

**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
Feb 12-13, 2001**

The National Advisory Environmental Health Sciences Council was convened for its one-hundred second regular meeting on February 12, 2001, at 8:45 a.m., in the Natcher Building 45, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public on from 8:45 a.m. until 5:45 p.m. and on February 13 from 8:30 a.m. until 9:00 a.m. The meeting was closed for consideration of grant applications on February 13, from 9:05 a.m. until 12:25 p.m. Dr. Kenneth Olden presided as Chair.

Members Present:

Daniel Baden, Ph.D.
David O. Carpenter, M.D.
Noreen M. Clark, Ph.D.
Deborah A. Cory-Slechta, Ph.D.
Deeohn Ferris, J.D.
Philip M. Iannaccone, M.D., Ph.D.
George Friedman-JimZnez, M.D.
Michael Karin, Ph.D.
Daniel Nebert, M.D.
Peggy Shepard
Martyn T. Smith, Ph.D.
Robert D. Wells, Ph.D.
Harriett M. Wieder
Gerald Wogan, Ph.D.

Members Absent:

S. Haunani Apoliona
Nancy Chuda

Barbara S. Hulka, M.D.
R. Michael McClain, Ph.D.

Ex Officio Members Present:

David N. Erwin, Ph.D.
Roberta F. White, Ph.D.

Ex Officio Member Absent

Susan M. Sieber, Ph.D.

Liaison Members Present:

Daniel Acosta, Ph.D.
David Ringer, Ph.D.
Thomas Sinks, Ph.D.
Robert Spengler, Ph.D.

Liaison Members Absent:

Roy Fleming, Ph.D.
Hal Zenick, Ph.D.

Members of the Public Present:

Christopher Bradfield, Ph.D., McArdle Laboratory for Cancer Research
Joan Cranmer, Ph.D., University of Arkansas Medical School
Dale Dirks, President of the Health and Medicine Counsel of Washington
T. J. Dunlap, JTxCo, Texas
Michael Gallo, Ph.D., Rutgers, the State University of New Jersey and
University of Medicine and Dentistry of New Jersey
Frederick Guengerich, Ph.D., Vanderbilt University
David Mineo, University of Georgia
Al Nugent, Midwest Research Institute

Pat Phibbs, BNA
Leona Samson, Ph.D., Harvard School of Public Health

Federal Employees Present:

NIEHS Staff:

Beth Anderson
Martha Barnes
Linda Bass, Ph.D.
Perry Blackshear, M.D., D.Phil
David Brown
Gwen Collman, Ph.D.
Allen Dearry, Ph.D.
Dorothy Duke
Thorsten Fjellstedt, Ph.D.
Mary Gant
Bill Grigg, M.D.
Jerry Heindel, Ph.D.
Zoe Huang, M.D.
Ethel Jackson, D.D.S.
Annette Kirshner, Ph.D.
Cindy Lawler, Ph.D.
Edith M. Lee
Leping Li, Ph.D.
Francine Little
Carolyn Mason
J. Patrick Mastin, Ph.D.
Michael McClure, Ph.D.
RoseAnne McGee
Joan Packenham, Ph.D.
Jerry Phelps
Christopher Portier, Ph.D.
Anne Sassaman, Ph.D.
Carol Shreffler, Ph.D.
William Suk, Ph.D., M.P.H.
Raymond Tennant, Ph.D.
Claudia Thompson, Ph.D.
Fred Tyson, Ph.D.
Bennett Van Houten, Ph.D.
Jose Velazquez, Ph.D.
Denise Warren
Clarice Weinberg, Ph.D.
Brenda Weis, Ph.D.
Charles Wells, Ph.D.
Samuel Wilson, M.D.
Carolyn Winters
Gerri Wolfle

Other Federal Staff:

David Batson, FDA
Paul DiStefano, FDA
Ellie Ehrenfeld, Ph.D. CSR
Cassandra Jackson, FDA
Peggy L. Jones, FDA

Debra Lewis, FDA
Michael Martin, Ph.D., CSR
Christine Melchoir, Ph.D., CSR
Marie Nolte, FDA
Juanita Pointer, FDA
John Ruffin, Ph.D., NCMHD
Barbara Simms, FDA
Rass M. Shayiq, Ph.D., CSR

I. CALL TO ORDER AND OPENING REMARKS

The one hundred second regular meeting of the National Advisory Environmental Health Sciences Council was called to order by Dr. Olden, who welcomed the Council members and expressed his regrets for the ones who were not able to attend. Dr. Olden acknowledged Dr. Acosta who was attending his first Council meeting as a liaison member from the Society of Toxicology. He also acknowledged the incoming members present. They included: Drs. Cranmer, Friedman-JimZnez, Guengerich and Gallo. Ms. Dale Eastman has also been appointed but was unable to attend this meeting.

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

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

III. CONSIDERATION OF MINUTES OF SEPTEMBER 11-12, 2000 MEETING

Council members accepted the minutes without change.

IV. FUTURE COUNCIL MEETING DATES

May 21-23, 2001 (Monday, Tuesday, and Wednesday) in Research Triangle Park (will include Retreat)

September 10-11, 2001 (Monday and Tuesday) in Research Triangle Park

Feb 11-12, 2002 (Monday and Tuesday) in Bethesda

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

Dr. Olden began his report with a discussion of the budget. The budget had been approved since the last meeting and NIEHS has a 13.5% increase over Fiscal Year 2000. The Congress is committed to doubling the NIH budget over a 5-year period and this completes the third year. The new administration is also committed to doubling the NIH budget on the same cycle. We hope to see increases of 14-15% for the next two years. The Secretary is supportive of biomedical research so we expect things to go very well for NIH. There have been discussions of NIH receiving a disproportionate share of the science budget. Congressman Boehlert has

expressed his concern about other science agencies not receiving adequate funding. He has indicated that environment is an area that is under-funded. There was a concern that Senator Specter would step down as the Chairman of Labor HHS Appropriation Committee, but he decided not to after receiving letters from many science advocacy groups. Congressman John Porter, a good friend of biomedical research has retired. He was replaced by Ralph Regula from Ohio, who is also very supportive of biomedical research. Department of Health and Human Services (DHHS) Secretary Thompson plans to meet with NIH Institute directors soon. Indications are that the transition will be smooth.

Dr. Olden noted that this year institute directors will have limited time to present their case before the House of Representatives Labor HHS Appropriation Committee. Chairman Regula is scheduling information meetings prior to the hearings, at which 2-3 institute directors will participate in a panel to provide information to Congress.

Dr. Olden then reported on other items of interest.

- The Superfund Basic Research and Workers Education and Training Program funds will be appropriated directly to NIEHS this year instead of being a part of the Environmental Protection Agency budget. While this does not change the Superfund Program in terms of what we do, Dr. Olden will get a chance for the first time to testify before the HUD Independent Agencies Appropriation Committee.
- Congresswoman Louise Slaughter has introduced a bill co-sponsored by Congressman David Price to establish environmental research centers on women's health, to be developed by NIEHS. The centers will put emphasis on prevention and are modeled after our children's health centers that we initiated in 1998 in partnership with the EPA. She has proposed a first year budget of \$4M. This program is consistent with what we already doing but will move the research agenda at a faster pace.
- A few years ago, NIEHS and the EPA created the Inter-Agency Coordinating Committee for the Validation of Alternative Models of Toxicity Testing (ICCVAM). This Committee meets as often as necessary to review new technologies that have been developed and validated by the developer. It then reviews the method to make sure it is valid for the test the developer claims it is useful for. The Committee can only provide a scientific evaluation of the methodology. The regulatory agency has not been required to accept the methodology or respond to the Committee. However, there is new legislation requiring regulatory agencies to explain why they will not accept and use the new technology if validated by ICCVAM.
- Historically, a group of lay people, scientists, and a Nobel Prize Committee Group have testified before the Congress about the NIH budget. These hearings are likely to emphasize interdisciplinary science and new technologies, which is consistent with the direction of science. This approach will likely require new funding mechanisms as well as some restructuring at the institutional level. (Handout available upon request.)
- The National Research Council released a report on training needs and there has been considerable discussion at NIH on the subject. There are two conclusions from this report and NIH is preparing a response. (Handout available upon request.)
 1. The number of Ph.D. trained in biomedical science is more than adequate to meet the nation's needs. However, there is a recognition of variations in fields, as well a need in get M.D.'s attracted to science and to increase the number of underrepresented minorities being trained in the Ph.D. program.

2. The number of students receiving training fellowships decreased by about 50 percent since the mid-1970s. This may be due to the fact that these people were shifted to R01 grants.
 3. Congress has established the National Cancer Legislation Advisory Committee to take testimony from the scientific community as to what the National Cancer Program should look like in the years ahead. NIEHS has testified about the role of the environment in cancer etiology. The discussion was very productive and it is likely that there will be an emphasis on prevention.
 4. There was a productive discussion with the Adhoc Group for Medical Research Funding, which has a growing interest in and support for environmental research and NIEHS. In their recommendation to Congress they emphasized four things need to be done, among them toxicogenomics - developing new effective test systems to identify toxicants and carcinogens; and gene environment interaction with emphasis on the environment.
- NIEHS introduced our toxicogenomics effort in early December with a major press conference at the National Press Club. The New York Times did a full-page write-up on the toxicogenomics effort at NIEHS about two weeks prior to the conference. There were also articles in other publications following that write-up. Since that time we have held workshops around the country, the first one immediately following the press conference at MIT.
 - There is an article in the January issue of Environmental Health Perspectives on Toxicogenomics and gene arrays as applied to toxicology. The authors took three distinct classes of chemicals and demonstrated that they could generate a unique fingerprint or signature pattern. We believe that the Environmental Genome Project and toxicogenomics are the most exciting developments in environmental health and toxicology in decades and are investing considerable time and resources on these projects. (Handout available upon request.)
 - There will be a conference on ethical, social, and legal implications of genomics in September, co-sponsored by the NIEHS, the West Harlem Environmental Action Group, and the Columbia Environmental Health Sciences Center. A series of workshops to deal with the enormous regulatory implications of environmental genomics and toxicogenomics will follow.
 - NIEHS is sponsoring a symposium on Parkinson's disease at the Society of Toxicology (SOT) Annual Meeting, being held in San Francisco. Although the SOT meeting has not historically focused on diseases, the Society is working with NIEHS to make this a part of the program. There have been a lot of breakthroughs in Parkinson's disease as it relates to the environment and this is an opportunity to highlight the success and identify for toxicologists needs and opportunities.
 - We continue to have our town meetings around the country. Our most recent one was in Seattle where Congressman McDermott accompanied us on a tour to areas of the city where many toxic environmental problems exist. He then chaired one of the evening working groups. We try to have 3-4 town meetings per year, as these are a way to get important parties responsive to our needs, and to hear theirs.
 - The New England Journal of Medicine published an article by Professor Samet and colleagues from Johns Hopkins University confirming that fine particles in the air are associated with increased deaths. It is a confirmation of the Harvard's Six-Cities Study supported by NIEHS.
 - About seven years ago, a multi-center clinical trial involving five institutions initiated a study to determine if a chelating agent called Succimer would reverse the IQ loss caused by lead poisoning. The trial is now completed and a report has been written and accepted for publication in the New England Journal of Medicine.

- Dr. Olden congratulated Dr. Carpenter on a letter he wrote which appeared in the Wall Street Journal on January 4. The letter rebutted a claim the PCBs don't have a role in human cancers. The letter dealt with the scientific issues.
- There was a meeting with the National Breast Cancer Coalition in New York in October. The Coalition suggested that the Institute create a lay consumer advisory group. Dr. Olden is exploring various models of such groups and indicated his support for a process by which representatives from various disease advocacy groups can meet with the Institute staff and others to discuss their concerns and ideas.
- The most recent Centers Directors Meeting was held in Detroit and hosted by Wayne State University. This is a good way to encourage inter-center collaborations. Dr. Olden also announced plans to fund a new Environmental Health Sciences Center at the University of North Carolina at Chapel Hill.
- In order to promote collaboration with other institutes, Dr. Olden initiated a Directors Seminar Series where we invite a director from one of the other institutes to spend a day at NIEHS. Drs. Gerald Fishbach [former director of the National Institute of Neurological Disorders and Stroke (NINDS)] and Allen Spiegel [Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)] have been so far.
- NIEHS led a U.S. delegation to Singapore to meet with Vietnamese government leaders and scientists to talk about Agent Orange and the possibility of studying potential health effects of dioxin on the Vietnamese. The Department of Defense, Department of State, and Department of Health and Human Services are very interested in this issue. Agent Orange research and this interaction with Vietnam was one of the subjects the new administration asked to be briefed on. We are waiting to determine the next steps in this venture.
- NIEHS has an agreement with a publisher in China to publish the Environmental Health Perspectives journal six times a year in Chinese. This helps get information out and also increases subscriptions to our journal. They are going to select articles they feel are most relevant to their population from the twelve issues we publish. The first issue will come out soon.

Dr. Olden highlighted a couple of important announcements from the agenda book.

- Allen Wilcox, Chief of the Epidemiology Branch, will become the editor of the Journal of Epidemiology, effective March 1, 2001.
- While NIEHS started a clinical program a few years ago in collaboration with UNC and Duke hospitals, we recognized that our interaction with other institutes could be enhanced if we had space in the Clinical Center in Bethesda. We now have the first clinical scientists to be assigned to our space in the Clinical Center. Dr. Olden introduced Drs. Fred Miller and Lisa Rider. Dr. Miller is a rheumatologist/immunologist and Dr. Rider is a pediatric rheumatologist. Their interest is in autoimmune diseases.

Dr. Olden ended his report with remarks about a trip he took to Atlanta Georgia, where he attended a ceremony at the Morehouse College to install the first George and Barbara Bush Professor of Neurosciences at their School of Medicine. This was the culmination of several years of collaboration between Dr. Zach Hall, former director of the NINDS, and Dr. Peter McLeish, then at Harvard, to establish a neurosciences center at a historically black medical school. Dr. McLeish now heads the center, which has also been supported through NIEHS, the National Center for Research Resources, and the Office of Research on Minority Health. The center has flourished and Dr. McLeish has attracted

nationally competitive faculty. The Bushes endowed a professorship of \$1.5M in that division. It was an opportunity to celebrate a success story.

VI. REPORT OF THE DEPUTY DIRECTOR, NIEHS - Dr. Samuel Wilson

Dr. Wilson began his report with a note that he would continue on the same topic area as the last report he gave on environmental health and genomics. He followed up on recent events that have occurred since the last meeting. Today is the publication date of a series of articles in the journals Science and Nature dealing with sequencing of the human genome and the informatics challenge on understanding the significance of the wealth of information contained in that sequence.

Dr. Wilson drew attention to an article published in Nature Review that he and Dr. Olden wrote on environmental health and genomics. The article covered the concept of the environmental genome project. He also discussed the publication of the January edition of the Environmental Health Perspectives in which the first 37 or more pages were devoted to genomics and environmental health. The first article was done by Dr. Iannaccone - the "perspective" editorial.

Dr. Wilson briefly talked about the National Center for Toxicogenomics (NCT).

- He elaborated on the briefing at the National Press Club and the packet of material developed for that.
- He discussed highlights that have occurred in the NCT effort, referring to a handout for the workshop taking place on March 5 at N.C. State University on bioinformatics strategies. The workshop is part of the planning process for the NCT. It is being co-hosted by Dr. Afshari and Dr. Weir. This follows two workshops on messenger RNA profiling and proteomics. The former, developed by Drs. Leona Samson of MIT and Ben Van Houten of NIEHS, was held in December at MIT. The latter on proteomics was held in January and hosted by the University of Arizona in Tucson and organized by Drs. Dan Liebler of the University of Arizona and Dr. Ken Tomer, NIEHS. (Summaries of those workshops are available on the NIEHS Web site.) Both of these workshops included roundtable discussions and development of recommendations to the Institute.
- A request for applications announcement was released on November 7 for the extramural toxicogenomics consortium. The DERT-hosted pre-application meeting occurred on February 2 at NIEHS.

The success of the microarray workshop was the impetus for the scientific session for this Council meeting. Dr. Samson will discuss the work she has done. At the MIT Workshop there was a presentation by Dr. Ed Clark on the use of microarray approaches in terms of how to treat ovarian cancer. This was a very impressive example of reduction to practice of this technology of RNA profiling and illustrated how this field is fast-moving and has the potential of extraordinary impact in environmental health sciences. Dr. Wilson introduced the first of four speakers who discussed case studies on reduction to practice.

VII. PROFILING TOXICANTS WITH MICROARRAYS: IT WORKS! - Dr. Christopher Bradfield

An abstract of Dr. Bradfield's presentation is found in Attachment B. He began his talk by describing what he referred to as "grass roots" genomics or "mom and pop" genomics - genomics

that is being done by only a few people in the laboratory. The work he presented was done with a small group, and he gave some history of his laboratory and its movement into gene-environment interactions and how a microarray profile can serve as a diagnostic "fingerprint" to predict toxicity as well as to provide insights into basic molecular mechanisms.

VIII. MICROARRAY ANALYSIS REVEALS SURPRISES IN THE CELLULAR RESPONSE TO GENOTOXIC STRESS - Dr. Leona Samson

Dr. Samson chose to work in a yeast system because the complete genome, 6,200 genes, is known. She examined 3-methyl adenosine DNA glycosylase (MAG), which protects cells against alkylating agents, and specifically which transcripts changed on exposure to alkylating agents (AA). Six thousand two hundred (6200) genes were studied. Out of the entire genome, the expression of 294 increased and 139 decreased; and some 5000 genes were unchanged in their expression following exposure. What was more amazing is that if different doses of AA and times after exposure are examined, around 40% of all the genes change their expression levels. There was a 4-fold or greater change in a large number of gene categories (stress response, DNA repair, etc.), and at a 2-fold change, she saw massive up-regulation, especially in protein degradation. She speculated that there may be a down-regulation in protein synthesis while damage occurs. She also noted changes with time and dose and observed cell cycle effects.

Dr. Samson then looked at genes associated with effects on MAG, those co-regulated with MAG and DNA repair and protein degradation transcripts. If the transcription activator was deleted, function was lost and there was evidence that DNA repair and protein degradation genes are linked. She discussed the meaning of the roles of the 26S proteasome, including degradation of abnormal or damaged proteins and stimulation of base excision repair. A seminal question is what genes are important in the cell's reaction to damaging agents. She concluded that there are distinctive signatures of different alkylating agents, and that dose/time experiments are needed to finally determine the "signature" of a class of agents.

IX. GENE EXPRESSION ANALYSES REVEAL EFFECTOR PROFILES OF LIVER TOXICANTS - Dr. Ray Tennant

Dr. Tennant acknowledged the contributions of Drs. Cindy Afshari and Richard Paules of the NIEHS Microarray Center, and stated that there are several ways in which we can foresee the application of toxicogenomics. Among the primary areas of emphasis will be understanding how disease occurs, and efforts will be made to identify normal pathways of cellular responses to environmental agents or stressors and to identify the mechanisms of response of cells and organisms. In addition, toxicogenomics can be used to identify potential hazards through determining signature profiles of altered gene expression upon exposure to environmental agents. This information can be used to predict potential disease by identifying molecular pathways of pathogenesis revealed by global alterations in gene expression and to provide a digital pattern of injury and response that can be related to conventional indices of toxicity, including histopathology or clinical chemistry. Other important areas that toxicogenomics can contribute to will be in the identification of exposed individuals, and in the prevention of environmental diseases. He proposed that these can be most effectively accomplished through the development of a systematic reference database of chemical effects in biological systems. Dr. Tennant stated

that the Institute is taking incremental steps to establish the scientific foundation for these efforts and described the current gene expression cDNA array methodologies utilized by the Microarray Center.

One of the first issues they wanted to deal with is whether different toxicants lead to distinguishable gene expression patterns in exposed models, and he described a study conducted in collaboration with the Boehringer Ingelheim Pharmaceutical Company in which the effects of selected peroxisome proliferators, phenobarbital and d-manitol, were assessed in rats exposed for either 24 hours or two weeks. He described the protocol under which these experiments were conducted, involving three animals per test group and at least three independent hybridization/array analyses. The types of information that are yielded by these approaches can involve simply a list of the validated outliers or genes whose expression is significantly altered upward or downward. However, this information in itself is insufficient to adequately categorize the information obtainable from global gene expression arrays. Consequently, they have utilized a variety of analytical methods developed both in the NIEHS and in other companies. He described the results of the application of different computational analytical methods and demonstrated their ability to discriminate distinctive patterns of altered gene expression that reflected the pharmacologic activity of the chemicals in the exposed rates. Further analysis of animals that had been exposed for two weeks revealed subtle but important alterations that reflected not only the pharmacologic action of the chemical but also the incipient toxicity from prolonged exposure. Overall, they believe that these results validate the concept that gene expression arrays can be used to create a database of chemical- or drug-specific profiles that can ultimately be used in a predictive fashion.

X. USING EXPRESSION ARRAYS TO IDENTIFY DISEASE SUBTYPES AND ASSIGN PROGNOSIS - Dr. Clarice Weinberg

An abstract of Dr. Weinberg's presentation is found in Attachment C. Her presentation focused on the importance of subtypes in both clinical and epidemiological studies. They may result in differences in clinical management and prognosis, and be important in interpreting environmental epidemiology studies. She described analysis of gene expression data from 72 leukemia patients to look for different patterns, using the Genetic Algorithm to identify a subset of informative genes. After a series of manipulations of the data to develop specific patterns, her group concluded that expression arrays analyzed by this method can identify genes that discriminate between acute lymphoblastic leukemia and acute myeloid leukemia, and may also unmask clinically meaningful additional subtypes.

Following the presentations there was discussion among the council and presenters. Comments were made concerning the predictability of data and the fact that these efforts must be looked at as a long-term objective, as we must understand mechanisms through hypothesis-driven research. It was also suggested that we take advantage of models in which the genome has been sequenced to get at mechanisms and information on systems developed through evolution for protection against toxicants. Finally, the Institute was encouraged to develop partnerships with industry, which is putting significant resources into proteomics.

XI. REPORT OF THE ACTING DIRECTOR, NIH - Dr. Ruth Kirschstein

Dr. Kirschstein expressed excitement about the announcement of the day concerning the sequencing of the human genome and publication of the work from Celera and the Human Genome Project. She noted the prospects for exploring the more complicated issues around susceptibility to environmental effects and gene-environment interactions.

She reported to the Council that the new DHHS Secretary, Tommy Thompson, had met twice with Agency heads and that he is very interested in NIH, pledging to continue along the path of doubling the budget. The President's budget for Fiscal Year 2002 will be a "blueprint," or outline, as there has been no time for in-depth development. President Bush is trying to make good on his initiatives, NIH among them. However, Dr. Kirschstein reiterated Dr. Olden's comments that NIH will have to continue to justify budget increases and that Mr. Bohlert is interested in making sure that appropriations increase in all areas of science, including physical sciences. The justification will be particularly important with the changes in Congress, especially in the House. The new Labor/HHS Appropriations Committee Chair, Mr. Regula, plans to visit NIH soon.

New programs have been established within the NIH without significant new resources. These include the new National Center for Minority Health and Health Disparities and the National Institute of Biomedical Imaging and Bioengineering, for which no dollars were appropriated in the current fiscal year. The former will use funds previously allocated for its predecessor, the Office of Research on Minority Health. The latter will support basic, fundamental studies in bioengineering and bioimaging, but will not take funds or programs en masse from other institutes or centers. Other new issues include loan repayment programs for researchers in specific areas, particularly clinical research and health disparities.

Discussion with Council members ensued, focusing on translational research, career development mechanisms, and outreach programs. The question was raised as to new activities supported by increase in appropriations, and Dr. Kirschstein indicated that such information is being refined by NIH for the appropriations hearings. In response to a question, Dr. Kirschstein stated that she did not know if border health would be a priority for this administration.

There was further discussion about clinical research and loan repayment, particularly whether junior investigators in General Clinical Research Centers could apply. She replied that GCRCs are but one form of clinical center, and there are other more focused ones. Expansion of clinical research must be accomplished by a balance between these centers and individual research grants. Research itself is changing. Individual principal investigators need lots of resources at the institutional level, and all this will affect the dollars available for R01 grants.

In response to other questions, Dr. Kirschstein commented on the future of health disparities research and balance between that supported by the new Center and existing programs in institutes; the status of research using embryonic stem cells; human subjects protection and human tissue repositories; salaries for pre- and post-doctoral trainees; and non-American trainees.

XII. REPORT FROM DIRECTOR OF THE CENTER FOR SCIENTIFIC REVIEW, NIH - Dr. Ellie Ehrenfeld.

Dr. Ehrenfeld updated the Council on CSR reorganization activities and summarized her efforts and the report of the "Boundaries" Panel. The report of the Panel and updates on subsequent activities are available on the CSR home page. CSR is now in Phase II, which involves redesign of Study Sections within the Integrated Review Groups proposed by the Panel. Dr. Ehrenfeld described the process and the progress of the first "redesign" of hematology study sections. She also commented specifically on issues related to toxicology, which has been identified as a cross-cutting area that needs attention. A guiding principle in all of these activities is involvement of the scientific research community in the process. The schedule for the reorganization is on the Web site, though the process is somewhat behind the original projections. Dr. Ehrenfeld described the process as slow, but deliberative.

She then invited questions from the Council. She was asked about the status of Special Emphasis Panels, used in both CSR and institute review. She replied that she hoped to have fewer as a result of the reorganization.

One member stated that redesign of the process or of study sections was badly needed and expressed concern about considerable variation among the study sections. Dr. Ehrenfeld noted that the IRG Working Groups--a separate activity from the reorganization--are proving to be very helpful in addressing consistency, adequacy of expertise, and other issues. She stated that there will likely be new problems, but it is useful to "shake up the system." She expressed concern that there is a real lack of understanding about how the system works, so that communication is a high priority.

Finally, she responded to questions about self-referral and the need for appropriate information on which to base this; cross-cutting areas, such as epidemiology, biostatistics, bioinformatics, and how they are addressed in the reorganization; electronic submissions; and recruitment of senior investigators to study section service.

XIII. REPORT FROM THE DIRECTOR OF THE NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES, NIH - Dr. John Ruffin.

Dr. Olden introduced Dr. Ruffin, who stated that he is meeting with NIH groups and other constituencies to describe the goals and operation of the new Center (NCMHD). The Center will have grant-making authority, which its predecessor, the Office of Research on Minority Health, did not. Although the Office often got ideas from grass-roots efforts, there had to be a partner in another part of the NIH for funds to be allocated. However, this did lead to some successful programs, such as partnerships between minority institutions and comprehensive cancer centers.

Dr. Ruffin then described the legislative mandate for the Center: to conduct and support research and training; to disseminate information; and to develop programs for eliminating health disparities. The Director of the Center is responsible for coordination and dissemination of information on all NIH-supported research activities on health disparities. Dr. Ruffin will convene a group to develop a comprehensive plan and budget. Promotion of coordinated activities among the institutes, centers and offices will be high priority, and the Office of Behavioral and Social Sciences Research will have voting membership on a new Advisory Committee. Other agencies will also be involved with the Center. There are specific mandates

for the Center, which Dr. Ruffin summarized from the legislation. These mandates, along with a previously-developed strategic plan, also serve as the blueprint for initial operations of the Center. The Center's grant-making authority will be used sparingly, as most of the activity will be done as in the past as collaborative efforts.

Dr. Ruffin referred to "bad news" in terms of the initial funding level for the Center in light of the expanded responsibilities and existing commitments. He stated that the authorization exceeds the appropriation, and that he hopes to garner some additional resources from collaborating institutes.

XIV. DISCUSSION OF NEW INITIATIVES - Dr. Robert Wells.

Dr. Olden introduced this session by reminding Council that he had issued an invitation some time ago for members to identify topics or issues for discussion at the meeting. We have included some specific topics, such as nutrition, on previous agendas, but this session is more open-ended and will be led by Dr. Wells.

Dr. Wells began by stating that the identified title was somewhat misleading, and that his intention was to give members an opportunity to bring up any issues they would like discussed or addressed. He began by making comments and comparisons between the research in the intramural and extramural programs as well as with extramural programs of other institutes. Dr. Olden responded by reiterating the mission of the NIEHS and the fact that research in our portfolio is determined to a significant extent by that mission. The science is comparable to that in other institutes but different in its orientation.

In response to other comments by Dr. Wells, Drs. Olden and Sassaman offered to provide the Council with detailed information as to the new initiatives funded with increased appropriations as well as an annual listing of new awards made during the fiscal year.

The Council expressed their willingness to engage to a greater extent in the institute's priority setting and recommendations, and suggested some unstructured time periodically to initiate discussion and ideas for future directions. Dr. Olden pointed out that the annual institute Leadership Retreat, to which Council members are invited, is a very good time for this. Another suggestion was that a subcommittee of the Council to help in the development of meeting agendas might be considered.

Dr. Clark pointed out that Council must be respectful of the process and its particular role. Members may be particularly interested in certain areas, but no special agendas should predominate. The Director and his staff have the responsibility for portfolio balance, taking into account recommendations from the Council. She also noted that there is a wealth of information about the Institute's programs and activities on our web site.

Dr. Karin suggested that the Council might be particularly helpful in identifying emerging areas for NIEHS consideration, and that perhaps a subcommittee of the Council might be established to do this systematically.

Finally, Council members noted the critical need to train environmental/ occupational physicians, and expressed concern over the conclusions of the National Research Council's report on training.

XV. REPORT OF THE DIRECTOR - Dr. Anne Sassaman

Dr. Sassaman referred Council to the agenda book for Reports of the Directors, Division of Intramural Research and Extramural Research and Training, respectively. (See Attachments C and D)

She introduced two new staff members attending Council for the first time. Dr. Brenda Weis and Dr. Zoe Huang have joined the Scientific Review Branch as Scientific Review Administrators. Dr. George Malindzak, a long-time program administrator responsible for the portfolio in lung disease and air pollution, has retired and we hope to have his replacement on board soon.

Dr. Sassaman reported on an analysis of the Institute's use of the Small Grant mechanism that was prepared by the Program Analysis Branch. The Executive Summary for this is part of the Director's Report, found in Attachment D. Conclusion of the analysis of the first two small grants programs, "Linking Environmental Agents and Disease," and "Linking Environmental Agents, Oxidative Damage and Disease," were that this is a very useful mechanism that has resulted in subsequent funded research projects from investigators new to the NIEHS portfolio. In addition to these two solicited programs, the Institute has used the Small Grants mechanism in conjunction with the National Toxicology Program to encourage investigator-initiated applications to utilize animals, tissues, cells, or sera from NTP cancer bioassays. This, too, has been successful, and the NTP has accomplished its goal of obtaining mechanistic data on the chemicals under study.

The second special topic in Dr. Sassaman's presentation was the biennial Council review of NIEHS compliance with guidelines for the inclusion of women and minorities in human subjects research. She reviewed the relevant legislation and recommendations in a recent General Accounting Office Report concerning tracking, and NIEHS activities related to compliance. Data were presented on NIEHS-sponsored studies covered by the policy, and the Council was asked to assess these activities and their compliance with the policies and recommendations. (Details of the report are contained in the Report of the Director, DERT.) The Council concluded that the Institute is making appropriate efforts to comply and has adequate processes in place to assure that no research is funded that does not comply. Members also recognized the efforts with regard to staff training, using various means of communication.

You may access copies of the slides used in these two presentations by clicking on the following: [Slides from Presentations](#)

CLOSED PORTION OF THE MEETING

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.

XVI. REVIEW OF APPLICATIONS

The Council considered 162 applications requesting \$37,468,338 in total cost. The Council recommended all 162 applications with total cost of \$37,468,338.

XVII. ADJOURNMENT OF THE NAEHS COUNCIL

The meeting was adjourned at 12:15 p.m. on February 13, 2001.

XVIII. REVIEW OF FDA APPLICATIONS

The Council considered 30 applications requesting approximately \$5,664,803 in direct costs. The Council recommended approval of all submitted, approved applications.

ATTACHMENTS

A. Profiling Toxicants with Microarrays: It Works!

DR. CHRISTOPHER BRADFIELD

One of the major objectives of toxicology is to understand the adverse health effects of chemicals in humans. This understanding could be aided by the ability to group chemicals that generally act the same or are believed to produce their toxic endpoints through similar mechanisms. For example, toxicologists tend to classify a number of chemicals as having 'dioxin-like' activity due to their ability to bind the aryl-hydrocarbon receptor (Ahr) and induce a defined change in the expression of a small population of genes (e.g., CYP1A1). Research related to this type of chemical classification has, to date, largely consisted of serially characterizing responses in a small number of genes, which allows only broad generalizations of toxicological behavior. However, with the advent of modern genomic technologies, parallel analysis of large numbers of genes is possible and could change the traditional toxicological models for classifying chemicals. These new tools provide a relatively quick and easy analysis of the chemically induced transcriptional changes in a cell and may be useful in defining classes of toxicants. In an attempt to identify these toxicologically relevant gene expression patterns, we initiated a survey of chemically induced changes in liver gene expression through the use of custom cDNA microarrays. These microarrays were constructed from cDNA clones derived primarily from chemically treated and control mouse livers. Five broad chemical classes were selected for study: phenobarbital-like, inflammatory, hypoxia-like, Ahr-like, and peroxisome

proliferators. cDNA microarray analysis was performed on various chemicals within these groups and the results analyzed using various statistical techniques. Using a Bayesian analysis, the classification of these treatments and time-points into their respective toxicological classes was very poor using expression changes from the microarray as a whole (47.8% accuracy based on leave-one-out cross-validation). However, using a forward parameter selection scheme, a 'minimal' set of 5 genes was identified that allowed 100% accuracy in classifying the treatments and an 'optimal' set of 12 genes which still provided 100% accuracy, but also gave more robust predictions. These results provide significant evidence that the classification of chemicals according to their gene expression profiles is possible and opens the door to a potentially new era of toxicological testing.

Classifying and understanding chemical toxicants using DNA microarray technologies

Russell Thomas^{1,2}, David Rank¹, Sharron Penn¹, Stevan Jovanovich¹, Kalyan Pande² and Chris Bradfield²

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B. Using Expression Arrays to Identify Disease Subtypes and Assign Prognosis

DR. CLARICE WEINBERG

Identification of disease subtypes is useful both clinically and epidemiologically. Subtypes may respond differently to treatment strategies, and clinical management should be tailored accordingly. Subtypes may follow distinct clinical courses, with implications for aggressiveness of therapy. Finally, subtypes may arise from distinct causes. When studying environmental causes, analyses using subtypes can reveal etiologic factors that would otherwise be obscured.

Gene expression data can complement the histologic methods now used to identify subtypes. Subtypes may be revealed by "fingerprint" patterns produced by genes selectively expressed in subtype cells.

We analyzed gene expression data from 72 leukemia patients, 47 with acute lymphoblastic leukemia (ALL) and 25 with acute myeloid leukemia (AML). We wanted to use the expression data from 6,817 genes to find a set of genes that together are differently expressed in AML versus ALL. Consideration of all possible subsets, say of size 50, out of the 6,817 is impossible, even with a powerful computer. We used a search strategy called the Genetic Algorithm (GA) to identify a subset of informative genes. We developed the algorithm using "training set" data, consisting of 38 of the specimens. We then validated our methods by independently classifying the remaining 34 "test set" specimens.

The GA works by mimicking evolution. 150 sets of 40 genes are initially selected at random from the gene pool, each set forming a random mathematical entity called a "chromosome." Together these chromosomes form an initial generation of 150 possible choices. Each chromosome may or may not be passed to the next generation, with a transmission probability

proportional to its "fitness." Fitness is defined according to the proportion of training-set specimens correctly classified by a mathematical rule, the "K-nearest-neighbor" criterion. This evolutionary process (with a small number of mutations introduced at each generation) continues until an optimally fit chromosome has been found. We repeat the process many times, developing a long list of optimal chromosomes (sets of genes). Finally we select the best 50 genes according to the frequency with which they were selected in the GA.

When the top 50 were used to classify specimens in our test set, 33 out of 34 were correctly classified as ALL versus AML. Further clustering analysis based on the 50 identified genes revealed two new subclusters within ALL, which we later learned corresponded to B-cell/T-cell ALL. Thus, expression arrays analyzed with the GA/KNN method can identify genes that discriminate between ALL and AML, and may also unmask clinically meaningful additional subtypes.

C. [Report of the Director, DIR](#) In [Adobe Acrobat](#) Format

D. Report of the Director, DERT

EVALUATION AND ANALYSIS OF THE NIEHS R03 GRANT PROGRAM

December, 2000

Prepared by:

Program Analysis Branch

Office of Program Development

Division of Extramural Research and Training

Executive Summary

In 1996 and 1998 the Division of Extramural Research and Training (DERT) at NIEHS used an R03 mechanism to support research in two targeted areas, namely, Linking Environmental Agents and Disease and Linking Environmental Agents, Oxidative Damage and Disease. The goals of the two RFA's were to determine whether there was sufficient mechanistic or epidemiologic evidence to justify further investment into research on the possible role of environmental agents in specific human diseases. The programs were designed to allow PI's to acquire preliminary data to support a larger and more detailed R01 application. During the Spring and Summer of 2000, the Program Analysis Branch (PAB) assessed the scientific impact of this funding mechanism by:

- contacting each PI by phone for additional information including: an assessment of completion of specific aims, publication data, and submission of an R01 resulting from the work supported in the R03,
- analysis of IMPAC II data for grant applications emanating from the PI's receiving R03 support,
- surveying the National Library of Medicine Medline and Pubmed data files for publications resulting from these grants,
- examining the grant files for publications.

After repeated attempts at contacting the investigators, PAB could only collect direct information from 22 out of the 44 grantees. Consequently other mechanisms were used to collect publication and grant

application data. Use of Medline and PubMed were excellent and timely sources of publication data. The publications found electronically matched exactly those found in the grant files. In addition to the relative ease of finding the publications electronically, this method allows instant access as compared to waiting for the annual submission of progress reports from investigators.

Twenty of the 22 respondents were able to accomplish at least a portion of their specific aims (reports vary between 40% and 100% success). Some grantees are still working on their projects and expect further results. The two grantees who were unable to meet their aims have made changes in their experimental designs and systems and are continuing to pursue their initial research hypotheses. Several grantees were able to establish links between exposure to specific environmental agents and diseases sufficient to warrant support of further research. An evaluation of research results, publications, and later grant applications identified several highly scientifically successful grants. Twenty-four (24) NIH R01 applications have been submitted as a direct result of this program. Eight (33%) were funded, six (25%) are pending, and 10 (42%) were unfunded. All eight funded are NIEHS grants. The funded grants bring four new investigators to the NIEHS portfolio.

The R03 grants produced 29 publications in peer reviewed journals. The mean impact factor of the publishing journals is 3.3, equivalent to a mid-level journal. The investigators report an additional 10 manuscripts in various stages of preparation. Considering the low amount of funding for each grantee (\$50,000 direct cost), this is an impressive publication record.

The grantees were all very positive about their experiences with R03 grants. In general their suggestions for improvement focused on two limitations: 1) increase the funding limit, and 2) extend the duration of the award. The epidemiologists were especially insistent on these two points citing the amount of time necessary for start-up of a grant and the expense of this type of research.

A final recommendation from PAB is that any program launched from DERT should have an evaluative arm built in. Planning the evaluation into the program will help make data collection and analysis easier and provide a basis for determining the effectiveness of the program.

Biennial Advisory Council Review of NIEHS Compliance with Inclusion Guidelines

Background

The establishment and implementation of policies for the inclusion of women and minorities in clinical research has its origins in the women's health movement of the mid-1980s. Following a series of reports and institution of NIH policies, there was still a concern that there were differences among the Institutes and Centers (IC) in the implementation of the policies and that not all IC's factored adherence to these policies into the scientific merit review.

In order to ensure the policies for inclusion were firmly implemented by NIH, the Congress inserted a section into the NIH Revitalization Act of 1993, making what had been policy into

Public Law. The Revitalization Act essentially reinforced existing NIH policies, but with four major differences:

- that NIH ensure that women and minorities and their subpopulations be included in all human subjects research;
- that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- that cost is not allowed as an acceptable reason for excluding these groups; and
- that NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as volunteers in clinical studies.

Since revised guidelines went into effect in 1994, NIH has not funded any project, intramural or extramural, that did not comply with the policy. More details regarding implementation of the policy and other activities conducted primarily through the NIH Office of Research on Women's Health can be found in Attachment C, the report of September 1, 2000.

In May, 2000, the General Accounting Office released a report (see also Attachment C), "NIH Has Increased Its Efforts to Include Women in Research," which indicated that the NIH has made significant progress in inclusion of women in the past decade. However, the report recommended to the NIH Director that NIH should ensure that it implements the requirement that Phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men as fully as it implements other elements of the inclusion policy. In addition, a second recommendation related to tracking of information:

To improve the accuracy of NIH's tracking data on the inclusion of women and minorities, we recommend that the Director of NIH ensure that NIH staff who transmit data to the tracking system receive ongoing training on the requirements and purpose of the system.

The NIH concurred with the recommendation and proposed specific steps to respond. The NIEHS's concurrence with new training requirements and attention to the GAO report in general will also be covered in this report.

The NIH Revitalization Act of 1993, Public Law 103-43, Section 465B(2)(f) states the following:

(f) REPORTS BY ADVISORY COUNCILS - The advisory council of each national research institute shall prepare biennial reports describing the manner in which the institute has complied with this section. Each such report shall be submitted to the Director of the institute involved for inclusion in the biennial report under section 403.

Discussion

As required for this biennial review, aggregate data on the participants in NIEHS-supported research broken down by gender and ethnicity for Fiscal Year 1998 is shown in Attachment D. This represents the information gathered from 97 protocols covered by the inclusion policy. The Division of Extramural Research and Training has developed procedures for identifying those projects for which tracking is required and the entry of the data into the National Library of

Medicine's National Clinical Trials Database (Attachment E). The responsibility for reporting and updating the data lies with the Principal Investigator (PI) of the funded project and he or she is provided with the necessary information to comply. The PI is also advised that future awards may be delayed if he or she fails to provide the required information in a timely manner. Compliance with the policy and also adequate progress towards achieving target numbers are monitored by the responsible NIEHS Program Administrator at the time of the non-competitive renewal.

As part of the peer review process, the IRG is asked to review the adequacy of plans for enrollment of women and minorities into the study or to identify reasons for an exemption. This becomes part of the scientific merit review, and those applications for which there are concerns are so identified and a bar-to-funding placed on them. The Division has in place procedures for resolving these situations which require a formal response by the PI, review by the Program Administrator, and final approval or disapproval by the Director, Division of Extramural Research and Training. These procedures are outlined as Attachment F.

Recently, in response to the GAO recommendation regarding Phase III clinical trials, the Director, Division of Extramural Research and Training, provided to the Office of Research on Women's Health the information contained in Attachment G. The only NIEHS-supported study meeting the criteria of a Phase III clinical trial has just recently been funded. However, responsible staff are monitoring the study closely for compliance with the policy and the first meeting with the PI and his advisors will take place this spring.

Education and training of staff with various responsibilities is a major component of the NIH response to the GAO report. Thus, training seminars and symposia have been conducted and made available for continuing education via streaming video and videotape. NIEHS staff have participated, in person, by videoteleconference, or by videotape, in the two major events: Human Subjects Update: A Symposium (October, 2000) and Grants Policy Updates: Humans and Animals (December 2000). The videotapes of these meetings are available and archived portions available on the Internet for use in training of new staff and further participation of current staff.

Action

The NAEHSC is required to review the material presented and in particular the Institute's procedures and process for monitoring adherence to the policy. The last report to this Council was made in February, 1999 and Council's concurrence/approval reported to the Director, NIEHS and the Director, ORWH for inclusion in the overall NIH Biennial Report. Your consideration of the information provided and recommendation for action (approval/disapproval, with comments, if desired) are required.

NIH Director's Panel on Clinical Research 1997 Report

The Panel's Definition of Clinical Research

:

In 1997, the NIH Director's Panel on Clinical Research reached a consensus on a working definition of "clinical research". This definition has been approved to be used as the NIH definition of clinical research involving human subjects.

The following definition will be used in documents related to the policy for the inclusion of women and minorities in NIH-funded clinical research studies.

Clinical research is:

1. Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects and/or obtains readily identifiable private information. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies.
2. Epidemiologic and behavioral studies,
3. Outcomes research and health services research.

DERT Scientific Retreat Executive Summary

The DERT second annual scientific retreat was held in Southern Pines, North Carolina on December 4 & 5, 2000. The purpose of the retreat was to explore research opportunities in both new and existing topics and to consider how emerging technologies can be incorporated into current environmental health science research. Another goal was to provide a setting that was conducive to stimulating discussion and interactions among DERT scientific staff, colleagues in academia and invited speakers.

The retreat was developed around three scientific sessions: Molecular Epidemiology and Role of Polymorphisms in Populations; Imaging in Environmental Toxicology; and Cellular and Molecular Pathophysiology: Intergenerational Toxicity and Fetal Programming. Each session included scientific presentations by invited speakers followed by facilitated discussion sessions. The goal was not only to educate but to encourage participation. A brief description of each session follows.

Session 1: MOLECULAR EPIDEMIOLOGY AND ROLE OF POLYMORPHISMS IN POPULATIONS

Through the Environmental Genome Project (EGP) researchers have identified various classes of genes and have been able to look at the stress response to xenobiotics. Sequencing and resequencing of genes has been a major focus in light of environmental agents. Molecular epidemiology studies have been supported by NIEHS for sometime, with the portfolio growing slowly. It is our expectation that with new epidemiology initiatives, specifically as part of EGP, epidemiologists can take advantage of new information on discovery and sequencing of SNPs/Polymorphisms to study critical gene-environment interactions and their role in risk of disease.

To assist NIEHS in determining promising areas of environmental molecular epidemiology and polymorphisms, DERT invited Drs. John Wiencke, University of California, San Francisco; Robert Millikan, University of North Carolina at Chapel Hill; and Clement Furlong, University of Washington to participate in this session. Their presentations highlighted the value and challenges of incorporating molecular genetics in population-based studies.

This session touched upon many issues and highlighted challenges of using SNPs in population-based research. The greatest challenge is deciding how best to advance the field of molecular epidemiology. Everyone recognizes future possibilities in this field considering the plethora of information that exists as investigators identify greater numbers of SNPs. However, it is this wealth of information that presents the largest obstacle. Principally, how can we begin making sense of it all for the benefit of public health? Participants made two concrete recommendations for the NIEHS. (1) Support of small venues to bring the necessary players (e.g. epidemiologists, molecular biologists, and statisticians) to the table, and (2) Develop multi- inter-disciplinary research programs. These mechanisms would encourage and nurture relationships between these experts, and further discussions on how to use SNPs more effectively in population-based studies.

Session 2: IMAGING IN ENVIRONMENTAL TOXICOLOGY

New techniques and technologies are being developed that allow for the visualization of biological processes at levels ranging from whole animal or organ to subcellular organelle. The second session of the retreat was focused on exploring opportunities for applying imaging technologies to the field of environmental toxicology. This session built on concepts discussed at an imaging workshop, "Defining the Potential of Multimodal Approaches to Research in Environmental Toxicology" which was held at NIEHS in July 2000.

Drs. Simon Watkins, University of Pittsburg; Peter Fox, University of Texas, San Antonio; Bruce Pitt, University of Pittsburg; and Tomas Guilarte, The Johns Hopkins University were invited to participate in the session to speak on the general state of the technology, whole animal imaging, and the application of imaging technologies in brain and lung.

Discussion following the presentations focused on what is needed to be able integrate existing imaging technologies with environmental sciences. For example, optical probes specific for environmental toxins are needed for large scale screening studies. Having the ability to conduct functional imaging studies in small animals is needed to provide for real time observation of molecular events. Bioinformatic systems are needed to allow for applying data from one technique to another and for data reduction. In general, the invited speakers felt that while there are technical challenges, the existing technologies are ready to be translated to an environmental health research agenda.

Session 3: CELLULAR AND MOLECULAR PATHOPHYSIOLOGY: INTERGENERATIONAL TOXICITY AND FETAL PROGRAMMING

Fetal programming is the concept that conditions present during the perinatal period can alter lifelong biological processes and disease susceptibility. A growing body of research suggests that fetal programming is as important as genotype in determining health status at adulthood.

Equally important to alterations in the developmental environment is the critical timing of these changes. Seemingly minor exposures or alterations may alter critical events leading to a cascade of impairments in development that have consequences into adulthood.

The speakers on this topic included Drs. Peter Nathanielsz, Cornell University; Kent Pinkerton University of California, Davis; David Abbott, University of Wisconsin, Madison; and Gail Prins, University of Illinois, Chicago. Their presentations focused on maternal nutritional status, impairment of lung development resulting in exposure to environmental tobacco smoke, prenatal androgen exposure resulting in the development of polycystic ovary disease, and prenatal exposure to diethylstilbestrol and altered prostate development.

The post presentation discussions centered on the question of which animal models to use. Some participants felt that non-human primate models are an invaluable resource for developmental investigations. Other recommendations included planning a meeting to further develop the concept of using placental tissue as a tool or model for fetal programming. The workshop would develop ideas on what types of studies could be done with placental tissue to shed light on fetal programming and possible mechanisms of action. Real-time fetal imaging studies were also suggested. It was pointed out that these technologies are available, but they are still invasive at this time. However, future improvements may make this technology more appealing.

Conclusion

The retreat was stimulating and was an excellent opportunity for discovery in new areas of research for NIEHS. Each session showed new perspectives and different ways of thinking. The sessions also demonstrated how interrelated the field of environmental health is and the need for the program administrators to incorporate an interdisciplinary research approach as they begin to develop research agendas in these areas. It is anticipated that ideas generated at this retreat will be further developed and will potentially result in new NIEHS research initiatives.

DERT Scientific Retreat Agenda and Speaker List

In [Adobe Acrobat](#) Format

STAFF ACTIVITIES

February, 2001

Dr. Collman, OPD/CEMBB, organized and participated in the Human Genome Epidemiology Workshop. The purpose of the meeting was to develop guidelines for evaluating and integrating data on using genetic information to improve health and prevent disease. The meeting was held at the CDC in Atlanta, Georgia, January 29-30.

Drs. Sassaman and Dearry participated in the latest in the Institute's Town Meetings held in Seattle, Washington September 29-30. It was hosted by the Environmental Health Sciences Center at the University of Washington, and involved a large number of community groups in the planning and execution of the meeting. Dr. Olden gave an address on the programs of the Institute, and other NIEHS staff assisted in the planning and logistics.

Dr. Van Houten, OPD/PAB, attended a Gordon Research Conference on Mammalian DNA Repair, January 21-26 where he presented a talk entitled, "Structure-function studies of UVrB, a protein with a helicase fold adapted for nucleotide excision repair." Dr. Sam Wilson is the chairman of this years Gordon Conference.

As part of its efforts to expand discussion on gene expression profiling, proteomics, and bioinformatics, NIEHS sponsored a workshop entitled, Functional Proteomics in Environmental Health Science. The workshop was held in at the University of Arizona, in Tucson, Arizona, on January 24 and was co-organized by Dr. Liebler, University of Arizona, and Dr. Tomer, NIEHS. The meeting was attended by Dr. Sassaman, DERT/OD, Drs. McClure and Heindel, OPD/OSTB, and Drs Dearry and Thompson, OPD/CEMBB.

The Superfund Basic Research Program cosponsored, with Colorado State University, the conference "Application of Technology to Chemical Mixture Research" in January 2001. Dr. Olden presented the Keynote address on NIEHS Chemical Mixture Research Initiative. Drs Suk, OPD, and Thompson, OPD/CEMBB, each chaired sessions and Dr. Suk served on the steering committee and presented an invited talk.

Dr. Van Houten, OPD/PAB, as part of the institute efforts in Toxicogenomics, gave a lecture entitled, "Gene Environmental Interactions: A Key to Understanding Human Health" on January 11, at the North Carolina Annual State Directors Conference, Radisson Governor's Inn, North Carolina.

Mr. Hughes OD/WETP, presented an update on the WETP Advanced Training Technology (ATT) Initiative at the Cross-Federal Agency Committee on Occupational Safety and Environmental Health Training in Washington, DC on January 4.

The Superfund Basic Research Program held its Annual Meeting on December 12-14 in Chapel Hill, North Carolina. The theme of the meeting was Oxidative Processes: Stress to Remediation. Drs. Fridovich, Duke University, Floyd, Oklahoma Medical Research Foundation and Olden presented keynote addresses. SBRP staff served on the organizing and program committee and participated in the sessions.

A workshop entitled, "Functional Genomics and Environmental Health" was held on December 10-11 at the Massachusetts Institute of Technology, Boston, Massachusetts. The Co-organizers were Dr. Leona Samson, Harvard University, and Dr. Van Houten, OPD/PAB. Other attendees from DERT included Drs. Sassaman, Heindel, Velazquez, and Bass, and Ms. Lewis and Mr. Gula.

Mr. Hughes and Ms. Beard, OD/WETP, were speakers presenting an update on the WETP Advanced Training Technology (ATT) Initiative at the National Advisory Committee on Occupational Safety and Health (NACOSH) in Washington, DC on December 5-6.

The Division of Extramural Research and Training held its second annual scientific retreat, "Molecular Basis of Environmental Disease" December 4-5. The retreat was developed around three sessions: Molecular Epidemiology and Role of Polymorphisms in Populations, Imaging in

Environmental Toxicology, and Cellular and Molecular Pathophysiology: Intergenerational Toxicity and Fetal Programming. Each session included scientific presentations from invited experts and was followed by an hour long discussion period.

Dr. Sassaman, Director, DERT, presented the keynote address, "Moving Environmental Health Sciences into the Twenty-first Century" at a meeting co-sponsored by NIEHS, the U.S. Army Soldier and Biological Chemical Command, the U.S. Navy, U.S. Air Force, as well as other Federal and private sector organizations. The meeting, "Alternative Toxicological Methods for the New Millennium: Science and Applications," held November 28-December 1 at NIH, Bethesda, Maryland, was planned to address the mandates of the National Defense Authorization Act and the National Institutes of Health Revitalization Act regarding the bi-agency establishment of programs to reduce, refine, or replace the use of research animals. Dr. Heindel, OPD/OSTB, was on the program committee and chaired a session on The Role of Transgenics and Toxicogenomics in the Development of Alternative Toxicity Tests. Dr. Van Houten, OPD/PAB, was a speaker in that session.

Dr. Dearry, Mr. O'Fallon, Ms. Ryan, and Ms. Johnson, OPD/CEMBB worked with Dr. Suk, Ms. Anderson, and Ms. Haithcock OPD, to organize a one-day, binational roundtable to discuss environmental health priorities in the U.S.-Mexico border region. The meeting was held in Research Triangle Park, North Carolina, November 28. The 13 participants included eight researchers from the U.S. and five from Mexico. Mr. O'Fallon moderated the meeting, Ms. Anderson served as rapporteur, Dr. Sassaman welcomed the participants, Dr. Wilson spoke on the NIEHS mission as it pertains to U.S.-Mexico border environmental health concerns, Dr. Suk outlined the objectives for the meeting, and Dr. Dearry synthesized the major discussion points at the end of the day.

On November 28, the NIEHS hosted the second biennial meeting of the Directors of the Institutional National Research Service Award (T32, T35) training grants. The meeting was organized by Dr. Shreffler, OPD/OSTB. Other participants from NIEHS included Dr. Wilson, Dr. Van Houten, OPD/PAB, and Dr. Sassaman.

The Superfund Basic Research Program at Columbia University sponsored a meeting "Health Effects and Geochemistry of Arsenic: The Crisis in Bangladesh" on Nov 13 in New York City, New York. Dr. Thompson, OPD/CEMBB, Ms. Anderson, OPD and Mr. Phelps, OPD/PAB, attended the meeting.

Mr. Hughes, OD/WETP, chaired a session entitled "Internet Resources and the Digital Divide in Occupational Health: Health Disparities in Training and Protecting Workers" which highlighted the accomplishments of the NIEHS Advanced Training Technology Initiative at the 128th American Public Health Association Annual Meeting in Boston, Massachusetts, November 12. Ms. Beard, OD/WETP, was also in attendance. She gave a presentation entitled "Hazardous Materials Job Training for People of Color: A Collaborative Approach." Dr. Tyson, OPD/CEMBB, was also in attendance and chaired and moderated two scientific sessions. One was on Community-Academic partnerships to reduce pesticide exposures to farmworkers and their families and the other was on airborne particulates (PM10) and mortality.

The Superfund Basic Research Program cosponsored the conference 'Metals in Eastern and Central Europe: Health Effects, Sources of Contamination and Methods of Remediation' held in Prague, Czech Republic on November 8-10. Dr Suk, OPD, served on the steering committee and chaired a session on "Health Effects of Metals."

Dr. Collman, OPD/CEMBB organized and participated in a meeting of the Centers for Children's Environmental Health and Disease Prevention, Nov 6-8, held at the University of California at Berkeley. The meeting included a review of research findings coming out of the centers program and a site visit to its community intervention field site in Salinas, CA

Dr. McClure, OPD/OSTB, coorganized with Dr. Burka, Director, Herbal Medicine Program, NTP/NIEHS and Dr. Miller, University of Missouri Center for Phytonutrient and Phytochemical Studies, a workshop entitled "PCR-Based Approaches to Identify and Quantitate Botanicals in Dietary supplements." The workshop, held November 2-3 at the NIEHS and cosponsored by the NIEHS and the Office of Dietary Supplements, NIH, explored the possibilities and limitations PCR offers for genetically characterizing particulate botanicals in dietary supplements.

DERT held a Management Retreat at the Triangle Training Center on October 27 in Pittsboro, North Carolina. The retreat was attended by most of the DERT staff and focused on Process Improvements. In a variety of formats, each branch presented brief summaries of its tasks and responsibilities and how it works with other DERT and NIEHS entities. Many suggestions for improvements were made by individual staff members. The Process Improvement Team has been formed to facilitate the implementation of these suggestions.

Dr. McClure, OPD/OSTB, coorganized and participated in the "2000 Ethics, Legal, and Social Implications Human Genetic Variation Consortium Meeting" held October 24-25 at the Ramada Inn in Rockville, Maryland. The meeting drew together collaborating Trans-NIH extramural programs and the projects cofunded and cosponsored by a 1999 RFA initiative by the NHGRI (Human Genome ELSI Program), the NIGMS (Pharmacogenetics/genomics Program), the NIDCD (Genetics of Communication Disorders Program) and the NIEHS (EGP and Toxicogenomics Program). The charge to the consortium program, as presented to the group by Dr. Francis Collins, Director, NHGRI, is to carry out state-of-the-art research on ethical issues in human genetic variation research associated with identifiable human subpopulations. The intended outcome is guidance for improved designs for such research and providing effective communications with such populations.

Dr. Tyson and Mr. O'Fallon, OPD/CEMBB, planned the annual meeting of the Environmental Justice (EJ) and Community-Based Prevention/Intervention Research (CBPIR) grantees which was held in Seattle Washington, Oct 23-25. This meeting had representation from 17 Environmental Justice Grantees (2 supported by the EPA), nine CBPIR projects and eight Children's Centers CBPIR Projects and marked the first time these three sets of CBPIR projects convened. Dr. Tyson presided over the meeting. Mr. O'Fallon presented the results of the evaluation of the EJ program to meeting participants.

Drs. Lawler OPD/OSTB, Collman OPD/CEMBB and Bishop organized a brainstorming session on "The Role of the Environment in Autism." Dr. Olden chaired the one-day session, which was

held October 23 on the NIH Bethesda campus. The session brought together parent advocates concerned with the potential etiologic role of mercury and other environmental agents in autism with a group of extramural scientists with collective expertise in autism, developmental neurobiology and neurotoxicology. A meeting report has been prepared that summarizes the highest priority issues identified for research in this area.

Mr. Hughes, OD/WETP, and staff hosted the NIEHS/Worker Education and Training Program semi-annual grantee meeting in Research Triangle Park, North Carolina, on October 16-18. The theme of the meeting was "The WETP Lessons Learned for Future Vision -- The Next 5 Years."

Mr. O'Fallon, OPD/CEMBB, worked with a planning committee of COEP Directors and Coordinators to organize the first COEP Directors' meeting in 2 years which was held in conjunction with the Center Directors' Annual Meeting in Detroit, Michigan, October 14-15. In addition to organizing the meeting, Mr. O'Fallon moderated it and presented the COEP Resource Center concept and contractor to the meeting participants.

Dr. McClure, OPD/OSTB, participated in and presented at the Burroughs Wellcome Fund Board of Scientific Counselors and Faculty Retreat held October 11-12 at the BWF Headquarters in Research Triangle Park, North Carolina, for the BWF-NIH cosponsored/cofunded "Frontiers in Reproduction Training Course" held annually at the Marine Biological Laboratory, Woods Hole, Massachusetts.

Ms. Beard, OD/WETP, was a speaker at the Brownfields 2000 Conference in Atlantic City, New Jersey, on October 11. The theme of the conference was "Research & Regionalism: Revitalizing the American Community." The meeting provided an excellent setting to promote the WETP Minority Worker Training Program and Brownfields Minority Worker Training Program.

Dr. Collman, OPD/CEMBB and Dr. Kirshner, OPD/OSTB sponsored a working group meeting for grantees doing epidemiology studies on Parkinson's Disease research, Sept. 19-20. The meeting, which was held at NIEHS, was to review similarities and differences in current research studies looking towards the possibility to combine or pool data on selected topics in the future. A follow-up meeting is being planned for March 31 at the Parkinson's Institute in Sunnyvale, California.

Drs. McClure and Heindel, OPD/OSTB, sponsored a national meeting entitled, "Polycystic Ovary Syndrome: Basic Biology and Clinical Intervention" at NIEHS Sept 17-20. They co-chaired with Dr. Estella Parrott, NICHD, Center for Population Research the "Summary and Future Directions" session. The well-attended conference drew leading experts from the basic and clinical PCOS research field and specifically explored the role of Genetics and Environmental Influences in Session Six. The meeting was cosponsored by NICHD, the NIH Office of Rare Diseases, NIH Office of Research on Women's Health and SmithklineBeecham, Bristol-Meyers Squibb, Ferring Pharmaceuticals and Organon. The proceedings of this meeting, which highlighted the genetic and environmental components of this disease, will be published by Marcel Dekker this spring.

Drs. Dearry and Collman and Mr. O'Fallon, OPD/CEMBB co-authored a publication on the children's environmental health research efforts at the NIEHS, predominately the NIEHS-EPA-CDC Centers for Children's Environmental Health and Disease Prevention Research. Entitled, "The National Institute of Environmental Health Sciences' Research Program on Children's Environmental Health," the article appears in the Journal of Exposure Analysis and Environmental Epidemiology (2000).

Drs. Dearry and Tyson and Mr. O'Fallon, OPD/CEMBB, co-authored an article on the translational research activities supported by the NIEHS. Entitled, "Improving Public Health Through Community-based Participatory Research and Outreach," the article appears in a special issue of the Journal of Environmental Epidemiology and Toxicology (Volume 2, Nos. 2-3, April-September 2000). Dr. Olden and Ms. Riley co-authored an article that is featured in the same issue.

STAFF HONORS and AWARDS

The recipients of the 2000 Teamwork/Leadership Awards, given to those whose work in the Division exemplifies the characteristics embodied in the DERT Leadership Philosophy Statement are: Jose Velazquez, OPD/CEMBB - for his work on inter-branch collaborative efforts in a spirit of teamwork and cooperation that improves the overall quality of programs; Judy Hanson, OPD/OSTB - for her collegiality and willingness to help and be a resource person regardless of the task or her other obligations; and Sandi Manness, OPO/RCB - for her leadership on the Social Committee and outstanding communication with the group and staff on the social activities of the year. Nominations came from DERT staff.

Ms Beth Anderson, OPD, received an NIEHS Peer Award in December "For her exemplary role as a model in partnering initiatives within NIEHS and the state of North Carolina that reflect positively on the image of NIEHS with the local community."

The following DERT staff received NIH Merit Awards: Mr. Phil Jones, OPO/RCB, "For exceptional and lasting leadership and administrative management within the NIEHS R & D Contracting Program"; Ms. Mary Alexander, OPO/RCB, "For continual excellence in administrative support activities for the NIEHS Research Contracts Branch"; Ms. Sharon Beard, Ms. Patricia Thompson and Mr. Joseph Hughes, OD/WETP, and Ms. Carolyn Mason and Ms. Dorothy Duke, OPO/GMB, "For sustained exceptional efforts in implementation and management of a national extramural program of hazardous waste worker health and safety training"; Dr. J. Patrick Mastin, OPO/SRB, and Drs. Frederick Tyson and Allen Dearry, OPD/CEMBB, "For exceptional leadership in developing, implementing, and coordinating a trans-NIH initiative on domestic health disparities to link physical and social environmental influences with health status"; and Dr. Claudia Thompson, OPD/CEMBB, "For exemplary service as a member of the NIEHS/NTP Review Committee for the Report on Carcinogens (RGI) for 1997-1998."

GRANTEE HONORS and AWARDS

Dr. Gary Isom, Purdue University, was appointed to the Defense Intelligence Agency Science Advisory Board during the past year.

Dr. Carey Pope is Sitlington Endowed Chair in Toxicology at Oklahoma State University. He was a member of the external review panel evaluating the U.S. Army's research programs on "Scavengers and Biotechnology," June 5, and "Effects of Low Level Chemical Warfare Agents," June 6, and was appointed a member of the External Advisory Board for the Oklahoma Center for Toxicology, February, 2000.

Dr. Noreen Clark, Dean, School of Public Health, University of Michigan and Council member has been elected to the National Academy of Sciences Institute of Medicine.

Dr. Sherman James, past council member and Chair of the Department of Health Education and Behavior at the University of Michigan has been elected to the National Academy of Sciences Institute of Medicine.

Dr. Mark Utell, Professor of Medicine at the University of Rochester School of Medicine, has been named Chair of the Health Effects Institute Health Research Committee.

Ms. Marianne P. Brown, University of California at Los Angeles, has been elected Chairperson of the Occupational Health Section of the American Public Health Association.

UPCOMING MEETINGS and WORKSHOPS

Dr. Collman, OPD/CEMBB, has been invited to give the keynote address at the Massachusetts Breast Cancer Research Symposium. This is an annual meeting which brings together research scientists and advocates to discuss research supported by the State of Massachusetts Breast Cancer research program. The meeting will be held in Boston, Massachusetts.

A workshop on Bioinformatics and Biostatistics is scheduled for March 5 on the campus of North Carolina State University. Dr. Bruce Wier, North Carolina State University and Dr. Cindy Afshari, NIEHS, are the co-organizers. This is the third workshop in a series on gene expression profiling, proteomics, and bioinformatics being sponsored by NIEHS.

Mr. Hughes, OD/WETP, will chair a session at the National Conference, "Training 2001," in Atlanta, Georgia, on March 5, 2001 entitled "Lessons Learned in Advanced Training Technology in Health and Safety" which will examine the progress, problems and lessons learned to date among NIEHS grant recipients in e-learning deployment.

NIEHS (through the Worker Education and Training Program) and the Occupational Safety and Health Administration are co-sponsoring a Technical Workshop on "Best Practices in Occupational Safety and Health Training" on April 17-19 in Chicago, Illinois. Staff attending the workshop and participating in various activities will include Mr. Hughes, Ms. Beard, and Ms. Thompson, OD/WETP. The morning of April 17, the semi-annual WETP Awardee Meeting will be held. Ms. Mason, OPD/GMB, will also participate in the meeting.

Ms. Beard, OD/WETP, will present at the 2001 American Industrial Hygiene Conference and Exposition, in New Orleans, Louisiana on June 7, 2001 at a forum entitled "Perspectives on Using Advanced Training Technologies (ATT) in Environmental Health & Safety Training." This forum will review the issues surrounding the use of ATT (such as multimedia, computer and web-based training, teleconferencing, and DVD-facilitated live training) in environmental health & safety training. Ms. Beard will discuss lessons learned from the NIEHS Worker Education & Training Program ATT pilot programs for training workers.

STAFF CHANGES

Recruitments:

Ms. Trinetta Black has joined OPO/GMB as a Grants Technical Assistant.
Ms. Kenya Brumby has joined OPD/OSTB as the Branch Secretary.
Ms. Mary Butts has joined OPO/GMB as the Branch Secretary.
Ms. Michelle Mayo has joined OPO/SRB as a Grants Technical Assistant.

Dr. Brenda Weis has joined OPO/SRB as a Scientific Review Administrator. Dr. Weis has been employed in the environmental health field for the past 17 years. She comes to NIEHS from CDC/ATSDR where she served as a senior scientist in the Office of the Associate Administrator for Science. She has an MSPH in public health/epidemiology and a PhD in toxicology.

Dr. Zoe Huang has joined OPO/SRB as a Scientific Review Administrator. Dr. Huang comes to NIEHS from the University of Wisconsin where she was an assistant scientist in the section of Geriatrics and Gerontology studying insulin resistance diabetes. She earned an MD from Beijing Second Medical College, Beijing, China, and she completed postdoctoral research fellowships at NICHD (pediatric endocrinology) in Bethesda and the Johns Hopkins School of Medicine (geriatrics and diabetes) in Baltimore.

Departures:

Ms. Cynthia Radford left to pursue other opportunities within NIEHS.
Ms. Helen Campbell left to pursue other opportunities.
Dr. George Malindzak retired after 13 years of service with NIEHS.
Ms. Mary Owens left to pursue other opportunities.

DERT PAPERS OF NOTE

The Aryl Hydrocarbon Receptor--A New Role in Vascular Development

Background: The aryl hydrocarbon (Ah) receptor was discovered in the 1970=s and was found to regulate responses to a variety of environmental agents such as the polycyclic aromatic hydrocarbons found in cigarette smoke and the polychlorinated dioxin compounds found in industrial agents and the defoliant Agent Orange. When these chemicals bind to the receptor, the resulting complex interacts with another receptor known as the aryl hydrocarbon nuclear translocator (ARNT). This new complex then enters the nucleus of cells where it interacts with DNA and turns on a set of enzymes which in turn start to break down the chemicals and thus help to protect organisms once exposure has occurred.

More recent research has shown that the Ah receptor is expressed in a variety of tissues and at stages in development suggesting other roles for the receptor. Experiments using knock-out mice that have no copies of the gene coding for the Ah receptor provided evidence that the receptor was necessary for survival, growth, and reproduction. This study was undertaken to identify how the receptor might influence vertebrate development.

Advance: Mice without the Ah receptor were found to have livers about 25% smaller than normal mice. This finding was due to reduced blood flow to liver tissue by a process known as portosystemic shunting. The source of the shunt was determined to be the ductus venosus--a remnant of the fetal vascular system that had failed to close. Closer examinations of the mice determined that other fetal vascular structures were present in the eyes and kidneys.

Implication: These findings indicate the Ah receptor plays a very important role in regulating the development and maturation of the vascular structure in vertebrates. Given the receptor's known activity as a transcription factor, a likely mechanism for this effect is that the receptor is necessary for the regulation of genes involved in vascular remodeling and development. These experiments also suggest that health effects seen in response to dioxin and other exposures mediated by the Ah receptor may be as the result of perturbations in vascular development.

Lahvis, GP, Lindell, SL, Thomas, RS, McCuskey RS, Murphy C, Glover E, Bentx M, Southard J, Bradfield, CA. Portosystemic shunting and persistent fetal vascular structures in aryl hydrocarbon receptor-deficient mice. PNAS. 2000 Sept 12; 97(19):10442-47.

Nitrosylation of Cysteine Residues Activates the Skeletal Muscle Calcium Release Channel

Background: Oxidation/reduction induced-modifications of the cysteine residues in proteins have emerged as a molecular mechanism which drives many cellular processes including DNA transcription, protein folding, and enzyme function. A great deal of on-going research suggests that redox-related modifications of ion channels may be involved in a variety of complex physiological responses such as constriction and dilation of blood vessels, muscle contraction, and synapse function. However, the nature of redox-related protein modification which occurs is unclear. This change could be a "redox signal" or perhaps just an oxidative stress response. Oxygen concentration changes have been shown to modulate ion channel activities with NO playing a possible role; however, the molecular mechanisms have not been determined.

Advance: In this study, the role of oxygen concentration in NO-redox control of the skeletal muscle intracellular calcium release channel was explored under ambient oxygen concentration and a much lower concentration such as that normally found in muscle tissue. The results show exposure of the channel to ambient oxygen leads to oxidative changes that are likely to be artificial and that the NO concentration necessary to activate the channel in ambient oxygen is physiologically unattainable. The experiments demonstrate the importance of tissue oxygen concentration in ion channel function and demonstrate that NO activates the channel by interacting with a single cysteine residue in a reaction called S-nitrosylation.

Implication: This work provides a model for future studies of redox-related signaling that may broadly apply to ion channels and membrane proteins. Understanding the mechanisms of these

channels and how they can be altered are the first steps toward designing drugs and treatments for diseases that result from damaged or inoperable ion channels.

Eu JP, Sun J, Xu L, Stamler JS, Meissner G. The skeletal muscle calcium release channel: coupled O₂ sensor and NO signaling functions. *Cell*. 2000 Aug 18;102(4):499-509.

Nutrients in Cruciferous Vegetables Reduce Risk for Lung Cancer: Gene-Diet Interaction

Background: Many previous studies using animal models have shown that a class of compounds known as isothiocyanates (ITCs) inhibit lung cancer. ITCs are found in cruciferous vegetables such as broccoli, cabbage, bok choy, and cauliflower. Epidemiologic studies have suggested that high intake of these vegetables reduces risk for lung cancer. However, there have been no studies performed where ITC levels were measured in relation to lung cancer risk to provide direct evidence that these, compounds as opposed to others in the diet, are responsible for the reduced risk.

GSTs are a family of enzymes known to detoxify many foreign substances in many species. GSTM1 detoxifies the carcinogenic metabolite of benzo[a]pyrene which is found in tobacco smoke. However, GSTs also metabolize ITC thus decreasing its beneficial effects. Some individuals lack the genes coding for GSTs suggesting that they metabolize ITCs slower which may have impacts on their risk for lung cancer. This study was performed to determine if the lung cancer preventive effects of ITCs might be heightened if the GSTs that eliminate them are missing. The research team included NIEHS grantees and intramural scientists.

Advance: ITC measurements were carried out on urine collected from a cohort of men in Shanghai, China. This group was followed for lung cancer incidence from 1986 to 1997 and included 232 men diagnosed with lung cancer and 710 matched controls. The technique for measuring ITC was developed by the researchers. Subjects with detectable levels of urine ITC had a 40% reduction in the risk for lung cancer. Among those subjects lacking the genes coding for GSTs, the risk for lung cancer was reduced by 64%.

Implication: This study demonstrates that ITCs reduce the risk of lung cancer in humans. The effect is stronger in people without the gene coding for GST who are predicted to metabolize ITCs slower. Other scientists are trying to determine which of the ITCs has the greatest potential for intervention treatments. These findings add significant human data to this effort.

London SJ, Yuan J-M, Chung F-L, Gao Y-T, Coetzee GA, Ross RK, Yu MC. Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. *The Lancet*, August 26, 2000; 356(9231):724-729.

Peroxisome Proliferator Inhibits Hormone Production in the Testis

Background: Peroxisomes are small intracellular organelles that are found in high concentrations in liver cells. Their main function is detoxifying chemicals such as therapeutic drugs and chemicals such as lubricants, corrosion inhibitors, plasticizers. These compounds have become known as peroxisome proliferators because they stimulate a marked increase in the number and

size of peroxisomes in liver tissue. Many of these compounds are known to cause liver cancer in laboratory animals.

In addition to their effects on the liver, peroxisome proliferators induce pathological changes in the testis. Perfluorodecanoic acid (PFDA), an industrial chemical used in some of the above processes has been reported to cause anatomical disturbances to the testis and specifically to the Leydig cells. Leydig cells in the testis produce testosterone which is necessary for normal sexual function and fertility. PFDA has also been reported to cause decreases in the circulating levels of testosterone. These researchers performed experiments to determine the mechanism by which PFDA harms the Leydig cells and inhibits testosterone production.

Advance: Working with an animal model, the researchers found that a receptor known as the peripheral-type benzodiazepine receptor (PBR) was the target of PFDA. PBR is located on the outer membrane of mitochondria where it acts as a transport mechanism for cholesterol, a precursor of testosterone.

Implication: Without properly functioning and appropriate numbers of receptors, cholesterol cannot move into the mitochondria where hormone production occurs decreasing the ability of the Leydig cells to produce normal levels of testosterone. Ultimately, these changes inhibit the production of sperm and reduce fertility. Industrial and pharmaceutical peroxisome proliferator compounds, some of which are extensively used by and for humans, may exert similar negative effects on hormone production.

Boujrad N, Vidic B, Gazouli M, Culty M, Papadopoulos V. The peroxisome proliferator perfluorodecanoic acid inhibits the peripheral-type benzodiazepine receptor (PBR) expression and hormone-stimulated mitochondrial cholesterol transport and steroid formation in Leydig cells. *Endocrinology*. 2000 Sep;141(9):3137-48.

Genetic Influence for Systemic Lupus Erythematosus

Background: The prevalence of systemic lupus erythematosus (SLE) varies among and within ethnic groups and is influenced by multiple genes. SLE is common in populations of sub-Saharan African ancestry (SSAF); however, there are differences in the incidence of this disease and lupus gene frequencies that may be due to geographically disparate SSAF-derived populations. One source of this genetic variation is admixture of Caucasian genes in African Americans. Admixture can be observed by comparing genetic markers of disease that are shared between the two populations, such as the association between heterozygous C4A gene deletion and SLE seen in Caucasians, African Americans, and Afro-Caribbeans.

Finding: C4A gene deletions are known to have associations with certain human leukocyte antigen (HLA) types. HLAs are proteins that are found on the surface of cells and are important in the acceptance or rejection of organ transplantations. A specific HLA type is the major source of C4A gene deletions in Caucasians with SLE, but previous research suggests that a different HLA type is observed in African Americans with SLE. These researchers explored this difference by performing C4A gene analysis on DNA samples from African Americans and

Afro-Caribbeans. They found new HLA types in these people that are not present in Caucasians with SLE.

Implication: This is the first study to define the HLA type in a SSAF population with C4A gene deletions. By comparing these people to a study of 18 different SSAF populations in the Twelfth International Histocompatibility Workshop the researchers reached the conclusion that the C4A gene deletion is not the result of Caucasian admixture. Future studies will determine the molecular basis of the gene deletion.

Fraser PA, Lu L-Y, Ding, W-Z, Najundaswamy SN, Chen D-F, Uko G, Tonks S. HLA-B44031; DRB1*1503 and other sub-Saharan African major histocompatibility complex haplotypes in African Americans and Afro-Caribbeans carry C4A gene deletions: implications for ethnicity-specific lupus susceptibility genes. *Arthritis & Rheum.* 2000 Oct;43(10):2378-2379. NIEHS grant R21ES10295.

In utero and Postnatal Exposure to Polybrominated Biphenyl Causes Early Puberty in Girls

Background: In 1973, an accidental contamination of animal feed in Michigan caused human exposure to polybrominated biphenyls (PBB). The PBB containing fire retardant Firemaster7 was inadvertently added to livestock feed in place of Nutrimaster7, a magnesium supplement. In the months following many Michigan residents ate animal and dairy products that had been contaminated. After discovery of the contamination, a registry of exposed individuals was established in 1976.

Maternal ingestion of PBB and polychlorinated biphenyls leads to exposure of the fetus through the placenta and to infants via breastfeeding. PBB rodent studies demonstrated effects on the reproductive system of female pups from exposed mothers. These studies suggest that exposure to PBB during gestation and early infancy may alter hormonal signaling pathways necessary for proper growth and maturation. The present study evaluates the association between perinatal PBB exposure and age at menarche, breast development, and pubic hair development in daughters of women exposed to PBB.

Advance: Breastfed girls exposed to high levels of PBB in utero (>7 parts per billion) had an onset of menses one-half to one year earlier than breastfed girls exposed to lower levels of PBB (11.6 years vs. 12.2-12.6 years respectively). Perinatal PBB exposure also caused earlier pubic hair development in breastfed girls but little association was found with breast development. A possible mechanism of action may involve the thyroid gland. The main PBB component of Firemaster7 is known to affect thyroid hormone concentrations. Normal pubertal development is partially dependent on thyroid hormones. Other animal studies have shown that exposure to PBB during pregnancy and lactation causes decreased thyroxine levels in neonates. Five of the daughters in this study have reported thyroid problems.

Implication: The associations reported from this research lend support to the hypothesis that in utero and lactational exposure to PBB have profound effects on normal pubertal development. The reports of thyroid dysfunction suggests the possibility of thyroid involvement as a

mechanism of action and opens a new line of investigation for future epidemiologic and animal studies.

Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, Hertzberg VS, Zhang RH, Cameron L. Age at Menarche and Tanner Stage in Girls Exposed In Utero and Postnatally to Polybrominated Biphenyl. *Epidemiology*. 2000 Nov;11(6):641-647. NIEHS grant R01ES08341.

Understanding How Humans Adapt to Light/Dark Environments

Background: Research into dioxin toxicology and the Ah receptor-ARNT signal transduction pathway has revealed a superfamily of proteins that appear to play central roles in how humans adapt to a number of different environmental stresses and stimuli. These factors, referred to as PAS proteins, appear to act as both sensors of environmental cues and transmitters of these signals to the nuclei of cells. The recent explosion in the number of known members of the PAS superfamily led to the discovery of sensors that are involved in responses to low atmospheric oxygen, tissue hypoxia, as well as exposure to polycyclic aromatic pollutants. A recent series of discoveries now appears to explain how organisms respond to the most fundamental environmental signals--day and night. In a flurry of recent papers, a number of laboratories used the dioxin signal transduction pathway to model the mechanism that underlies circadian rhythmicity in both mammals and *Drosophila*. Surprisingly, the basic transcriptional unit that drives these rhythms is a heterodimer of proteins called MOP3 and Clock. These heterodimers act in a manner that is strikingly similar to the Ah receptor-ARNT complex that mediates responses to polycyclic aromatic hydrocarbon and dioxin pollutants.

Advance: The discovery that circadian biology is regulated in a fashion similar to dioxin signal transduction recently gained additional support. These researchers at the University of Wisconsin and Northwestern University described a mouse model in which the gene encoding the MOP3 protein was knocked out. These MOP3 null animals were outwardly normal yet displayed a complete loss of circadian behavior. This work provides a molecular proof describing the core of the circadian cycle which is shared by many organisms.

Implication: These researchers have provided a simple animal model for use in better understanding circadian behavior and for screening drugs that might influence this biology. In addition to value in circadian rhythm biology, these mice also may be valuable in studies of depression and other disease states that are related to aberrant biological rhythms.

Bunger, MK, Wilsbacher, LD, Moran, SM, Clendenin, C, Radcliffe, LA, Hogenesch, JB, Simon, MC, Takahashi, JS, and Bradfield, CA (2000). Mop3 is an Essential Component of the Master Circadian Pacemaker in Mammals. *Cell*. 103:1009-1017

Fine Particulate Matter Air Pollution and Mortality in U.S. Cities

Background: NIEHS supported research has been critical in establishing air quality standards aimed at protecting public health. This research and the regulations promulgated by the EPA in response, have led to great improvements in air quality. In 1987, the EPA added particulate matter less than or equal to 10 mm (PM10) in diameter to the list of regulated pollutants. Despite

improvements in air quality, epidemiologic studies have shown associations between PM10 concentrations well below the standard and number of deaths per day in several U.S. cities. In response to these findings, in 1987, the EPA promulgated new standards for particulate matter less than or equal to 2.5 mm (PM2.5). Both the studies and the new standard have been criticized. A major issue is the cost of compliance with the standards for industry. Estimates to bring power plants, diesel trucks, and other sources into compliance range between \$10 billion and \$60 billion annually. However, the resulting health benefits are valued at \$20-\$100 billion per year.

Advance: These researchers assessed the effects of PM10, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide on daily mortality rates in 20 of the largest cities in the U.S. The studies found consistent evidence that the level of PM10 is associated with increased rates of death from all causes and from cardiovascular and respiratory illnesses. The estimated increase in risk was 0.51% for each 10 mg/cubic meter increase in the PM10 level. This estimate is consistent with studies done by other researchers for other cities in the U.S. and other countries. There was weaker evidence that increases in ozone levels increased the risk of death in summer months. None of the other pollutants were significantly related to mortality rate.

Implication: This study adds to the body of data showing a correlation between increases in particulate matter and risk of death from all causes including cardiovascular and respiratory illnesses. These analyses provide evidence that particulate matter pollution continues to cause adverse health outcomes and strengthens the argument for maintaining air quality standards for this pollutant.

Samet JM, Dominici F, Curriero FC, Coursac I, and Zeger SL (2000). Fine Particulate Air Pollution and Mortality in 20 U.S. Cities. *New England Journal of Medicine*. 343 (24):1742-1749.