible using original data obtained from all investigators in this field, and produced results that weaken the evidence that low-level exposures in humans may have adverse effects.

Daniels, J.L., Longnecker, M.P., Klebanoff, M.A., Gray, K.A., Brock, J.W., Zhou, H., Chen, Z. and Needham, L.L.: Prenatal exposure to low level polychlorinated biphenyls in relation to mental and motor development at 8 months. Am. J. Epidemiol., 157: 485-92, 2003.

Longnecker, M.P., Wolff, M.S., Gladen, B.C., Brock, J.W., Grandjean, P., Jacobson, J.L., Korrick, S.A., Rogan, W.J., Weisglas-Kuperus, N., Hertz-Picciotto, I., Ayotte, P., Stewart, P., Winneke, G., Charles, M.J., Jacobson, S.W., Dewailly, E., Boersma, E.R., Altshul, L.M., Heinzow, B., Pagano, J.J. and Jensen, A.A.: Comparison of Polychlorinated Biphenyl Levels across Studies of Human Neurodevelopment. Environ. Health Perspect.111: 65-70, 2003.

Gene Expression Changes Found in Individuals Accidentally Exposed to Dioxin in 1976.

A long-term collaborative research study between the NIEHS, the National Cancer Institute, the Centers for Disease Control and Prevention and Italian investigators at the University of Milan and the Hospital of Desio examined gene expression in people environmentally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a result of an industrial accident in Seveso, Italy in 1976. This population-based study evaluated the impact of TCDD exposure on mechanistically based biomarkers of dioxin response in peripheral blood mononuclear cells from approximately 120 men and women. Changes in gene expression were analyzed with respect to serum TCDD levels, genetic polymorphisms, demographic variables such as age and gender, and experimental variables related to laboratory techniques. In this study, expression of the gene encoding the aryl hydrocarbon receptor, a TCDD-activated transcription factor, and cytochrome P4501A1 dependent enzyme activity was negatively associated with TCDD body burden. Furthermore, in vitro inducibility of cytochrome P4501B1 gene expression was found to be associated with variant alleles of the CYP1B1 gene. Together, these findings provide valuable data describing variability in gene expression in TCDD-exposed individuals, highlight the importance of accounting for laboratory measurement variability in molecular epidemiology studies, and identify genetic determinants of human variability in response to dioxin exposure and possible adverse health outcomes.

Landi, M.T., Bertazzi, P.A., Baccarelli, A., Consonni, D., Masten, S.A., Mocarelli, P., Patterson, D.G. Jr., Needham, L.L., Lucier, G., Caporaso, N. and Grassman, J.A.: TCDD-mediated alterations in AHR-dependent pathways in Seveso, 20 years after the accident. Carcinogenesis, 24: 673-680, 2003.

Landi, M.T., Baccarelli, A., Bertazzi, P.A., Pesatori, A., Consonni, D., Caporaso, N., Patterson, D.G. Jr., Needham, L.L., Mocarelli, P., Grassman, J.A., Masten, S.A. and Lucier, G.W.: Correspondence re: Toide et al., Aryl Hydrocarbon Hydroxylase represents CYP1B1, and not CYP1A1, in human freshly isolated white cells: trimodal distribution of Japanese population according to induction of CYP1B1 mRNA by environmental dioxins. Cancer Epidem., Biomark. Prev., in press.

Chromatin structure in Drosophila telomeres is regulated by mechanisms that control telomere length.

Chromatin structure in telomeric regions can be monitored using a transgene inserted into a telomere. Expression of a telomeric white reporter gene increases in response to deletion of the telomere associated sequence (TAS) on the homologue, but only when the reporter is next to a terminal transposon array that includes at least one complete HeT-A element. The level of expression, which is a function of the number of highly expressing spots, increases with the number of HeT-A elements in cis. It should be noted in this regard that telomere length in Drosophila is maintained by the targeted transposition of the non-LTR retrotransposons, HeT-A and TART to chromosome ends, and that transcription is the first step in the retrotransposition cycle. Thus, the transcriptional activation of HeT-A seems to counteract the previously described telomeric silencing that spreads from TAS in cis.

Mason, J.M., Konev, A.Y., Golubovsky, M.D. and Biessmann, H.: Cis- and trans-acting influences on telomeric position effect in Drosophila melanogaster detected with a subterminal transgene. Genetics, 163:917-930, 2003.

Elucidation of the Mechanism of Brain Formation

It has been believed for long that BMPs play critical roles for formation of neural tissues, but lack of proper in vivo models has prevented the exploration of actual mechanisms. NIEHS scientists have established a knock-out mouse model of one of the BMP receptors, BMPr1a, specifically in the most dorsal section of the elencephalon. This unique model has provided evidence that BMP is required for formation of the most dorsal structure of telencephalon, choroid plexus.

Hebert, J.M., Mishina, Y. and McConnell, S.K.: BMP signaling required locally to pattern the dorsal telencephalic midline. Neuron 35:1029-1041, 2002.

Damage To DNA Can Lead to Cancer and Heritable Birth Defects Unless Repaired.

Over the past several decades, several ways have been discovered by which such damage can be repaired. However, no fundamentally new mechanism has surfaced for many years. Now, a process called "replication repair" has been described by NIEHS scientists. The DNA damage is circumvented rather than removed, by a process in which a growing DNA strand jumps to an alternative template--the DNA strand already copied from the other parental DNA strand.

Kadyrov, F.A. and Drake, J.W.: Properties of bacteriophage T4 proteins deficient in replication repair. J. Biol. Chem., 278:25247 - 25255, 2003.

Large New Prospective Cohort, The National Children's Study, Being Planned To Evaluate Environmental Effects On The Health Of Children.

In response to the Children's Health Act of 2000, investigators at NICHD, NIEHS, EPA, and CDC are planning a large new cohort study of the determinants of child health. The planning process includes a careful evaluation of priorities in child health and the design

of a national study that will allow huge advances in studying the determinants of child health.

The National Children's Study Interagency Coordinating Committee. The National Children's Study of Environmental Effects on Child Health and Development. Environ. Health Perspect. 111:640-6, 2003.

Inactivation of a NADH Kinase Gene Involved in the Natural Defense Against Oxidative Stress Causes Mutations in Mitochondrial DNA.

Using a new methodology to assay the genetic stability of mitochondrial genomes readily, NIEHS scientists have identified a mitochondrial NADH kinase (Pos5) in Saccharomyces cerevisiae that functions to protect mitochondria against oxidative stress. The Pos5 is used as part of our natural anti-oxidant defenses and mutation of this gene can cause an increase in mutations in the mitochondrial genome by over 50-fold.

Strand, M.K., Stuart, G., Longley, M.J., Graziewicz, M.A., Dominick, O.C. and Copeland, W.C.: POS5 gene of Saccharomyces cerevisiae encodes a mitochondrial NADH kinase required for stability of mitochondrial DNA. Eukaryotic Cell, 4: in press, 2003.

Computational Evidence For a Protective Mechanism Against Common Cause of Mutations in Human Genome.

Human DNA is constantly subjected to environmental forces that result in mutations and some of these mutations can eventually lead to serious diseases such as cancer. By analyzing several million DNA patterns surrounding human genetic variations, NIEHS scientists have uncovered "fingerprint" sequences that reveal the impact of important mutation mechanisms. Existing theories of mutagenesis have been validated using this approach. Genome features called "CpG Islands" are apparently protected from mutation. This analysis provides new insights into the forces that govern variation in the human genome, represents a substantial advance in our capability to perform high-throughput computational analysis of the human genome, and has generated numerous valuable leads for ongoing studies of human disease.

Tomso, D.J. and Bell, D.A.: Sequence context at human single nucleotide polymorphisms: overrepresentation of CpG dinucleotide at polymorphic sites and suppression of variation in CpG islands. J. Mol. Biol. 327:303-308, 2003.

Metabolic Pathway Differences For Nitrotoluene Isomers Lead to Different Carcinogenic Outcomes.

O-Nitrotoluene and p-Nitrotoluene are structurally related chemicals, differing only in the placement of the nitro group on the aromatic ring. NIEHS toxicologists found that o-nitrotoluene caused a broad spectrum of cancer in rodent models including colon carcinomas, hemangiosarcomas, skin tumors, and mammary tumors. In contrast, p-

nitrotoluene did not cause these cancers. The metabolic pathways for o-nitrotoluene and p-nitrotoluene differ, and only the ortho isomer is capable of forming a carcinogenic metabolite. These studies show that understanding differences in metabolism of environmental chemicals can be used to predict carcinogenic outcome.

Dunnick, J.K., Burka, L.T., Mahler, J. and Sills, R.: Carcinogenic potential of o-nitrotoluene and p-nitrotoluene. Toxicology 183, 221-234, 2003.

Rat Central Serotonin 5-HT_3 Receptors: Functional and Molecular Characterization in Rat Hippocampus, and Regulation by Casein Kinase II.
Using electrophysiological and molecular techniques, NIEHS scientists have found evidence, at least in some cells, for the co-expression and co-assembly of the 5-$HT_{3A\text{-short}}$ and α4 n-acetylcholine receptor subunits, the first demonstration of co-assembly of subunits from diverse ligand-gated ion channels in vivo. However, no functional or molecular evidence for the heteromeric co-assembly of the 5-HT_{3A} and 5-HT_{3B} subunits could be found in hippocampal interneurons. In addition, they found no evidence to suggest that either the 5-HT_{3B} or the 5-$HT_{3A\text{-long}}$ subunits are expressed in these neurons. In addition in NG108-15 cells, a model cell line, the 5-HT_3 receptors are directly regulated by the enzyme, casein kinase II, the first such demonstration to date.

Sudweeks, S.N., van Hooft, J.A. and Yakel, J.L.: Serotonin 5-HT_3 Receptors in Rat CA1 Hippocampal Interneurons: Functional and Molecular Characterization. J. Physiology 544:715-726, 2002.
Jones, S. and Yakel, J.L.: Casein kinase II (protein kinase CK2) regulates serotonin 5-HT_3 receptor channel function in NG108-15 cells. Neuroscience 119: 629-634, 2003.

Diethylstilbestrol Exposure Can Lead to Leiomyomas.
NIEHS scientists have found that prenatal exposure to diethylstilbestrol (DES) can lead to increased incidence of smooth muscle uterine leiomyomas in mice. These DES-induced leiomyomas have typical histomorphologic and some immunohistochemical characteristics of spontaneously occurring smooth muscle tumors.

Newbold, R.R., Moore, A.B. and Dixon, D.: Characterization of uterine leiomyomas in CD-1 mice following developmental exposure to diesthylstilbestrol. Tox. Pathol. 30:611-616, 2002.

Determination of the Solution Structure of Ribonuclease H
NIEHS scientists determined the first solution structure of the Ribonuclease H domain of HIV reverse transcriptase. This enzyme is essential for replication of the human immunodeficiency virus, and contains two catalytic sites – a polymerase site and a second site with RNase H activity. Although there has been extensive drug development targeting the polymerase site, there are currently no clinical drugs that target the RNase H

site. It is anticipated that the availability of the solution structure will contribute toward the development of such drugs.

Pari, K., Mueller, G.A., DeRose, E.F., Kirby, T.W. and London, R.E.: Solution structure of the RNase H domain of the HIV-1 reverse transcriptase in the presence of magnesium. Biochemistry 42:639-650, 2003.

Development of a Specific Boronic Inhibitor of γ-Glutamyl Transpeptidase

Boron is an essential trace element but at higher levels exhibits significant toxicity, particularly to male reproductive function. Based on proposed ternary borate complexes with the enzyme γ-glutamyl transpeptidase, NIEHS scientists have developed a specific boronic acid inhibitor of this enzyme. During the past year, they obtained the first evidence for the covalent binding of borate to an enzyme, in this case trypsin, as a ternary complex. The demonstration of ternary covalent complexes involving enzymes, alcohols and borate provides a potential basis for the physiological activity as well as the toxicity of borate.

London, R.E. and Gabel, S.A.: Formation of a trypsin-borate-4-aminobutanol ternary complex. Biochemistry 41:5963-5967, 2002.

Transue, T.R., Krahn, J.M., Gabel, S.A., DeRose, E.F. and London, R.E.: Crystal structures of ternary and quaternary complexes formed from trypsin, borate, and alcohols, in preparation.

Dynamic Behavior of the Glucocorticoid Receptor Probed.

NIEHS scientists studied the mobility of the glucocorticoid receptor in the nuclei of living cells using fluorescence recovery after photobleaching (FRAP). They found that ligand binding decreases mobility of the receptor and that the extent of this decrease can vary in an affinity-dependent manner for different ligands. Furthermore, they found that DNA-binding and ligand-binding domains both play a role in this decreased mobility. These results suggest that ligand binding to glucocorticoid receptor may cause a conformational change that targets the receptor to relatively immobile nuclear domains, and provides new insight on the behavior of this receptor system in the nucleus.

Schaaf, M.J.M. and Cidlowki, J.A.: Molecular determinants of glucocorticoid receptor mobility in living cells: the importance of ligand affinity. Mol. Cell. Biol. 23:1922-1934, 2003.

Development of Potent Opioid Mimetic Agonists and Antagonists.

NIEHS scientists designed a new class of opioid mimetic compounds, substances that interact within the brain similar to the action of morphine, that are stable when injected peripherally in mice. Essentially, the material consists of two unusual amino acids tethered together by a simple carbon chain. The simplicity of this new material underscores its effectiveness for potential application in clinical treatment or veterinary

applications. Based on those results, another new group of similar synthetic compounds exerted oral bioavailability; that activity was approximately half of that found with morphine. This indicates that this substance was absorbed through the gut and transported in the blood to the brain where it crossed the blood-brain barrier to produce analgesia. Further, subtle modification of another family of antagonists, which had been transformed into an agonist, reverted back to an antagonist; however, in this conversion the compounds became even more potent antagonists by factors of 5 to 10. These results indicate that small, discrete changes in an opioid substance can exert profound affects on its activity. Several of these compounds are under review for patent protection in both the U.S. and in Japan.

Okada, Y., Tsuda, Y., Yokoi, T., Sasaki, Y., Ambo, A., Nagata, M., Yunden, J., Bryant, S.D. and Lazarus, L.H.: Unique high affinity synthetic δ-opioid receptor agonists with central- and systemic-mediated analgesia. J. Med. Chem., on-line 16 June, 2003.

Okada, Y., Jinsmaa, Y., Miyazuki, A., Fukita, Y., Fujisawa, Y., Shiotani, K., Li, T., Tsuda, Y., Yokoi, T., Ambo, A., Sasaki, Y., Bryant, S.D. and Lazarus, L.H.: Oral availability of a new class of analgesics. Nature, submitted, 2003.

Balboni, G., Salvadori, S., Guerrini, R., Negri, L., Giannini, E., Bryant, S.D., Jinsmaa, Y. and Lazarus, L.H.: Synthesis and opioid activity of N,N-dimethyl-Dmt-Tic analogues: acquisition of potent δ antagonism. Bioorg. Med. Chem. submitted, 2003.

Molecular Model of the δ-opioid Receptor and Docking of Opioid Ligands.

A computer-generated model of the δ-opioid receptor based mutations introduced into the X-ray diffraction structure of bovine rhodopsin revealed new residues buried within the receptor that may be responsible for the differential action of agonists and antagonists.

Bryant, S.D., Okada, Y., Tsuda, Y., Fujita, Y., Yokoi, T., Yunden, J. and Lazarus, L.H.: Molecular modeling of structurally related bioactive δ-opioidmimetics: parameters defining δ- and μ-receptor selectivity. In, Benedetti E, Rocchi R (eds.) Peptides 2002, in press 2003.

Bryant, S.D., Salvadori, S., Guerrini, R., Balboni, G., Yunden, J. and Lazarus, L.H.: Computational docking and opioidmimetics: investigation of δ-opioid agonist and antagonist receptor interactions. In, Benedetti E, Rocchi R (eds.) Peptides 2002, in press 2003.

Bryant, S.D., Yunden, J., Salvadori, S., Okada, Y. and Lazarus, L.H.: Dmt and opioid peptides: a potent alliance. Biopolymers/Peptide Science, 71, 86-102, 2003.

Dogma of Chemically Induced Somatic Mutagenesis: Germ Cell Mutagenesis Refuted With Implications For Risk of Acrylamides in Foods.

NIEHS scientists have shown that NHMA induced high levels of genetic damage in mouse germ cells with no induction of mutations in somatic cells of these same mice.

These results refuted the long held dogma that all chemicals which cause heritable genetic damage in germ cells, that can lead to birth defects, infertility and predisposition to cancer, also cause somatic cell mutations, that can lead to cancer. These results indicates the need for the NTP to evaluate chemicals for their germ cell mutagenicity independent of their somatic cell mutagenicity or lack thereof and also suggest this acrylamide congener bioaccumulates such that total accumulated dose is critical for its adverse effect; this may have important implications for assessing the human health risk of chronic exposures to acrylamides in foods.

Witt, K.L., Hughes, L.A., Burka, L.T., Mcfee, A.F., Mathews, J.M., Black, S.L. and Bishop, J.B.: Mouse bone marrow micronucleus test results do not predict the germ cell mutagenicity of n-hydroxymethylacrylamide in the mouse dominant lethal assay, Environ. Molec. Mutagen. 41:111-120, 2003.

Correcting the Draft Human Genome

NIEHS scientists have shown that some errors in the draft human genome sequence are the results of both mis-assembly and loss of specific DNA sequences during cloning in E. coli. Theire results suggest that transformation-associated recombination cloning in yeast might be a valuable method that could be widely used during the final stages of the Human Genome Project to isolate missing DNA segments.

Kouprina, N., Leem, S.H., Solomon, G., Ly, A., Koriabine, M., Otstot, J., Pak, E., Dutra, A., Zhao, S., Barrett, J.C. and Larionov, V.: Segments missing from the draft human genome sequence can be isolated by transformation-associated recombination cloning in yeast. EMBO Rep. 4:257-262, 2003.

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. 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. 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. 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. 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 (NTP) UPDATE

Dr. William Stokes Named Chief Veterinary Officer for PHS

NIEHS' Capt. William (Bill) Stokes has been named veterinarian chief professional officer for the Public Health Service Commissioned Corps. The appointment, by U.S. Surgeon General Richard H. Carmona, went into effect on May 1. As the chief veterinary officer, Dr. Stokes will coordinate veterinary professional affairs and oversee recruitment, retention, career development and readiness of the more than 100 PHS veterinary officers, stationed throughout the NIH, the Centers for Disease Control and Prevention, the FDA, and other federal agencies. Dr. Stokes will continue to direct the NTP's Interagency Center for the Evaluation of Alternative Toxicological Methods, which has led the federal government's reform of animal testing by introducing the use of scientifically acceptable non-animal testing to replace tests that expose animals to harsh chemicals.

NTP Launches New Technical Report Series

The NTP launched a new technical report series to be called Genetically Modified Models, or GMM series at the May 22 meeting of the NTP Board of Scientific Counselors Technical Reports Review Subcommittee, a standing subcommittee of the NTP Board of Scientific Counselors. At that meeting, the Subcommittee peer reviewed the draft findings and conclusions from the first two NTP technical reports in this series, aspartame (GMM-1) and acesulfame potassium (GMM-2). This new series will contain the results from NTP toxicology and carcinogenicity studies conducted in genetically modified models, such as transgenic mice that have had a key gene related to cancer or other diseases added, "knocked out" or slightly changed.

The actions from this meeting, including the subcommittee's recommendations on the findings and conclusions from carcinogenicity studies on aspartame and acesulfame potassium in p53 haploinsufficient mice as well as four other NTP studies conducted in traditional rodent models - 2-methylimidazole, propylene glycol mono-*t*-butyl ether, stoddard solvent IIC and triethanolamine - are available on the web. As the final reports from this new series are published, they will be available along with reports from the NTP Technical Report and NTP Toxicity Report series in hardcopy and electronic format from Environmental Health Perspectives. The electronic files are available free-of-charge.

NTP Board of Scientific Counselors

The annual meeting of the NTP Board of Scientific Counselors is scheduled for September 10-11, 2003 at the NIEHS. The NTP Board of Scientific Counselors ("the Board") is composed of scientists from the public and private sector and provides primary scientific oversight to the NTP. Primary agenda topics include: 1) a vision for the NTP that includes its concept and projection of new areas into which toxicology will develop in the next 5-10 years; 2) a presentation on the development of new, publicly accessible, electronic databases for NTP studies; 3) a demonstration of an interactive, web-based, 2-D-imaging system to evaluate the pathological outcomes of NTP studies; and 4) updates on the NTP testing program including the design of studies on radio-frequency radiation from cellular phone devices, collaborations with the National Institute of Occupational Safety and Health, studies on medicinal herbs and dietary supplements and the recommendations of the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) for substances nominated to the NTP for study. There will also be updates on the NTP Board of Scientific Counselors Technical Reports Peer Review Meeting held on May 22, 2003, the status of the 11th Edition of the Report on Carcinogens and the NTP Center for the Evaluation of Risks to Human Reproduction. Time is allotted during the meeting for the public to present comments to the Board and NTP staff on agenda topics.

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

A meeting of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee, a standing subcommittee of the NTP Board of Scientific Counselors is scheduled for October 14-15, 2003 at the Marriott at Metro Center in Washington, DC. Scheduled for peer review are the second set of nominations to the 11th Edition of the Report on Carcinogens: diazoaminobenzene, hepatitis B virus, hepatitis C virus, human papillomaviruses (genital-mucosal types), X-radiation and gamma-radiation, neutrons, and lead and lead compounds. Background documents for these nominations, public comments received on them and details about the meeting are posted on the NTP web site.

Digitized Atlas of Rodent Kidney Lesions

The Laboratory of Experimental Pathology, Environmental Toxicology Program, announces the availability of a digitized atlas of rodent (rat and mouse) kidney lesions and lower urinary tract lesions. The purpose of this atlas is to familiarize pathologists and others with the spontaneous and chemically induced lesions seen in the kidneys of laboratory rodents. It contains a list of references on lesions of the rodent kidney and lower urinary tract. This atlas is available on the NTP web site.

The web site also links to two additional atlases released previously: *A Digitized Atlas of Mouse Liver Lesions* and *Lesions of Genetically Altered Mice*.

NTP Study Nominations

The NTP continuously solicits and accepts nominations for toxicological studies to be undertaken by the program. The nominations are subjected to several levels of review before selections for testing are made and toxicological studies are designed and implemented. As part of this review process, the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) met on June 10, 2003, to review 14 new nominations and make study recommendations. Internet links to electronic versions of supporting documents for each nomination and further information on the NTP and the NTP Chemical Nomination and Selection Process can be accessed through the NTP web site. The NTP is currently soliciting public comments on the nominations and study recommendations (Federal Register July 16, 2003: Vol. 68, No. 136, pages 42068 – 42071). The public is also invited to provide oral comments at the September 10-11, 2003 meeting of the NTP Board of Scientific Counselors.

Substances recommended for testing by the ICCEC

- Acrylamide [79-06-1] and Glycidamide [5694-00-8]: recommended studies - toxicological characterization, toxicokinetics, mechanistic (hemoglobin adducts), carcinogenicity and bioavailability from food and drinking water.

- Antimony trisulfide [1345-04-6]: recommended studies: chronic toxicity/carcinogenicity.

- Cadmium telluride [1306-25-8]: recommended studies - toxicological characterization and chemical disposition (oral and inhalation routes).

- Cedarwood oil, Virginia [8000-27-9]: recommended studies - toxicological characterization and developmental toxicity.

- Chondroitin sulfate [9007-28-7]: recommended studies - chronic toxicity/carcinogenicity and carcinogenicity of chondroitin sulfate and glucosamine combined.

- Dimethylethanolamine [108-01-0]: recommended study – metabolism.

- Drugs positive for QT Interval Prolongation/ Induction of *Torsade* Proarrhythmia [No CAS No.]: recommended studies - initiate a study program to develop *in vitro* and *in vivo* test systems for assessing QT interval prolongation.

- Glucosamine [3416-24-8]: recommended studies - chronic toxicity/carcinogenicity and carcinogenicity of chondroitin sulfate and glucosamine combined.

- Nanoscale materials [No CAS No.]: recommended studies – size- and composition-dependent biological disposition of nanocrystalline fluorescent semiconductor materials, toxicological characterization of high-aspect-ratio carbon nanomaterials,

role of particle core and surface composition in the immunotoxicity of the above listed materials, and phototoxicity of representative metal oxide nanoparticles.

- *trans*-Resveratrol [501-36-0] recommended studies - toxicological characterization, carcinogenicity and reproductive toxicity.

- Tetrabromobisphenol A [79-94-7]: recommended studies - toxicological characterization, neurodevelopmental toxicity, and carcinogencity.

- Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) [21850-44-2]: recommended studies - toxicological characterization, *in vivo* genotoxicity, metabolism and carcinogencity.

- Tungsten [7440-33-7]: recommended studies - toxicological characterization and carcinogenicity; studies should focus on a representative soluble tungsten compound.

Substance for which the ICCEC recommends no study at this time

- 4-Phenylcyclohexene [4994-16-5]: low suspicion of hazard based on available human exposure and toxicity information.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The following report, *ICCVAM Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays* (NIH No. 03-4503) is available on the NICEATM/ICCVAM web site or by contacting NICEATM. It contains recommendations by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) on minimum procedural standards and reference chemicals for standardization and validation of *in vitro* estrogen and androgen receptor binding and transcriptional activation assays. The Environmental Protection Agency asked ICCVAM to evaluate the validation status of these assays proposed as possible components of the EPA Endocrine Disruptor Screening Program (EDSP) Tier 1 screening battery. ICCVAM agreed to this evaluation based on their potential interagency applicability and public health significance.

The ICCVAM Dermal Corrosivity and Irritation Working Group has proposed Minimum Performance Standards (MPS) for three types of *in vitro* methods used for assessing the dermal corrosivity hazard potential of chemicals. The ICCVAM developed the proposed MPS to communicate criteria that can be used to determine if similar test methods have comparable accuracy and reliability. After the public comment period (Federal Register July 1, 2003: Vol. 68, No. 126, pages 39104-5) ends and the report is finalized, ICCVAM MPS will be published as an addendum to previously published ICCVAM reports on these test methods and forwarded to federal agencies for their consideration. Copies of the MPS will be made available electronically on the ICCVAM/NICEATM web site or in hardcopy by contacting NICEATM.

ICCVAM and NICEATM are collaborating with the European Centre for the Validation of Alternative Methods (ECVAM) to conduct a validation study on *in vitro* test methods for assessing dermal irritation. NICEATM is soliciting chemical and protocol information/test data on commercially available chemicals used for dermal or ocular irritancy in rabbits and/or for dermal irritancy in humans using standardized testing methods (Federal Register July 16, 2003: Vol. 68, No. 136, pp. 42067-8). ICCVAM and its Dermal Corrosivity and Irritation Working Group will review the data and identify chemicals that might be appropriate for use in the upcoming validation study. The resulting list of chemicals tested for skin irritancy in rabbits and/or humans and supporting data will also be provided to ECVAM its consideration.

NICEATM and the ECVAM are conducting a collaborative validation study to evaluate two *in vitro* basal cytotoxicity assays proposed for predicting starting doses for *in vivo* acute oral toxicity assays and lethal concentrations in humans. Three laboratories are participating in the evaluation of the neutral red uptake assays using both a mouse cell line (*i.e.,* BALB/c 3T3 fibroblasts) and a primary human cell line (*i.e.,* normal human epithelial keratinocytes). The cytotoxicity results for 72 coded chemicals, representing a wide range of toxicity, will be used to predict starting doses for the *in vivo* acute oral toxicity assays. Phase I testing was completed in May 2003. All labs have Phase II protocols in place and testing of nine coded chemicals began on June 2. Following

completion of Phase II, final optimized protocols will be prepared and used for Phase III, which will involve testing 60 coded chemicals.