

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

**Minutes Of The National Advisory Environmental Health Sciences Council  
May 21, 2001**

The National Advisory Environmental Health Sciences Council was convened for its one-hundred third regular meeting on May 21, 2001, at 8:38 a.m., in the Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. The meeting was open to the public on from 8:38 a.m. until 2:05 p.m. The meeting was closed for consideration of grant applications from 2:05 p.m. until 4:10 p.m. Dr. Kenneth Olden presided as Chair.

**Members Present:**

Daniel Baden, Ph.D.  
Joan M. Cranmer, Ph.D.  
Dale Eastman  
George Friedman-Jiménez, M.D.  
Michael A. Gallo, Ph.D.  
Frederick P. Guengerich, Ph.D.  
Barbara S. Hulka, M.D., M.P.H.  
R. Michael McClain, Ph.D.  
Daniel Nebert, M.D.  
Peggy Shepard  
Robert D. Wells, Ph.D.  
Harriett M. Wieder

**Members Absent:**

Nancy Chuda  
Noreen M. Clark, Ph.D.  
Deeohn Ferris, J.D.  
Philip M. Iannaccone, M.D., Ph.D.  
Michael Karin, Ph.D.  
Martyn T. Smith, Ph.D.

**Ex Officio Members Present:**

N/A

**Ex Officio Members Absent**

David N. Erwin, Ph.D.  
Susan M. Sieber, Ph.D.  
Roberta F. White, Ph.D.

**Liaison Members Present:**

Daniel Acosta, Ph.D.  
Thomas Sinks, Ph.D.  
Robert Spengler, Ph.D.  
Hal Zenick, Ph.D.

**Liaison Members Absent:**

Roy Fleming, Ph.D.

**Members of the Public Present:**

Evan Myers, Ph.D., Duke University Medical Center

**Federal Employees Present:****NIEHS Staff:**

Beth Anderson  
Martha Barnes  
Linda Bass, Ph.D.

Sharon Beard  
David Brown  
Juanita Clement  
Gwen Collman, Ph.D.  
Allen Dearry, Ph.D.  
Dwight Dolby  
Dorothy Duke  
Thorsten Fjellstedt, Ph.D.  
John French, Ph.D.  
Mary Gant  
Lerlita Garcia  
Bill Grigg  
Jerry Heindel, Ph.D.  
J.T. Hughes  
Zoe Huang, M.D.  
Ethel Jackson, D.D.S.  
Laurie Johnson  
Annette Kirshner, Ph.D.  
Cindy Lawler, Ph.D.  
Edith M. Lee  
Pamela Lemon  
Francine Little  
Tara Lovekamp  
J. Patrick Mastin, Ph.D.  
Michael McClure, Ph.D.  
Julie McCormick  
RoseAnne McGee  
Claudia Miller, M.D.  
Sheila Newton, Ph.D.  
Liam O'Fallon  
Joan Packenham, Ph.D.  
Jerry Phelps  
Christopher Portier, Ph.D.  
John Pritchard, Ph.D.  
Jackie Russell  
Anne Sassaman, Ph.D.  
Carol Shreffler, Ph.D.  
William Suk, Ph.D., M.P.H.  
Claudia Thompson, Ph.D.  
Fred Tyson, Ph.D.  
Bennett Van Houten, Ph.D.  
Jose Velazquez, Ph.D.  
Denise Warren  
Brenda Weis, Ph.D.  
Samuel Wilson, M.D.  
Carolyn Winters  
Mary Wolfe, Ph.D.  
Gerri Wolfle

Other Federal Staff:

Peggy L. Jones, FDA  
Debra Lewis, M.D., FDA  
Rass M. Shayiq, Ph.D., CSR  
Robin Wagner, Ph.D., ATSDR

## **I. CALL TO ORDER AND OPENING REMARKS**

The one hundred third 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.

## **II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST PROCEDURES**

- Dr. Kenneth Olden

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

## **III. CONSIDERATION OF MINUTES OF FEBRUARY 12-13, 2001 MEETING**

Council members accepted the minutes without change.

## **IV. FUTURE COUNCIL MEETING DATES**

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

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

May 20, 2002 (Monday, the Retreat will follow on May 22-23) in Research Triangle Park

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

Dr. Olden began his report with a brief discussion on the retreat, and explained that he would have to leave the retreat early to attend the Senate hearings. The delay in determining the results of the election and having a new administration has caused the hearings to be delayed this year. Topics that would be discussed at the retreat include: Parkinson's Disease, Uterine Fibroids, and Toxicogenomics. Congresswoman Louise Slaughter will participate in the retreat. She is interested in women's health issues and previously introduced a bill on women's health and the environment.

He mentioned that a director for the National Institutes of Health has not been selected. According to comments from Dr. Tommy Thompson, Secretary, Department of Health and Human Services, the decision may be a long way off.

Dr. Olden reported on several budget issues.

- We are in the midst of budget hearings. NIH testified in an unusual manner because we didn't have the President's budget to defend. The budget in detail had not yet been forwarded. The House of Representatives had what were called "theme hearings." Institutes were invited to make presentations as parts of a panel, and NIEHS testified under the "Lifespan" theme. Participants used 3-5 minutes to make their case without having to defend a budget. Historically every institute was given one hour to make its

presentation and answer questions. This year, four institutes had one hour. At least four institutes did not get a chance to testify at all because the last panel was canceled.

- Congressman Regula is a champion of biomedical research. Many members of the Appropriations Committee are interested in the NIH, and several of them have visited DHHS organizations. Since many of the members are new, it is important that we all get a chance to make a case before them, because there is a competition for dollars. This year the competition is very severe. NIH has been singled out among scientific agencies for an increase, whereas other agencies have not fared as well. There is a lot of concern about giving NIH a 13.5% budget increase while some agencies are actually losing money. This is the best budget we have had from the Office of Management and Budget (OMB) in more than 20 years. We had the NIH budget hearings last week in the House of Representatives and they went well. The Senate hearings are scheduled for May 23.
- We also had a new set of hearings this year - the Superfund (SF) Basic Research and Worker Training Program. The Agency for Toxic Substances and Disease Registry (ATSDR) and NIEHS had the opportunity to make their case directly to the Committee (VA/HUD and Independent Agencies). Historically, the SF budget has been provided to us through the Environmental Protection Agency (EPA). This was our first increase that went all the way to Congress. It was not hard to make a case for the continuation of the program and for more dollars because the products generated have been very impressive.

Dr. Olden discussed several congressional concerns.

- The Senate is very interested in stem cell research. They are mostly concerned about adult stem cells versus embryonic stem cells. At this point, we simply do not know enough about the two types of cells to really know whether one is better or worse than the other.
- Citizens have contacted members of Congress about the increase of health care costs. They have intimated that research contributes to that increase. There is a sentiment that the emphasis should be on behavioral research: altering behavior to stop smoking, exercise more, have better diets, etc. One is more likely to have better health and fewer health problems by adopting lifestyle changes, thus lowering costs of health care. Prevention is also high on the public's list of priorities. The prevention interest would serve our Institute because everything we do is in the arena of prevention.
- Congress is also concerned about what NIH is doing to recruit more mathematicians, engineers, and computer scientists into biomedical research. It is something we have been thinking about but we are going to have to do some more cross-training in order to make this work.
- They are also interested in access to quality care. They believe that quality of care tracks where the research dollars are. In other words they believe research dollars are concentrated on the east and west coasts. If this is the case, they believe that the quality of care decreases in the middle U.S. If there is no good research institution or health research facility in a particular state, it is unlikely that the quality of care is comparable to the quality of care of those living in states with better research facilities. Disparity in rural health is another concern.
- Stability of biomedical research is something we are all concerned about. We are talking about the stability after 2003. What happens when the budget doubling effort ends? If the

budget does not increase, there is a concern about how well we will manage our grant portfolio and our research dollars to make sure we can provide the infrastructure to universities and support our commitment without devastating our capacity for funding new grants and initiatives.

- Congress is very much concerned about environmental causes of breast cancer. Congresswoman Nita Lowey, Senator Harry Reid and Senator Lincoln Chafee have introduced a bill proposing to create multidisciplinary breast cancer centers throughout the U.S. to look at the environmental causes of breast cancer. (Handout is available upon request). The bill authorizes \$30M/year for five consecutive years to get this effort accomplished. Dr. Olden has had conversations with Dr. Richard Klausner [Director of the National Cancer Institute (NCI)] in case this does occur. Previously they had discussed creating joint centers between NIEHS and NCI. Those institutions that have centers from both Institutes have a critical mass of expertise to address environmental and the genetic basis and clinical components of cancer. Dr. Olden stated that this should be an easy and much-needed marriage between the two Institutes. (Handout is available upon request).

Dr. Olden also discussed for the following:

- NIEHS attended a meeting with the U.S. Geological Survey (USGS) sponsored by Congressman Regula. The idea of the meeting was to talk about partnerships we already have with USGS. Impressive research activities exist in the area of exposure with USGS. The hearing went very well. State health agency officials from Seattle, Washington also participated.
- Dr. Olden participated in an event organized by the Children's Health Environmental Coalition (CHEC). CHEC's founders, James and Nancy Chuda, had a reception on Capitol Hill to introduce the new initiative, "child-proofing your home." This initiative was also aired on "Good Morning America" and an evening talk show. Several senators attended this event, among them Senator Clinton, who is very interested in children's health. NIEHS, EPA, and the Centers for Disease Control (CDC) have been major players in children's health as it relates to environmental health and safety. Senator Clinton is also interested in prevention.
- Dr. Daniel Acosta, outgoing President of the Society of Toxicology, allowed NIEHS to hold a Parkinson's Disease workshop at the Society's recent meeting. NIEHS had not in the past been able to have a session on a disease-oriented topic. NIEHS chose to have the session on Parkinson's Disease since there have been several exciting breakthroughs. We invited grantees to participate and we had a good turnout. Chemicals used in the studies may not be the ones primarily responsible as environmental factors, but ones which allowed investigators to develop interesting models of the disease. Dr. Olden believes that in time we will be able to identify some of the environmental risk factors.
- NIEHS has begun discussions with the American Chemical Council (ACC) and others concerning what to do with the volume of new information NIEHS will obtain from using toxicogenomic technologies in the next 5-10 years. We want to generate partnerships and friendships with industries. Having this new data will present more opportunities for successes. Unfortunately, this will also create more opportunities for conflict and opposition. We will have a large amount of data that will be complex and confusing for

awhile. We don't want interest groups and the press using the data prematurely to frighten the American public or to misinterpret the data - we want the data used wisely. We want to be able to agree on what some of the scientific issues are and maybe organize an "environmental court" or blue ribbon panel of experts to look at the data as they are being developed and interpret the information for the public and for policy makers. Discussions about how to accomplish this are ongoing.

- The General Accounting Office (GAO) report on cell phones has been released. The GAO looked at all the studies that were done on cell phones and they concluded that there does not appear to be a major health impact; however, these are small studies. The National Toxicology Program is looking at studies being done abroad and may decide to invest in additional studies. However, the GAO report to Congress concludes that no additional research dollars need to be appropriated for this type of research.
- There is an interesting report released by the Institute of Medicine on Agent Orange. The report is on a link between acute myelogenous leukemia in children and paternal exposure to Agent Orange. If this is confirmed, it is similar to studies that have been done at NIEHS with DES which demonstrated that the risk of cancer has been passed on to the second generation. This generated a fair amount of concern and we are in the midst of Agent Orange discussions with the Vietnamese Government and scientists.

Dr Olden commented on several staffing changes in the Institute

- Dr. Olden reported on the status of the Scientific Director search. NIEHS has identified an individual to fill this position; however, an announcement cannot be made until the Department reviews the appointment.
- NIEHS will announce the new director of the Environmental Toxicology Program about the same time we announce the Scientific Director.
- NIEHS is initiating a search under the Tenure Track Program for an X-ray crystallographer. This position will be announced soon.
- Dr. Allen Wilcox has been named editor of the Journal of Epidemiology. He has been chief of the Epidemiology Branch for the past 8 or 9 years. Dr. Wilcox is an internationally-respected epidemiologist. Dr. Dale Sandler will replace Dr. Wilcox in this position. He will stay on as a staff investigator but some of his time will be devoted to running the Journal.

Dr. Olden concluded his report with several papers he passed out on the following subjects (handouts are available upon request):

- A paper published in the New England Journal of Medicine by Dr. Walter Rogan on the study supported by the NIEHS on effect of chelation therapy with Succimer on neurocognitive development in children exposed to lead. He also included an article that was published in the New York Times Science on the same study, which concluded that chelation therapy had no effect on reversing neurocognitive consequences of low levels of lead.
- A paper co-authored by Dr. Gwen Coleman based on studies that NIEHS co-funded with the NCI looking at the link between exposure to DDT and PCBs and breast cancer. The conclusion is that there appears to be no link, based on a meta analysis of five groups of

1400 cases and 1642 controls. This article was published in the Journal of the National Cancer Institute.

- An article by a grantee in the Superfund Basic Research Program, Dr. Joshua Hamilton, on arsenic as an endocrine disrupter. We had known for years that arsenic not only is toxic, but is also a carcinogen; however we didn't understand the mechanism.
- A paper by Dr. John Peters and his colleagues from UCLA on the association between air pollution and lung growth and development in children. They looked at particulate matter in the 2.5-10 micron range and found major impairments of development and function in the most severe air pollution.
- An article on climate and amphibian declines by Dr. J. Alan Pounds of work supported through the NIEHS/Fogarty International Center/ National Science Foundation initiative, "Ecology of Infectious Disease." The article demonstrated that exposure to UV radiation as a function of climate change causes developmental problems to exposed eggs and more infections when the eggs are hatched.

As an introduction to the scientific presentations to follow and presentations at the Leadership Retreat, Dr. Olden reported to the Council that NIEHS will focus its new clinical activities under an intramural program called the "Center for Complex Diseases," which will ultimately focus on prevention. The Laboratory of Women's Health is a part of this effort. He then introduced Dr. Evan Myers, Assistant Professor of Obstetrics and Gynecology, Duke Medical Center.

## **VI. MANAGEMENT OF UTERINE FIBROIDS - RESULTS OF A SYSTEMATIC REVIEW - Dr. Evan Myers**

An abstract of Dr. Myers' presentation is found in Attachment A. He began his talk by describing the work of Duke's Evidence-based Practice Centers funded by the Agency for Healthcare Research and Quality and the history of the topic, management of uterine fibroids. This issue was suggested by the American College of Obstetrics and Gynecology and addressed nine specific questions. Those questions and the study's findings related to them are described in the attached abstract.

## **VII. AN APPROACH TO STUDY WOMEN'S HEALTH AND THE ENVIRONMENT - Dr. Barbara Davis**

An abstract of Dr. Davis' presentation is found in Attachment B. Dr. Davis' abstract describes the background of the Division of Intramural Research's Laboratory of Women's Health, and she indicated that a number of diseases that uniquely or disproportionately affect women are being studied at the Institute. She emphasized their integrative approach utilizing epidemiology, pathology, animal models, cell-based mechanistic studies and clinical studies in investigating the potential environmental links to reproductive and developmental defects, breast and ovarian cancer, and osteoporosis. She focused her report on the fibroid study as an example of a significant new effort involving this integrative approach.

## **VIII. FUTURE DIRECTIONS OF THE NATIONAL TOXICOLOGY PROGRAM - Dr. Christopher Portier**

Dr. Portier reviewed the goals of the National Toxicology Program (NTP), which may be summarized as the coordination, development, and validation of test methods and communication of the results to stakeholders. Regarding the current testing program, there are 150 on-going studies, and the NTP expects to start 60 new tests of various sorts this year. Special areas of emphasis include DNA-based products (e.g., genetically modified foods, gene therapy, vaccine vectors) and herbal medicines.

The purpose of the two NTP Centers--the Center for Evaluation of Alternative Toxicological Methods and the Center for Evaluation of Risks to Human Reproduction--is the translation of NTP output into regulatory action. Dr. Portier described the activities of these and also the Report on Carcinogens. A very important aspect of NTP activities relates to databases. NTP is working towards making these widely available on the World Wide Web. This effort will also address the redesign of the bioassay, where there is a great need to use existing information, and linkages between existing toxicology data and information that will come from the new toxicogenomics initiatives. Finally, an important question that will be asked relates to what important risk assessment issues can be addressed by databases.

Dr. Portier told the Council that the NTP will hold a retreat in August to discuss research initiatives. The topics include transgenic models and toxicogenomics studies, transgenic animals in cancer testing, and toxicogenomics research, and will address mechanisms to accomplish these initiatives. He concluded his remarks with a comment that new hires within the Environmental Toxicology Program reflect the shift in emphasis to non-cancer endpoints, and reminded Council of the goal of NTP (to improve the scientific basis for risk assessment) and the Institute's mantra ("Good Science for Good Decisions").

There followed a lively discussion of a number of issues regarding Dr. Portier's comments and directions of the NTP.

## **IX. 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)

Dr. Sassaman began her report with a summary of the NIEHS activities in the Minority Supplements Program. She described the Program and provided statistics on NIEHS's participation since 1996. She also gave the Council some example of "success stories" from the recipients of these supplements and engaged in a discussion of ways to promote and enhance the Program. Council members were pleased at the Institute's efforts and results and encouraged staff to seek ways to expand it.

In April the Division sponsored a Science Forum, bringing to the Institute senior post-docs and early career ("K") awardees supported by NIEHS. The meeting was deemed by all participants to be a success, an effort that should be repeated on a regular basis. The participants were able to 1) learn about the scope of NIEHS-supported science and program areas; 2) network with other developing scientists and present their work in a friendly setting; 3) learn about NIH extramural



process in a "grantsmanship" session; 4) learn about the "TIP" or K22 program and its benefits; 5) benefit from sharing of job search experiences; and 6) develop a relationship with NIEHS and its staff. Benefits to the Institute included a stronger relationship with this cadre of young scientists and the possibility of thereby strengthening the research portfolio through their interest and participation.

She concluded her presentation with two additional items. Council concurred with the topics for Fiscal Year 2002 SBIR contracts which had been reviewed in more detail by an ad hoc Council subcommittee. The Council was also provided with information about the status of NIH's newest institute, the National Institute of Biomedical Imaging and Bioengineering, especially how grant applications that would ultimately be funded in/by that Institute are being handled until the Institute structure can be put into place.

You may access copies of the slides used in Dr. Sassaman's presentations by going to the web site.

## **X. CONCEPT CLEARANCES**

***Small Animal Neuroimaging.*** The concept document is found on the list of attachments under D. Dr. Cindy Lawler presented this initiative, which is designed to identify the most promising applications of imaging modalities and suitable mechanisms for supporting neurotoxicologists in their use of brain imaging. The plan calls for a workshop to address and identify the opportunities and needs, followed by appropriate initiatives to address these. The Council unanimously endorsed the plan and, noting the high costs of instrumentation, urged staff to leverage the costs by collaborating where possible with other institutes and centers that may have common interests.

***New Concepts in Reproductive and Developmental Toxicology.*** (See list of attachments under D.) Dr. Jerrold Heindel, Organ and Systems Toxicology Branch, provided background on recent advances in developmental biology, molecular biology, and genomics as they relate to new opportunities to examine the site and mechanism of action of environmental toxicants that may affect reproduction and development. While NIEHS has a long-standing history of the support of research into developmental and reproductive toxicology, this particular initiative would propose to use new technologies and model organisms to develop a complete description of the mechanism of action of specific toxicants that affect the developing organism or any aspect of the developing or functional reproductive system. It is envisioned as a multi-step program with the unique feature of collaboration with the American Chemistry Council (ACC) in some aspects. The first step, which would involve funding from the ACC but with no deviation from the usual process of peer review and funding, is expected to be a solicitation for exploratory research, followed by additional Requests for Applications or Program Announcements to develop hypothesis-driven, mechanistically based projects that fully develop the mode and mechanism data. Council members were supportive of the concept, expressing the opinion that it is timely and that the interactions with the ACC represent a potentially productive partnership. The vote was for approval.

## **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.

## **XI. REVIEW OF APPLICATIONS**

The Council considered 125 applications requesting \$39,664,380 in total cost. The Council recommended all 125 applications with total cost of \$39,664,380.

## **XII. ADJOURNMENT OF THE NAEHS COUNCIL**

The meeting was adjourned at 4:10 p.m. on May 21, 2001.

## **XIII. REVIEW OF FDA APPLICATIONS**

The Council considered 41 applications requesting approximately \$8,439,681 in direct costs. The Council recommended approval of all submitted, approved applications.

## **ATTACHMENTS**

- A. [Abstract - Dr. Myers](#)
- B. [Abstract - Dr. Davis](#)
- C. [Report of the Director, DIR](#) In [Adobe Acrobat](#) Format
- D. [Report of the Director, DERT](#)
  - [SBIR Concept Clearance](#)
  - [Announcement of New Biomedical Imaging and Bioengineering Institute](#)
  - [Bioimaging Powerpoint Presentation](#)
  - [DERT Staff Activities](#)
  - [Small Animal Neuroimaging](#)
  - [New Concepts in Reproductive and Developmental Toxicology](#)

**National Institute Of Environmental Health Sciences**

**Division of Extramural and Research Training**  
**Office of Program Development**  
**Organs and Systems Toxicology Branch**

**National Advisory Environmental Health Sciences Council**  
**Small Business Innovation Research Program Committee**  
**May 21 2001**

**Concept Clearance**  
**for**  
**New Concepts in Reproductive and Developmental Toxicology**

***Introduction***

Recent advances in developmental biology, molecular biology and genomics present a unique and timely opportunity to examine the site and mechanism of action of environmental toxicants that affect reproduction and development and to thereby set the stage for intervention and prevention strategies. Major discoveries have recently been made in the areas of components, mechanisms and processes of normal development at the molecular level in various models including the fruit fly, zebrafish, frog, nematode, yeast and the mouse. Seventeen signaling pathways are currently recognized which probably represents the majority of the pathways used in development and differentiation of organs and tissues of these species. It appears that the molecular components of these pathways are substantially conserved among animal phyla and that they are used repeatedly in various combinations at different times and locations in the developing embryo and fetus. As described in a recent review (Scientific Frontiers in Developmental Toxicology and Risk Assessment: National Academy Press, Washington D.C. 2000), species differences in development involve different times, locations, and combinations of these pathways. Many of the kinds of cell responses to signals are also conserved, including selective gene expression, secretion, and cell proliferation and cell migration. This information allows the use of model organisms in mechanistic research in reproduction and development and extrapolation to humans by examination of gene orthologs and homologs.

In addition, the recent sequencing of the human genome along with that of several other species is providing information on the similarities and differences in

the number, type and organization of genes. Recent technological advances in genomics now allow for the examination of the control of gene expression during development using RNA isolated from embryos and fetuses. The use of DNA micro-array technologies to assess changes in gene expression is a rapidly growing research area that will have a large impact on many fields, including developmental toxicology and reproduction. This technology will allow a global perspective on how an organism responds to a specific stress, drug, or toxicant. Data generated in these experiments will provide information on the signature of cellular networks of responding genes, help define the important target molecules involved in toxicity, and aid in the development of future biomarkers. Experiments using micro-array technology will help define the complex regulatory circuitry within a cell, tissue and organ that responds to specific stressors. This technology may help pinpoint the relevant cascade of biochemical and molecular events that are potentially amenable to positive modulation, thereby preventing birth defects.

The science of proteomics promises to take over where genomics leaves off and provide data on tissue and time specific protein expression as well as post translational modifications altering protein activity. Finally, metabonomics will soon provide a profile of cellular metabolism.

The use of these new technologies and model systems in reproductive and developmental toxicology will have a major impact on our ability to develop a thorough understanding of basic mechanisms of development and reproductive function as well as an improved knowledge of species differences which will all contribute to improved public health via the development of intervention and prevention strategies.

It is also clear that there is great potential to use the model organisms and genomics approaches to develop new high throughput screens for the determination of the developmental or reproductive toxicity of environmental agents. These screens based on gene expression profiling or proteomic or metabonomic technologies would be expected to be faster and cheaper than current animal models.

The program developed under this concept clearance will be, in part, done in collaboration with the American Chemistry Council (ACC). The ACC is a not-for-profit organization sponsored by member companies of the U.S. chemical manufacturing industry. The ACC administers the industry's environmental, health, and safety performance improvement initiative known as Responsible Care. The ACC and its members have affirmed their commitment to Responsible Care and the American public's right to know by initiating a five-year Long-Range Research Initiative (LRI) program supported by \$100 million in funds committed to fund essential research and expedited product testing. These funds are targeted toward increasing the knowledge of the potential effects that chemicals have on human health and the environment. The joint sponsorship of initiatives related to reproductive and developmental toxicology by the NIEHS and the ACC is a unique collaboration of Government and Industry to support novel, high potential research that will contribute to the improvement of the health of the American public by improving the quantity and quality of data available on reproductive and developmental toxicants that can be used in the risk assessment process.

### ***Research Goals and Scope***

The objectives of this proposed multistep program are to use the new

technologies and model organisms to develop a complete description of the mechanism of action of specific toxicants that affect the developing organism or any aspect of the developing or functional reproductive system. The mode and mechanism data will include the toxicants interaction with specific molecular components of cellular or developmental processes and the consequences of those interactions, namely the developmental defect and/or functional deficit that may alter an individuals sensitivity to the development or exacerbation of disease. A complete description of the mechanism of action of a toxicant must also include the metabolism and disposition of the agents. Therefore this program will also develop metabonomic technologies that will aid in the acquisition of this data. Further, information on species sensitivity and genetic polymorphisms in the genes found to be involved in the toxic effect will be examined. This information will then be used to develop human studies, including epidemiological studies, in order to evaluate the human relevancy of the animal data and to develop, where appropriate, intervention and prevention strategies. It is anticipated that the accomplishment of these goals will require the interaction and collaboration of developmental biologists, molecular biologists, developmental toxicologists and epidemiologists. These collaborations will be encouraged by the activities of the planned program.

In the animal studies the use organ/tissue selective toxicants that have been well characterized in vivo as to the site of action will be encouraged. Applicants for this program will also be encouraged to use environmentally relevant doses, dose response curves and to relate the molecular mechanism proposed to the developmental or reproductive defect in a cause and effect manner.

Human and/or epidemiological studies that will be developed under this concept will build on the data from the animal studies and will therefore examine the same/similar environmental agents and pathways in humans in order to determine the relative sensitivity of the human, the role of polymorphisms and metabolism in this sensitivity and to develop the extrapolations needed to inform the risk assessment process and develop intervention and prevention strategies.

Another goal of this program is to use the new technologies of transgenics, model organisms, genomics, proteomics and metabonomics to develop, design, test and validate new high throughput screens to detect reproductive and developmental toxicants. The development of these high throughput screens are a critical component of this overall program as the data developed in these screens can then be used to continue the cycle of examining newly discovered reproductive and development toxicants for their mechanism of action and role in human toxicity.

### ***Mechanism***

It is anticipated that this program will use multiple mechanisms to achieve the stated goals. These include R21 exploratory/developmental grants requests for applications (RFAs) for the first phase of the mechanistic, epidemiologic and high throughput screens areas followed by either program announcements or additional RFAs as a follow up to use the information gained in the exploratory grants to develop hypothesis-driven, mechanistically based R01s that fully develop the mode and mechanism data.

### ***Timetable***

The first phase of this program is expected to be an R21 RFA entitled, "Developmental Toxicology Exploratory (R21) Grants". This will be a joint

initiative supported by the NIEHS and the ACC with the NIEHS contributing \$1.5M per year for two years and the ACC contributing \$500,000 per year for two years. This initiative would support 12-15 awards.

***Proposed Release Date:*** August, 2001

***Proposed Receipt Date:*** December, 2001

***Council Review:*** May, 2002

***Anticipated Funding Date:*** July, 2002

Other initiatives under this program may or may not involve the ACC and their exact goals and timetable will depend on the results of the first initiative and fiscal priorities.

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**Concept Clearance**  
**for**  
**Small Animal Neuroimaging**

***Introduction and Background:***

Recent fundamental advances in the neurosciences have begun to provide insight into myriad aspects of normal and disordered brain function. These insights have emerged at levels ranging from the identification of molecular partners that coordinate dynamic synaptic events to new understanding of circuit formation and organization that underlie complex behavioral traits. The expanding knowledge base created by these findings provides renewed hope that prevention, treatment and cure of many brain disorders are achievable goals. To understand the urgency of the need, conservative estimates for the United States alone indicate that over 20 million individuals are impaired by some type of developmental brain disorder and many millions more suffer from a neurodegenerative disorder. The manifestations of the developmental disorders are often lifelong and include behavioral, neurocognitive and emotional deficits. The symptoms of the neurodegenerative disorders, although restricted primarily to later ages, are equally debilitating and, other than Parkinson's disease, are untreatable. Other than a few syndromes that cause mental retardation, such as Down's syndrome or Fragile X syndrome, most developmental disorders are of unknown etiology.

Within the past decade, functional, molecular, and morphologic quantitative in vivo imaging techniques have become widely used tools for providing data about biochemical, genetic or pharmacological processes in living human brain. Techniques such as positron emission tomography (PET), single photon emission tomography (SPECT) and functional magnetic resonance imaging (fMRI) allow neuronal processes to be imaged noninvasively and repetitively, whereas

structural magnetic resonance imaging (MRI) provides detailed anatomical information. These methodologies have been used with great success in humans to elucidate the substrates for a diverse array of brain disorders, including schizophrenia, autism, Parkinson's disease and clinical depression. In many cases, the ability to collect time series data has been crucial for testing hypotheses about disease progression and/or influence of treatment interventions.

Many toxicants (heavy metals, pesticides) are suspected of contributing to neurodegenerative and neurodevelopmental disorders but the scientific linkage has yet to be definitively shown for most. Controlled exposure experiments in animals are essential to accomplish this goal, but have been hampered by a lack of tools for assessing in vivo brain structure and function. Recent technological innovations now make it possible to apply a variety of neuroimaging technologies to small animals, including nonhuman primates, rats and mice. The availability of these new technologies coincides with progress in developing animal models of various neurodevelopmental and neurodegenerative dysfunctions and improvements in assessment protocols for identifying deficits in animals that correlate well with human deficits. The integration of neuroimaging techniques with traditional neurotoxicological assessments has the potential to enhance greatly the ability to relate behavioral, cognitive or motor dysfunction induced by a toxicant to structural and functional brain pathology.

### ***Research Goals and Scope:***

Small animal models, particularly genetically engineered mice, are increasingly recognized as powerful discovery tools in medical research. In the field of environmental health sciences, genetic engineering aids evaluation of potential interactions between disease susceptibility gene(s) and environmental factors in the etiology of a variety of brain disorders. In most cases, however, the potential utility of these animal models has not been fully realized. One of the limitations has been the need to euthanize the animals to perform postmortem tissue or molecular analyses. This prevents the researcher from observing in vivo, within the same subject, the natural or perturbed evolution of the processes under study. Instead, between-subjects designs are used typically, with the attendant increases in variability and reduction in statistical power for detecting effects of interest. The use of non-invasive imaging methodologies circumvents such problems, as repetitive sampling allows detailed examination of the temporal course of toxicant-induced functional and structural alterations.

A notable recent application of imaging technology has been the noninvasive and repetitive measurement of the extent, duration and localization of transgene expression in living animals. This has been achieved most often by using a classic reporter gene approach, whereby a transgene is introduced whose mRNA encodes a protein product that can serve as a membrane-bound receptor or, alternatively, as an enzyme. A labeled probe is then introduced that interacts selectively with the reporter transgene-encoded protein product, as either a ligand or a substrate. This interaction is assayed by appropriate methodology (e.g., PET) to allow quantitative measurement of gene expression. The ability to measure cell-specific temporal regulation of gene expression in response to carefully defined environmental perturbations in animal experiments represents a powerful tool for elucidating environment-disease linkages.

The many recent technological innovations in biologic imaging were the focus of a Division of Extramural Research and Training (DERT) workshop "Defining the



Potential of Multimodal Approaches to Research in Environmental Toxicology", held at NIEHS in July 2000, and a featured topic at a subsequent science retreat in December 2000. The growing realization of the promise of imaging approaches was underscored by a special session held at the March 2001 annual meeting of the Society of Toxicology, entitled "Innovations in Applied Toxicology: Applications of Noninvasive Imaging in Toxicology" and sponsored by the Neurotoxicology Specialty Section. Experts who currently use and/or develop imaging technologies were the featured speakers at these events. Recent progress in diverse imaging modalities, ranging from light microscopy of signaling elements in single cells to functional brain mapping with magnetic resonance imaging were highlighted. The significant advantages afforded by imaging were noted with numerous examples from disciplines where these approaches are well established. Some of the critical needs that must be met to allow environmental health science researchers to adopt these approaches were described as well. Costs associated with these neuroimaging technologies are very high and new instrumentation is often required. Combined NMR-PET equipment is under development and will offer the opportunity to study brain structure and function simultaneously. In the case of PET, while radiolabeled glucose and some other compounds are easily obtainable, the availability of an on-site cyclotron is needed to generate many of the necessary radiolabeled tracer ligands.

At present, neurotoxicologists have limited knowledge of, and access to, these innovative technologies and the associated expertise; this presents a formidable barrier to their application in areas of environmental health science. The NIEHS can play an important role in ameliorating these obstacles by supporting collaborations among neuroimagers and neurotoxicologists and providing targeted funds for imaging instrumentation acquisition and/or augmentation. Partnering efforts with other NIH institutes and Centers will be critical if NIEHS is to achieve this goal. At present, the National Center for Research Resources (NCRR) supports a variety of imaging resource Centers and provides funding for shared neuroimaging instrumentation. Most recently, the National Institute of Health has initiated a new, congressionally mandated institute, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) whose mission is to support the development of the technology needed for all aspects of imaging including neuroimaging. NIBIB has a broad mandate to develop new techniques and devices, advance existing modalities, enhance current applications, and develop enhancement agents for contrast media, molecular and genetic imaging, and image-guided surgery. Initially, NIEHS can work in collaboration with NCRR and NIBIB to foster the technology development and infrastructure support though our end goal will be to support the application of the technology to neurocognitive and neurodegenerative research problems.

### ***Management Plan:***

The previous DERT-sponsored imaging workshop and retreat focused on technology development for a variety of imaging modalities, with examples of potential applications drawn from many fields outside of environmental health scientists. Although these events drew attention to the potential of noninvasive imaging for elucidating brain biology, there is a need for additional input to identify the most promising applications and suitable mechanisms for supporting neurotoxicologists in their use of brain imaging. To accomplish this, the NIEHS will organize a workshop on brain imaging to which researchers in the field of neuroimaging as well as neurologists, neurotoxicologists and neurobehavioral toxicologists who would benefit from using the technology for research will be brought together. Special emphasis will be given to application of the multiple

technologies to study neurocognitive and neurodegenerative diseases (Parkinson's disease, Alzheimer's, and Amyotrophic Lateral Sclerosis ) for which there is some evidence implicating an environmental exposure as a risk factor and for which there are some small animal/transgenic models for the diseases. Also emphasized will be neurobehavioral/cognitive research on deficits like ADHD for which small animal models are also being developed.

The workshop recommendations will be used to guide a series of NIEHS-sponsored multidisciplinary initiatives that support increased access of neurotoxicologists to appropriate neuroimaging instrumentation. It is likely that the first initiative will involve partnering with NIBIB and NCRR and will take the form of augmentation of instrumentation (e.g., microPET and small bore, high field strength MRI) at established imaging Centers. Such Centers would be expected to have sufficient animal handling facilities and geographical proximity to a collection of neurotoxicologists with research interests that could benefit from such technologies.

## Featured Activities of DERT May, 2001

DERT staff have been involved in the initiation and development of a variety of meetings since the last Council. The following are three meetings of note.

### ***Bioinformatics Strategies for Application of Genomic Tools to Environmental Health Research***

March 5, 2001

The McKimmon Center

North Carolina State University, Raleigh, North Carolina

*Introduction:* The National Institute of Environmental Health Sciences (NIEHS) established the National Center for Toxicogenomics (NCT) in June 2000. Toxicogenomics is an emerging scientific field that combines studies of genetics, genome-wide mRNA expression, cell and tissue-wide protein expression, and bioinformatics to understand the roles of gene-environment interactions in disease. The NCT was created to facilitate application of toxicogenomics to improve human health.

A series of three workshops were held through which the research community could learn about the NCT and provide input during its early stages. The third workshop in the series entitled "Bioinformatics Strategies for Application of Genomic Tools to Environmental Health Research" was held at North Carolina State University (NCSU) on March 5, 2001. The meeting was co-organized by Bruce Weir (NCSU), Cynthia Afshari (NIEHS) and Pierre Bushel (NIEHS) and co-sponsored by NIEHS and NCSU.

*Meeting Highlights:* A series of invited speakers presented current and emerging approaches for analysis of DNA sequence and gene expression data. John Quackenbush from the Institute for Genomic Research (TIGR) described efforts to use sequence homology to map orthologs in different species and to develop microarray analysis tools for spot identification, image normalization, data mining, pattern recognition and clustering. Alex Lash (National Center for Biotechnology Information) provided an overview of the NCBI Gene Expression Omnibus (GEO), a public gene expression data repository. Gary Churchill (Jackson Laboratories) and Terrence Speed (University of California, Berkeley) reviewed statistical issues in microarray experiments and emphasized the importance of experimental design and the use of replication to allow for separation of systematic and random variation in microarray experiments and to facilitate data normalization.

A panel discussion included consideration of strategies for establishing the NCT's national reference and relational database on "Chemical Exposures in Biological Systems" (CEBS). Panelists supported the establishment of an independent database by NCT to allow quality assurance filters that may not be present in other existing databases. The advantages of encouraging more annotation and information of gene expression data were noted, including recording of image analysis tools used for analysis and access to raw data (intensity values, raw images). Panelists emphasized the need for experimental replicates and hybridization replicates, including fluor-flip replicates. The merits of inclusion of replicated spiked standards were discussed. Advantages and limitations of the use pooled control samples were described. Difficulties in the ability of microarray technology to handle low dose or early time point data were discussed; panelists urged the use of biological context and a consideration of signal to noise ratio to aid interpretation in such cases. Finally, the need to promote development of quantitative proteomics was discussed.

### ***Diets, Antioxidants and Environmental Influences On Health and Disease***

March 13-14, 2001

NIEHS, East Campus

*Introduction:* It has long been recognized that reactive oxygen species (ROS) can lead to, or are often associated with, a large number of human diseases. Furthermore many environmental toxicants are associated with the production of ROS either directly or indirectly by affecting physiological processes. The purpose of this workshop was to bring together experts in the field of ROS, diet and antioxidants to discuss current findings, identify information gaps, and to develop a research agenda in this area. This meeting, which lasted one-and-a-half days, covered three major topics: 1) Epidemiology/human exposure; 2) effects of dietary restriction and antioxidants on longevity; and 3) assays for biomarkers of oxidative stress. A committee from NIEHS and EPA organized the meeting that was chaired by Ron Mason, and Ben Van Houten. Gary Hatch (EPA), Frank Kari (NIEHS), and Maria Kadiska (NIEHS) chaired the individual sessions. The meeting consisted of nine presentations by invited speakers and ample discussion time for NIEHS staff and seven invited guests. A full meeting report is being prepared.

*Meeting Highlights:* The premise underlying the meeting was in the form of three postulates by Norman Krinski: Many chronic diseases are associated with oxidative stress; antioxidants can decrease oxidative stress; therefore, antioxidants can (should) prevent chronic diseases. The main problem with this theory is that examples of chronic environmentally induced diseases in humans that are mitigated by dietary manipulation are inconclusive and incomplete. Balz Frei reviewed several human studies involving the use of dietary antioxidants in preventing or reversing cardiovascular disease. He commented that "no data are available from prospective or nested case control studies" and for this reason, the hypothesis of a role for oxidative stress in these diseases has not been proved or disproved. Combined results of the many nutritional studies are promising; however, they link general types of diets with outcomes, and many confounding factors are present. Two very obvious confounders were pointed out by many of the speakers: genetics and total calorie restriction. Examples include the findings that genetic factors can greatly influence bioavailability of dietary vitamin E (M. Traber), and that rats and primates show large positive influences of calorie restriction on tissue antioxidant balance and (F. Kari) and on susceptibility to diabetes (B. Hansen.) Future research must focus on:

- definite case-control human studies;
- pharmacokinetic models for the adsorption and redistribution of dietary antioxidants during oxidant stress;
- profiling of oxidant sensitive genes;
- search for genetic polymorphisms predisposing individuals to increased stress from ROS;
- reliable high throughput biomarkers of oxidant stress using state of the art techniques such as real time imaging, proteomics and DNA microarrays; and
- more useful transgenic and knockout mouse models in which to test these endpoints.

Clearly, these problems can be best addressed by multi-disciplinary teams that bring together a wide range of expertise and experimental tools.

***An Extramural Grantee Meeting and Workshop on Mechanisms of Apoptosis, Growth Factors, Signal Transduction and Oxidative Stress: Future Directions***

April 11-12, 2001

NIEHS, East Campus

Research Triangle Park, North Carolina

*Introduction:* On February 7, 1997, the National Institute of Environmental Health Sciences issued a Request for Applications (RFA) entitled "Modulation by Growth Factors and Signal Transduction Pathways of Environmental-Induced Disease/Dysfunction." The purpose of the solicitation was to encourage innovative, mechanistically based research to elucidate how growth factors modulate environmentally induced altered gene functions; and conversely, how environmental agents alter or modulate the function of growth factors and the cellular signaling cascades.

The goals of the Grantee meeting and Workshop, which was organized by Dr. Joan Packenham, NIEHS, were twofold: First, it promoted an exchange of information among grantees, invited speakers, and the NIEHS intramural and extramural communities. Second, it served as a workshop to set new research agendas for future funding opportunities in the areas of apoptosis, growth factors, signal transduction and oxidative stress. The meeting provided a forum for the exchange of scientific views to discuss:

- The accomplishments of the present RFA.
- The current state of research in the field.
- Where data gaps of knowledge existed.
- The tools/incentives needed to fill those gaps.
- Suggested mechanisms or novel approaches for future research in the field.
- Areas of research that should be prioritized by NIEHS

The meeting included ten NIEHS grantees whose research was funded through the RFA as well as numerous invited speakers from the intramural and extramural communities. Session topics included: Signaling and Apoptosis - Elizabeth Murphy, Chair and Carl Bortner, NIEHS-Co-Chair; Signaling and Growth Factors - Kenneth Adler, N.C. State Univ., Chair and James Bonner, NIEHS-Co-Chair; and Signaling and Oxidative Stress - Brooke Mossman, Univ. of Vermont, Chair and Aaron Barchowsky, Dartmouth Medical School-Co-Chair.

*Meeting Highlights:* The outcome of the meeting was the development of new

research initiatives for future funding opportunities in the areas of signaling and: apoptosis, growth factors and oxidative stress. A few of the recommendations were as follows:

- Causally relate stimulation or inhibition of individual signaling pathways and interrelationships or cross-talk between signaling cascades in relationship to downstream functional outcomes. (apoptosis, proliferation, cell survival).
- Examination of concerns in bullets 1 in differential target cells and at various stages in the development of environmental induced disease (ex: hyperplasia, metaplasia/dysplasia, carcinoma)
- Development of transgenic mouse models to down modulate signaling proteins (dominant negative, knock-outs, conditional mutants).
- Development of approaches (immunohistochemistry, screening of phosphoproteins) for localization and screening of activated signaling proteins in physiological models of oxidant exposures.
- Inhibition of signaling pathways as a means of examining linkage to cell injury, proliferation, cell death and disease.
- Examine the effects of stress on protein synthesis, RNA processing and on cell trafficking (mitochondrial/endoplasmic reticulum interactions)

Information generated from each of the breakout sessions will be summarized and reported in a meeting report to be published in Environmental Health Perspectives.

## **PUBLIC DATABASES**

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental. The NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies. As part of its communication outreach, NIEHS participates in three web-based, searchable public databases that provide information on various activities of the Institute.

*CHEHSIR* is a publicly accessible, web-based relational database created and maintained in response to presidential Executive Order 13045 "Protection of Children from Environmental Health Risks and Safety Risks." CHEHSIR's purpose is to ensure that federal research agencies, researchers at universities, community groups, and the public have access to information on all research conducted or funded by the federal government that is related to the adverse health risks for children resulting from exposure to environmental agents and safety risks. It is searchable by environmental health or safety topic, geographical area, funding agency, institution, or principal investigator. CHEHSIR was created through a multiagency working group of the Task Force on Children's Health and Safety Risks. Eighteen federal agencies participate in CHEHSIR, including the National Institutes of Health, the Environmental Protection Agency, the Centers for Disease Control and Prevention, the Department of Housing and Urban Development, the Consumer Products Safety Commission, the Agency for Toxic Substances and Disease Registry, the Department of Education, and others. To access CHEHSIR, point your Internet browser to <http://www.epa.gov/chehsir/>.

*GeneSNPs*, short for "single nucleotide polymorphisms", is a new bioinformatics tool created by the University of Utah Genome Center and funded through the Environmental Genome Project. The database is both a process and a tool for

integrating up-to-date public gene resources for single nucleotide polymorphism discovery and analysis. It provides current, integrated, sequence-based views for nearly 500 human genes implicated in cellular responses to exposures to environmental toxicants, genes using cDNA sequence, genomic sequence, and SNPs. Current gene categories include cell division, cell signaling, cell structure, gene expression, homeostasis, and metabolism. The list of human genes included in this resource is not exhaustive; new environmentally responsive genes will be added to GeneSNPs as information on their roles in vulnerability to environmental exposures becomes available. To access GeneSNPs, point your Internet browser to <http://www.genome.utah.edu/genesnps/>.

*ClinicalTrials.gov* was mandated by section 113 of the FDA Modernization Act, which was made law in November 1997. This law required the Department of Health and Human Services, through the NIH, to establish a registry of clinical trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases or conditions. NIH expanded the definition of clinical trial to include all NIH-supported patient oriented research, including epidemiologic and behavioral studies, as well as outcomes and health services research. This database, created by the NIH National Library of Medicine in collaboration with the Food and Drug Administration and all NIH institutes, provides patients, family members, health care professionals, and members of the public with easy access to information on clinical research for a wide range of diseases and conditions. To access *ClinicalTrials.gov* point your Internet browser to <http://clinicaltrials.gov/>. NIEHS-specific research can be found by entering NIEHS in the search box. Not all research projects listed are currently recruiting patients. To see all NIEHS trials check the box for "All Trials."

### ***SELECTED ACTIVITIES OF THE WETP and OPO***

Ms. Duke, OPO/GMB, presented an NIH Update at the North Carolina Society of Research Administrators on March 27 in Greensboro, North Carolina. She will be co-presenting the NIH Update at the following meetings: Society of Research Administrators, International, Annual Meeting, October 13-17, 2001 in Vancouver, British Columbia; National Institutes of Health, Grants Management Advisory Committee, Vision Subcommittee on Training, October 25, 2001 at NIH; and the National Council of University Research Administrators, Annual Meeting, November 12-14, 2001 in Washington, DC.

Mr. Hughes, OD/WETP, chaired a session at the National Conference, "Training 2001," in Atlanta, GA on March 5, 2001 entitled "Lessons Learned in Advanced Training Technology in Health and Safety" which examined 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 co-sponsored a Technical Workshop on "Best Practices in Occupational Safety and Health Training" on April 17-19 in Chicago, Illinois. Dr. Anne Sassaman gave the Keynote Address for NIEHS. Staff attending the workshop and participating in various activities included Mr. Hughes, Ms. Beard, and Ms. Thompson, OD/WETP. The morning of April 17, the semi-annual WETP Awardee Meeting was held. Ms. Mason, OPD/GMB, also participated in the meeting.

Ms. Duke, OPO/GMB, gave a presentation entitled "Project Budgeting and Expending: An Interactive Team Approach" at the Society of Research

Administers, International, Western Section Annual Meeting which was held May 7 - May 9, 2001 in Anchorage, Alaska. She also served as the moderator for the NIH Update session at this meeting.

## **STAFF RECRUITMENTS**

Dr. J. Patrick Mastin, OPD/OSTB. Dr. Mastin received his undergraduate degree from Centre College (Biochemistry and Molecular Biology) and his Ph.D. (Pathology) from Duke University. He developed and conducted an active research program studying the pathophysiology of respirable inorganic particulate matter (PM) in the lungs of exposed individuals that included both animal and human studies. Dr. Mastin served as the Chief, Immunochemistry Research Section, NIOSH prior to being recruited to the NIH. Dr. Mastin will be responsible for the Pulmonary and Cardiovascular Toxicology program - a major NIEHS extramural program component of significant importance to the NIEHS, NIH and DHHS mission and national public health priorities. He brings to the OSTB significant NIH extramural program experience acquired during his highly accomplished tenure as a Scientific Review Administrator with the Scientific Review Branch within OPO/DERT.

Ms. Melissa Pittman, has joined OPO/RCB from OM/Acquisitions Management Branch.

## **UPCOMING MEETINGS and WORKSHOPS**

The NIEHS/EPA Superfund Basic Research Program is co-hosting the Seventh International Congress on Combustion By-Products: Origins, Fate, and Health Effects at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C., June 4-6, 2001. Dr. Suk, OPD, is the Congress Chair. Emissions from combustion sources continue to be a controversial environmental issue. The risks associated with the widespread use of combustion have increased our awareness of the emissions of dioxins, other organic pollutants, complex mixtures, metals, and fine particulates. The goal of this conference is to provide an international forum to discuss topics on the origins, fate, and health effects of combustion. Researchers and practitioners will have the opportunity to interact and discuss recent developments and future goals in the control of combustion by-products and the effects of exposure on human and ecological health.

The 2001 American Industrial Hygiene Conference and Exposition will be held in New Orleans, Louisiana on June 7, 2001. Ms. Beard, OD/WETP, will present 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.

Dr. McClure OPD/OSTB and Dr. Philip Mirkes, University of Washington are co-organizers of the meeting entitled, Developmental Toxicology in the 21st Century: Multidisciplinary Approaches using Model Organisms and Genomics, which is to be held at the NIEHS Conference Center, Research Triangle Park, North Carolina on September 20-22, 2001. The purpose of this conference is to bring together a multidisciplinary group of research scientists (molecular biologists, molecular geneticists, developmental biologists, developmental toxicologists, model organism experts (Drosophila, zebrafish, C. elegans),



epidemiologists and risk assessors) in a joint forum to explore the use of new technology and research approaches for improving our ability to understand the site and mechanisms of action of developmental toxicants in order to develop new biomarkers of exposure and toxicity and improved intervention, prevention and risk assessment strategies. The goal is to define how developmental toxicology research should be carried out over the next 5-10 years considering the changes in the technology and the genomics revolution.

#### GRANTEE HONORS and AWARDS

Dr. Julian I. Schroeder, a professor of biology at the University of California, San Diego who has uncovered the molecular mechanisms that allow plants to remove toxic metals from contaminated soil and resist drought has won this year's \$250,000 Blasker Award for Environmental Science and Engineering. He will receive the prestigious award from The San Diego Foundation at a ceremony on June 13. He was cited by the committee of internationally renowned scientists who selected him for the award for his "significant contribution toward addressing a significant environmental issue."

Drs. George Bailey and Jerry Hendricks, Oregon State University, jointly were awarded the 2001 (Sixth) Prince Hitachi Prize in Comparative Oncology in Tokyo in May for work establishing the relationship between carcinogen dose and tumor response. The study revealed that tumor response at low dose becomes less than linear despite the fact that carcinogen-DNA adduct formation remains linear. This study provides the first experimental data that can be used to examine the degree of conservatism inherent in the EPA LED10 default linear low-dose extrapolation model.

Drs. Frank Speizer and Walter Willet, Harvard School of Public Health, will receive the Charles S. Mott Prize at the 23rd Annual General Motors Cancer Research Foundation Awards Ceremony and Banquet to be held in Washington, D.C. on June 6, 2001. The Charles S. Mott Prize is given for the most outstanding recent contributions to understanding the causes or ultimate prevention of human cancer.

Dr. James Trosko, University of Michigan, received the first ever awarded, "Scientific Achievement" award from the Society of Toxicology in San Francisco (2001) for his research on how most environmental toxicants, e.g., PCB's, PBB's, DDT, pentachlorophenols, TCCD, perfluorinated fatty acids, many of their chemically- and biologically-remediated products, as well as many PAH's, act via non-genotoxic mechanisms. The Scientific Achievement Award is presented to a member of SOT who has made substantial and seminal scientific contributions to the discipline of toxicology. The prime consideration for this new award is scientific accomplishments and not necessarily service to the Society.

Dr. Richard H. Finnell, Texas A & M, College Station, TX , has been named as Director of the Institute of Biosciences and Technology, a component of The Texas A&M University System Health Science Center, effective June 1, 2001.

Dr. Angela Brody, University of Maryland School of Medicine, was awarded the 2000 Brinker International Basic Research Award by the Komen Foundation for her ground breaking research on the use of aromatase inhibitors as treatment for breast cancer. The award was made at the 23rd annual San Antonio Breast Cancer Symposium this past December.

#### DEPT PAPERS OF NOTE

A current list of DERT Papers of Note can be found at <http://inside-www.niehs.nih.gov/dert/profiles/hilites/hilites.htm>

The following papers were highlighted for this Council round:

- **Polymorphisms in the Gene for Microsomal Epoxide Hydrolase -- Possible Answer to "Why Me?"**
- **Differing Amino Acid Residues are Critical for Differences in Phenylimidazole-Induced Inhibition of Cytochrome P450s**
- **ARNT Activity Unaltered by Phosphorylation**
- **Sniffing Impairment Contributes to Decreased Ability to Smell in Parkinson's Disease Patients**
- **Induction of Oxyradicals by Arsenite: Mechanism of Genotoxicity**
- **Fighting Oxidative Damage with Buckyballs**
- **Dithiolethiones: A Promising Class of Human Anti-Cancer Drugs**
- **Modest Increases in Ambient Ozone Concentration are Associated with Increases in School Absenteeism**



# National Institute of Biomedical Imaging and Bioengineering (NIBIB)

7/2/01

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**National Institutes Of Health**

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**National Institute of Biomedical Imaging and Bioengineering**

**NIH News Release**

**FOR IMMEDIATE RELEASE**

**Wednesday, May 9, 2001**

**CONTACT:**

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**NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING  
ESTABLISHED**

Acting Director Named

NIH Acting Director Ruth L. Kirschstein, M.D., has announced the appointment of Donna J. Dean, Ph.D., as Acting Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The NIBIB, the newest NIH Institute, was created by statute and was signed into law last December. Health and Human Services Secretary Tommy G. Thompson approved the establishment of NIBIB on April 20, 2001.

"Dr. Dean has extraordinary scientific and administrative skills, and I appreciate her willingness to lead NIBIB while we conduct a national recruitment effort to find its first permanent Director," Dr. Kirschstein said. HHS Secretary Thompson will appoint the permanent Director.

The mission of the NIBIB is to support the fundamental research that applies the principles of engineering and imaging science to biological processes, disorders and diseases. The Institute will facilitate the transfer of this basic research to medical application. "As part of the NIBIB mission," Dr. Kirschstein explained, "the new Institute will coordinate the on-going research of the NIH Institutes and Centers and will foster the exchange of information with other Federal agencies."

Dr. Kirschstein added that, "while dedicating an Institute to medical technologies rather than to diseases, organ systems, or populations may seem novel for the NIH, it is truly a reflection of what science is today -- and where science will be taking us tomorrow. "

The creation of an agenda for research and research training will be the primary activity for the NIBIB. These efforts will strengthen on-going NIH activities. In Fiscal Year 1999, predating NIBIB, NIH's Institutes and Centers awarded about \$447 million for bioimaging research and about \$697 million for bioengineering research. The President's budget request for FY 2002 includes \$40.2 million for NIBIB. "I expect that the majority of the activity in other Institutes will continue," Dr. Kirschstein explained, "while NIBIB will support important basic and crosscutting research in the bioengineering and imaging sciences."

Dr. Dean has served in the Office of the NIH Director (OD) as a senior scientific advisor for the past three years, and played a lead role in implementing the legislative establishment of NIBIB. In addition to her involvement in various research and policy activities at NIH, she served as NIH liaison to the Congressionally-mandated Commission on the Advancement of Women, Minorities, and Persons with Disabilities in Science, Engineering, and Technology during the past two years. Dr. Dean's experience in the scientific and administrative management of the NIH initial peer review process spans fifteen years.

She received the A.B. degree in chemistry from Berea College in 1969, and the Ph.D. degree in biochemistry from Duke University in 1974. After postdoctoral work in cell and developmental biology at Princeton University, she joined the NIH intramural research program as a research chemist in biochemical endocrinology.

**National Institute Of Environmental Health Sciences**

**Division of Extramural and Research Training  
Office of Program Development  
Organs and Systems Toxicology Branch**

**National Advisory Environmental Health Sciences Council  
Small Business Innovation Research Program Committee  
May 21 2001**

**Concept Clearance  
for  
Small Business Innovation Research Program: Contract Topics FY 2002 Solicitation**

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This Small Business Innovation Research Program (SBIR) uses a combination of research and technology transfer to develop new products that will aid the mission of NIEHS. A portion of the SBIR funds are allocated for contract solicitations that will improve the productivity of the Intramural scientists at NIEHS and the larger scientific community by providing specific reagents and technologies and instruments needed to further research. This concept is for approval of the contract portion of the SBIR program for FY 2002.

Topics under Consideration for the FY 2002 SBIR Contract Solicitation

***Development of Clinical Resources for Toxicogenomic Studies***

Dr. Ray Tennant

In order to translate the revolution in technology related to toxicogenomics to improvements in human health, human tissues from well-characterized populations with well-characterized exposures are needed. The goal of this project is to acquire and make available to researchers clinical samples from human populations in areas of high environmental pollution. The cryopreserved samples (e.g. tissue, blood, serum, and fluids) must be related to an extensive record of biological data (point of origin, clinical/disease phenotype, family history, exposure assessment etc). Ideally, health effects in children born to

exposed mothers (child-mother phenotypes) would be particularly useful. Such matched records/samples should allow the determination of birth outcomes, developmental milestones, adverse drug reactions, overall health status, extent of maternal exposure extent of fetal exposure and genotypes.

These records/samples should be appropriate for genotyping for polymorphism or genes determining or influencing disease susceptibility, and for gene expression analyses. Access to these samples and records could be made available to researchers on a contract or purchase basis.

***Development of Surrogate biomarkers of exposure or toxicity for safety evaluation of chemicals.***

Dr. Ray Tennant

A number of technological and conceptual advances in molecular biology and medicine, genetics and genomics have opened significant opportunities for the development of new tissue specific surrogate biomarkers. A surrogate biomarker is an endpoint measurement that allows the monitoring of the activity of a particular tissue and therefore would be helpful in determining tissue specific damage by virtue of alterations in its level or activity. The purpose of this initiative is to solicit the development and validation of new surrogate biomarkers that would be indicative of either exposure to a specific chemical or class of chemicals and/or of tissue or organ specific damage that can be measured either noninvasively or from a serum, urine or saliva samples. Surrogate biomarkers can be developed for any organ or tissue such as the liver, kidney, heart, reproductive system, immune system, central nervous system etc. One possible approach would be to screen all the tissue specific genes that have signal sequences as they are likely to be secreted from the tissue and thereby may be a possible biomarker of that tissues activity. The surrogate biomarkers must be easily measured, be specific and reliable and must be validated against known tissue toxicants.

***Development of Alternatives to Animals for Toxicity Testing.***

Dr. Bill Stokes

The NIEHS is committed to developing alternatives to animals for toxicity testing. In this regard we are interested in developing in vitro assays that could be part of a battery of tests that could replace animals for toxicity testing. To this end we solicit the development of in vitro cell cultures that mimic cell activity in vivo. It is well known that cells in culture are not the same as those in vivo. Now with the advent of gene expression analysis using microarrays it is possible to assess gene expression in cells in culture and cells in vivo and to then devise methods to make the cell cultures mimic the in vivo situation at least with regard to gene expression. This can also be done for proteomics. It is anticipated that the results of this project would be cell cultures that would, because of their similarity to the in vivo cells, be useful to be used as screens for toxicity assessment. Cells can be human or animal derived but should be amenable to alterations in growth rate in vitro so that toxicity can be assessed in static differentiated and growing cells. Cell cultures produced under this initiative should also be validated using tissue specific toxicant to assess that the in vitro response matches the known in vivo response. Skin cultures are not responsive to this request.

***Development of Novel Approaches to Proteomics***

Dr. Ken Tomer

Now that the human genome has been mapped, attention is beginning to turn to



the characterization of the proteome, which is the global protein profile reflecting cellular activity in relation to time, development, and interaction with the environment. Proteomics is the analysis of the proteome, and the current paradigm is based on separation of components by 2-dimensional gel electrophoresis, followed by protein identification based on mass spectrometric analysis of digests of the protein gel spots. This combination is laborious and relatively insensitive to low level proteins. Thus there is a significant need for new approaches to proteome characterization, such as affinity-and or chip-based techniques and/or new approaches to enrichment, detection and characterization of post-translationally modified proteins. Thus the NIEHS is soliciting proposals that address the need for high throughput, high sensitivity proteome characterization.

### ***Development of cDNA arrays for Male Reproductive Toxicology***

Dr. Mitch Eddy

The cDNA microarrays currently available are of limited use for male reproductive toxicology because of the lack of testis specific genes. This is particularly true for the testis where many unique genes and cell-types specific alternative transcripts are expressed. This the purpose of this initiative is to either develop or identify ESTs available representing genes expressed in the mouse testis and to verify, the identity of these ESTs in order to identify testis specific genes that are unique or have low homology to sequences of known genes. These genes would be used to develop testis specific cDNA microarrays (5-10,000 genes) that would be tested and validated with regard to quality, specificity and completeness of the genes arrayed.

# REPORT OF THE DIRECTOR DIVISION OF EXTRAMURAL RESEARCH AND TRAINING

7/2/01

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**THE DIVISION OF INTRAMURAL  
RESEARCH**

**NAEHS COUNCIL REPORT**

**MAY 2001**

## **DIR Recruitments February 2001**

### **Scientific Director**

A national search has been reopened to fill the position of Director, Division of Intramural Research, NIEHS. This individual serves as Scientific Director and directs laboratory and clinical research through 18 Laboratories and Branches with approximately 1100 government employees and contract personnel and an annual budget of approximately 140 million dollars. The Scientific Director is the principal advisor to the Institute Director on scientific affairs involving multidisciplinary biomedical research programs. The search committee, chaired by Dr. Samuel Wilson, has forwarded a short list of candidates to Dr. Olden.

### **Chief, Laboratory of Pulmonary Pathobiology**

A national search for a new Chief of the Laboratory of Pulmonary Pathobiology (LPP) is taking place. The LPP is engaged in research on the biology of the respiratory tract system at the cellular, biochemical and molecular level to develop a better understanding of pathogenetic mechanisms involved in development of airway diseases. The search committee, Chaired by Dr. Perry Blackshear (Clinical Director), has recommended a candidate and negotiations are in the final stages.

### **Staff Scientist-Veterinary Pathologist**

The Laboratory of Environmental Pathology is seeking a highly motivated Toxicologic Pathologist experienced in rodent toxicology and carcinogenicity studies to work within the National Toxicology Program (NTP). The successful candidate will be involved primarily in the management and oversight of the pathology peer review (evaluation) and interpretation and reporting of the data. Also the candidate will be expected to identify and pursue special projects that will advance the understanding of various biological endpoints. The search committee, chaired by Dr. Gary Boorman (National Toxicology Program), is reviewing applications.

### **Tenure-Track Neuroscientist**

The Division of Intramural Research is recruiting for a tenure-track neuroscientist to conduct independent research that will complement or expand ongoing activities in neuropharmacology, neuroimmunology, signal transduction, synaptic plasticity, reproductive and developmental toxicology and neurotoxicology. The search committee, chaired by Dr. Jean Harry, Acting Chief, Laboratory of Toxicology, has recommended a candidate to the Scientific Director.

### **Staff Scientist-Knockout Core Facility Manager**

The Laboratory of Reproductive and Developmental Toxicology is recruiting a Staff Scientist with expertise in mouse molecular genetics or a related discipline to serve as the Head of the Transgenic Knockout Core Facility. The successful applicant will generate mutant mice using embryonic stem cell technologies, plan and provide scientific oversight in the conduct of targeting vector design, and serve as a resource expert on mouse genetics and embryology. The Scientific Director has selected a candidate and the official offer is pending approval of Dr. Olden.

### **Staff Scientist-NMR Chemist**

The Laboratory of Structural Biology is seeking a chemist to serve as the technical expert for the preparation and structural analysis of isotopically labeled proteins using Nuclear Magnetic

Resonance (NMR) techniques. Experience in multidimensional NMR techniques as well as the design, preparation, isolation, purification and concentration of biological macromolecules is essential. After a national search, Dr. Geoffrey Mueller has been selected. Dr. Mueller received his Ph.D. from the University of Virginia in 1998 and is currently a post-doctoral fellow with Dr. Lewis Kay at the University of Toronto.

### **Tenure-Track Epidemiologist**

A national search is being conducted for a tenure-track investigator who will develop an independent research program in noncancer chronic disease epidemiology, with emphasis on the potential environmental causes of neurological diseases and dysfunctions in humans such as Parkinson's disease, Alzheimer's disease and multiple sclerosis. Individuals with the ability to integrate basic and molecular biology, genetics, toxicology, exposure assessment and epidemiology are sought. The Search Committee, chaired by Dr. Clarice Weinberg (Chief, Biostatistics Branch), has interviewed candidates and has forwarded a recommendation to the Scientific Director.

### **Tenure-track Molecular Toxicologist**

The Laboratory of Computational Biology and Risk Analysis is conducting a national search for a tenure-track researcher to develop an independent research program in molecular toxicology focusing on mechanisms of carcinogenicity and toxicity initiated through ligand-receptor interactions. A search committee, chaired by Dr. Douglas Bell, Laboratory of Computational Biology and Risk Analysis, has been formed and the position should be advertised in the very near future.

### **Chief, Laboratory of Toxicology**

The Environmental Toxicology Program plans to conduct an international search to recruit a senior research toxicologist to serve as Chief of the Laboratory of Toxicology with tenure. Priority will be given to applicants with demonstrated ability to foster effective utilization of molecular technology in the research of the Laboratory, is internationally recognized as an expert in the field of toxicology, and possess a level of managerial and executive ability to create an atmosphere for maximum creativity and scientific productivity. Priority will be given to researchers whose primary interests are in developmental and/or reproductive toxicology with a focus on the molecular basis for environmental causes of disfunction in these areas. A search committee chaired by Dr. John Pritchard, Chief, Laboratory of Pharmacology and Chemistry has been formed.

## **New Appointments in the Division of Intramural Research**

### **Dr. Frederick Miller**

Dr. Frederick Miller was recently recruited to initiate a new NIEHS clinical program at the Warren Grant Magnuson Clinical Center on the Bethesda campus to study genetic and environmental contributions to the pathogenesis of autoimmune diseases. He will serve as the Chief, Environmental Autoimmunity Group in the Office of Clinical Research. The Environmental Autoimmunity Group will conduct a broad program of clinical investigation in the area of adult and pediatric autoimmune diseases. These studies include epidemiologic surveys and clinical investigations in disease pathogenesis, as well as the development of clinical tools for assessment of innovative therapies. Volunteer patients are referred by physicians worldwide and participate in the studies by signed informed consent. This group will also serve as a liaison to others in NIEHS who wish to conduct clinical studies or obtain clinical specimens for research purposes.

Dr. Miller received his M.D. and Ph.D. degrees from the Case Western Reserve University School of Medicine and did post-doctoral clinical training at Emory University, Stanford University and the National Institute of Arthritis, Musculoskeletal and Skin Diseases, NIH. He is board certified in Internal Medicine and Rheumatology. Dr. Miller's research background is in the pathogenesis of human autoimmune diseases, focusing on multidisciplinary studies of the myositis syndromes.

#### *Selected Recent Publications*

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- Miller, F.W., Hess, E.V., Clauw, D.W., Hertzman, P.A., Pincus, T., Silver, R.M, Mayes, M.D., Varga, J., Medsger, T.A. and Love, L.A. (2000). Approaches for identifying and defining environmentally associated rheumatic disorders. *Arthritis Rheum* 43:243-249
- Rider, L.G., Artlett, C.M., Foster, C.B., Ahmed, A., Neeman, T. Chanock, S.J., Jimenez, S.A. and Miller, F.W. (2000). Polymorphisms in the interleukin-1receptor antagonist VNTR are possible risk factors for juvenile idiopathic inflammatory myopathies. *Clin Exp Immunology* 121:47-52.
- Artlett, C.M., Ramos, R., Jimenez, S.A., Patterson, K. Miller, F.W. and Rider, L.G. (2000) Chimeric cells of maternal origin in juvenile idiopathic inflammatory myopathies. *Lancet* 356: 2155-2156.

## **Training and Mentoring**

### **2001 NIEHS/NTA Science and Career Fair**

The Fourth Annual NIEHS/NTA Science and Career Fair was held on May 4, 2001 in the Rodbell Conference Center, NIEHS. The keynote speaker was Mr. David Jensen, Principal Consultant, Search Masters International who gave the presentation "Develop an Industrial Strength Job Search to Find Your Career Destiny." The panel discussion this year focused on "Exploring Career Opportunities in Science." It was moderated by Dr. Thomas Kunkel, Chief, Laboratory of Structural Biology, and Scientific Program Director, Environmental Biology Program, NIEHS. Panel participants included Mr. David Jensen; Dr. Laura Bottomly, Director of Women Engineering and Outreach, North Carolina State University; Dr. Salil Patel, President and Chief Scientific Officer, GeneEd, Inc.; Dr. Catherine Hammett-Stabler, Assistant Professor of Pathology and Laboratory Medicine, University of North Carolina-Chapel Hill; Dr. Ruth Winecker, Chief Toxicologist, Office of the Chief Medical Examiner, University of North Carolina; and Dr. Rueben Warren, Associate Administrator for Urban Affairs, ATSDR. Other events at the Science and Career Fair include two poster sessions, three breakout sessions run by Dr. Chandra Louise, President, Peer Productions, Inc. and Dr. George O'Neill, Career Consultant, American Chemical Society, and a reception. The breakout sessions covered resume preparation/review, interviewing skills, and opportunity and challenges for international trainees in the American workplace. There were approximately 250 attendees from institutions in the Triangle Area as well as from other universities and NIH Institutes. More than 25 companies were represented. The NIEHS, the North Carolina Biotechnology Center, the Chemical Industry Institute of Toxicology, the Burroughs Wellcome Fund, Merck and Co., Inc, and S & M Separation Technologies, Inc. cosponsored this event.



## **Awards and Honors in the Division of Intramural Research May 2001**

- Dr. Mike Cunningham (Environmental Toxicology Program) was named an Associate Editor for *Toxicological Sciences*.
- Dr. James Huff (Office of the Scientific Director) was appointed as Co-Chair of the Committee on Cancer Policy, International Ramazzini Foundation, Carpi, Italy for 2001.
- Dr. Larry Lazarus (Laboratory of Computational Biology and Risk Analysis) was invited to be a Plenary Speaker at the 4<sup>th</sup> Symposium on Frontiers in Protein Chemistry and Biotechnology at the Chengde Medical College, People's Republic of China, August 16-20, 2001.
- Dr. Ron Melnick (Laboratory of Computational Biology and Risk Analysis) was appointed as Co-Chair of the Committee on Cancer Policy, International Ramazzini Foundation, Carpi, Italy for 2001.
- Dr. Elizabeth Murphy (Laboratory of Signal Transduction) was selected as an Inaugural Fellow of the American Heart Association. She was also elected as a member of the International Council of the International Society for Heart Research.
- Ms. Retha Newbold (Laboratory of Toxicology) was invited as one of three key scientific lectures at the DES Action International Colloquium held April 1-2, 2001 in Washington, DC.
- Mr. Tomo Oshimura (Laboratory of Molecular Carcinogenesis) won an award in the Biological Sciences Category at the North Carolina State Senior Project Poster Presentation for his poster "Identification of Estrogen Responsive Genes in MCF7-C7 Breast Tumor Cell Line Using cDNA Microarrays".
- Ms. Kelli Reynolds (Laboratory of Molecular Carcinogenesis) won an award in the Engineering and Technology Category at the NC State Senior Project Poster Presentation with her poster "Automation of Bioinformatics Processes for Microarray Data.
- Dr. Ken Tomer (Laboratory of Structural Biology) presented a plenary lecture entitled Mass Spectrometry in the Characterization of Protein:Protein Interactions at the 34<sup>th</sup> Meeting of the German Society for Mass Spectrometry March 5, 2001 in Munich, Germany.
- Dr. Allen Wilcox (Epidemiology Branch) was elected President of the American Epidemiological Society for 2002-2003. He was invited to present the keynote address at the Annual Meeting of the ISEE (International Society of Environmental Epidemiology), in Garmisch, Germany, September 2001.
- Dr. Sam Wilson (Laboratory of Structural Biology) was Chair of the Mammalian DNA Repair Gordon Research Conference January 21-26, 2001. He was the Keynote Speaker at the Midwest DNA Repair Meeting held June 2 in Indianapolis, Indiana
- Dr. Darryl Zeldin (Laboratory of Pulmonary Pathology) has developed an asthma website which won the Lightspan Academic Excellence Award.

## HIGHLIGHTS FROM THE NATIONAL TOXICOLOGY PROGRAM (NTP) May 2001

- The NTP has received a request from the California Congressional delegation, the California Environmental Protection Agency, and the California Health and Human Services Agency to perform definitive rodent cancer studies on hexavalent chromium in response to concerns raised over contamination of source water supplies. While the toxicity and carcinogenicity of hexavalent chromium compounds have been recognized for some time, adequate long-term oral toxicity studies are largely unavailable and there remain gaps in our collective knowledge regarding any potential health risks. The NTP has accepted this nomination and is in the process of designing studies to address this issue.
- The technologies to allow genome-wide analysis of gene expression are heavily influencing drug discovery and preclinical safety studies in the pharmaceutical companies. Genomic expression analysis also has the potential to revolutionize toxicological evaluation of environmental chemicals. The NTP in collaboration with the NIEHS National Center for Toxicogenomics is exploring ways to incorporate these new technologies into NTP evaluations.

### NTP Board of Scientific Counselors

- The NTP Board of Scientific Counselors meets May 25, 2001 at the NIEHS. The meeting begins at 8:30 AM and is open to the public. The NTP Board of Scientific Counselors is composed of scientists from the public and private sectors and provides scientific oversight to the NTP. Primary agenda topics include:
  - review and discussion of draft guidelines for the NTP Center for the Evaluation of Risks to Human Reproduction's (CERHR) expert panels,
  - the NTP Interagency Committee for Chemical Evaluation and Coordination's (ICCEC) testing recommendations for substances nominated for future NTP studies, and
  - presentations about chemical disposition and toxicokinetic studies of substances by the NTP and use of this data in pharmacokinetic modeling.

There will also be updates on activities of the Board's Report on Carcinogens and Technical Reports Review Subcommittees. The Board will review a concept proposal for the continued use of a contract mechanism to investigate the mechanisms of toxicity, absorption, tissue distribution, metabolism, and clearance of substances under study by the NTP.

### NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

- The 9<sup>th</sup> Edition of the Report on Carcinogens (RoC) was published in May 2000. An addendum to the 9<sup>th</sup> Report was issued in January 2001 to change the listing of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (also known as "dioxin" or "TCDD") to a *known to be a human carcinogen* from *reasonably anticipated to be a human carcinogen*. Publication of the addendum followed the ruling by the US Court of Appeals for the District of Columbia Circuit denying the request for an injunction to prevent the listing of TCDD as a *known human carcinogen* in the 9<sup>th</sup> Report pending appeal of the district court's decision upholding the listing.

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

- NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) collaborate to develop, validate, and achieve regulatory acceptance of new and improved test methods. In 2001, ICCVAM/NICEATM expect to publish several reports from previous meetings that they sponsored.
  - the May 2000 Expert Panel Meeting evaluating the Frog Embryo Teratogenesis Assay—*Xenopus* (FETAX)
  - the July 2000 Peer Review Meeting on the Up-and-Down Procedure (UDP) for Acute Oral Toxicity
  - the October 2000 International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity
  - the Guidance Document on using *in vitro* data to estimate *in vivo* starting doses for acute toxicity, a report which resulted from the *In Vitro* Methods Workshop

## **NTP Workshops and Conferences**

- The NTP is a co-sponsor for the 23<sup>rd</sup> Annual Meeting of the Bioelectromagnetics Society (BEMS) being held June 10-14, 2001 in St. Paul, Minnesota. The NTP receives input on electromagnetic field issues relative to power lines and radio-frequencies from experts in this society.
- The *ICLAS-CCAC International Symposium on Regulatory Testing and Animal Welfare* is being held June 21-23, 2001 in Quebec City, Canada. The International Council for Laboratory Animal Science (ICLAS) fosters international harmonization of animal care and use practices. The Canadian Council of Animal Care (CCAC) has responsibility for overseeing the ethical use of animals in Canadian science. The NTP is a co-sponsor for this workshop and Dr. William Stokes, Director, NTP Center for the Evaluation of Alternative Toxicological Methods, is a member of the Steering Committee.
- The NTP, along with the EPA, FDA and the Office of Rare Diseases/NIH, is sponsoring a workshop, *Assessment of the Allergenic Potential of Genetically Modified Foods*, to be held September 24-26, 2001 at the Durham Marriott at the Civic Center in Durham, NC. This meeting will bring together experts in food allergy, genetically modified crops, and the regulatory aspects of these products along with bench scientists and clinicians. Topics to be covered include the current state of knowledge in this area, identification of critical issues regarding these materials, and the development of testing strategies for examining their potential toxicities. Dr. Dori Germolec, Laboratory of Toxicology, is the primary contact for this meeting.
- Since January 1, 2001 the National Center for Toxicogenomics (NCT) has conducted two workshops: *Functional Proteomics in Environmental Health Science* at the Arizona Cancer Center in Tucson, AZ and *Bioinformatics Strategies for Application of Genomic Tools to Environmental Health Research* at NC State University in Raleigh, NC. Summaries of these workshops can be found via the NCT web site [www.niehs.nih.gov/nct/workshop.htm](http://www.niehs.nih.gov/nct/workshop.htm).

## **An Approach to Study Women's Health and the Environment**

### **Abstract: Dr. Barbara J. Davis**

To understand the complexities of environmentally mediated diseases in women, research at the NIEHS and within the Laboratory of Women's Health is conducted with a highly interdisciplinary approach. We view health and disease of a woman as a function of the interaction between her individual genetics and environment within the context of her changing hormonal and physiological milieu. The ultimate goal is to reduce the burden of environmentally related diseases by discovering how diseases such as breast cancer, ovarian cancer, uterine leiomyoma, and reproductive dysfunctions develop and how these are influenced by environmental factors.

Our studies of uterine leiomyoma (fibroids) illustrate the integrative use of epidemiology, pathology, animal models, cell-based mechanistic studies, and clinical studies to advance our understanding of disease. Uterine leiomyomas are a major public health problem and are the most common reproductive tumor in women. Symptomatic fibroids are the leading cause of hysterectomy and the primary cause of emergency hospital visits for women in the US. Dr. Donna Baird at the NIEHS recently completed a cross-sectional epidemiological study of uterine leiomyomas in women 35-49, randomly selected from membership in a prepaid health plan in Washington, DC. The prevalence of ultrasound-detected fibroids identified from 1083 women was surprisingly high, especially in the African American participants: 72% for African American and 50% for Caucasian women. Health disparity issues for uterine fibroids are reflected in the high prevalence statistics and in the fact that African American women have larger and more numerous tumors. African American women are also more likely to have surgical intervention--myomectomy and hysterectomy--compared to Caucasian or Hispanic women.

The environmental components of this disease, such as exposures to estrogens, phthalates, and solvents are currently under study using exposure assessment methods in women with fibroids coupled with mechanistic studies in cell culture systems and animal models. One hypothesis derived from mechanistic studies is that uterine smooth muscle tumor cells closely resemble normal uterine smooth muscle cells during pregnancy but have escaped controls that cause these cells to regress or die. Specifically, the pregnancy-like phenotype allows these cells to proliferate in response to estrogens, estrogen-like compounds, and other environmental cues. However, the neoplastic cells fail to regress or die as do normal smooth muscle cells at the time of parturition (delivery) when

supraphysiological levels of prostaglandins, oxytocin, and other parturition-related hormones trigger the contractile response of the uterus during labor and remodeling of the uterus after delivery. Studies conducted in collaboration with Dr. Cheryl Walker, who has developed the Eker rat as an animal model for uterine leiomyoma, support the research hypothesis. For example, treatment of young rats with estrogenic compounds like DES accelerate the growth of the leiomyoma, while tumor incidence in aged rats is significantly reduced with multiple pregnancies and deliveries. Armed with the knowledge of the dramatic effect of parturition in the rat, Dr. Baird has further investigated pregnancy and parturition as risk factors for fibroids in her epidemiological study and found that full-term pregnancies culminating in parturition significantly decrease the risk for large leiomyomas in women.

We also know that fibroids are heterogeneous. Women typically have multiple tumors that may or may not cause similar problems or grow at similar rates. Indeed, individual leiomyomas may undergo episodes of rapid growth and can become large and clinically symptomatic in a short time period. Fast growing, large leiomyomas are the most problematic. However, the physiological and pathological causes of growth are currently unknown. With co-sponsorship from the Center for Research on Minority and Health and Health Disparities, we have initiated the Fibroid Growth Study to address this knowledge gap. This study will determine the molecular bases of why uterine leiomyomas are heterogeneous in terms of their growth characteristics and in their clinical symptoms or outcomes. The specific aims are to: (1) compare leiomyoma growth as a function of multiplicity and location by magnetic resonance image (MRI) analysis in women with high risk for surgical intervention (i.e., hysterectomy/ myomectomy); (2) examine the relationship between leiomyoma growth and clinical symptoms or outcome; (3) identify molecular, cellular, and pathological characteristics of the leiomyomas with differing growth dynamics; and (4) examine endocrinological parameters and environmental factors related to differential growth dynamics of uterine leiomyomas. Women will be enrolled in this study by our collaborating clinical investigators at University of North Carolina and Duke Medical Center. Upon completion of data collection, we will have detailed the heterogeneity of leiomyoma growth, location and molecular characteristics of these common tumors.

This thorough understanding of the molecular, cellular and hormonal characteristics of uterine leiomyomas will serve as the foundation for further investigations of the environmental components that initiate and promote tumor growth, that trigger development of the pregnancy-like phenotype, and/or that inhibit the apoptosis or dedifferentiation responses of these neoplastic cells. With the tools for exploration, discovery and translation of research findings in place, we are also poised to use the discoveries about the causes of fibroid growth to test potential therapies in cell culture studies and in preclinical studies in animal models. Because fibroids are hormonally responsive tumors, understanding the growth patterns in fibroids will also help us understand other hormonally mediated cancers in women such as breast cancer.

As the laboratory goal is to reduce the burden of environmentally related diseases in women, we also emphasize exploration of populations that may be particularly susceptible to environmentally mediated disease because of their genetics, their exposures, or both.

With respect to exposures, women now represent a major component of the workforce in all occupations and their exposures and exposure outcomes are only

beginning to be identified. Women in certain occupations are exposed to low levels of chemicals that contain mixtures of reproductive toxicants and carcinogens. Many of these women have reproductive problems and, as anecdotal reports suggest, also have increased occurrences of reproductive tract tumors including uterine leiomyomas, endometrial cancers, breast cancers and ovarian cancers. The underlying mechanisms by which these exposures contribute to reproductive dysfunction or to cancers are not yet known. Investigation into these problems would advance public health and the scientific understanding of how chemical mixtures interact and contribute to disease. Another preeminent concern is advanced onset of sexual development or puberty influenced by environmental exposures. Two recent studies implicate high exposures to polybrominated biphenyl compounds and phthalates as potential mediators of precocious development. Early onset of menarche is a consistent risk factor for the development of breast and uterine cancers. Thus, the health of these women may be especially complicated both by their environmental exposures contributing to early development and by the potential for increased cancer risks later in their life. Laboratory-based studies are in place to examine the mechanisms by which environmental exposures could contribute to precocious puberty. Research should also be focused on implementing intervention and prevention care. These research efforts are consistent with our mission to reduce the burden of environmentally mediated disease through an integrative, interactive and interdisciplinary research approach combined with a focus on translating discovery into intervention.

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#### *Clinical Studies - NIEHS Initiatives*

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- [McBride, G. 1999 Benign but no longer forgotten - fibroids get their own conference. \*Lancet\* 354:1450.](#)
- Uterine Leiomyoma Longitudinal Intervention Strategy: Fibroid Growth Study Progress Report, included in package.

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**Management of Uterine Fibroids:  
Results of a Systematic Review  
Abstract: Dr. Evan R. Myers**

Uterine leiomyomata, or fibroids, are benign tumors of the smooth muscle and extracellular connective tissue of the uterus. Although some fibroids are asymptomatic, they can also cause symptoms of heavy bleeding and pain, and may either cause difficulty in achieving pregnancy, or cause complications of pregnancy. They affect up to a third of all women of reproductive age, and are the single most common indication for hysterectomy.

The Center for Clinical Health Policy Research at Duke University is one of 12 Evidence-based Practice Centers (EPCs) funded by the Agency for Healthcare Research and Quality (AHRQ), a branch of the U.S. Public Health Service. The EPCs perform systematic reviews of topics suggested to AHRQ by various organizations, such as professional societies, patient advocacy groups, health maintenance organizations, or other federal agencies. The topic of management of fibroids was suggested to AHRQ by the American College of Obstetricians and Gynecologists (ACOG). The primary focus of each report is a systematic review of the literature, focused on questions provided to the EPC by AHRQ and the interested organization. Supplemental analyses, such as meta-analysis, decision analysis, or cost-effectiveness analysis, may also be performed. Each report utilizes an interdisciplinary team with expertise in both methodology and the specific topic being reviewed.

Over 1000 articles published in English between 1975 and 2000 were identified through a systematic search of the literature. Of these, only 200 met criteria for more detailed review. The majority of the literature had serious limitations. Notably, there is a major lack of randomized trials for all but a very few treatments. Most of the nonrandomized studies, especially those of invasive treatments, did not provide details on basic patient characteristics or provide details on long-term outcomes.

The report addressed 9 specific questions. Findings for each question are summarized below.

**Question 1:** What are the risks and benefits of hysterectomy and myomectomy (surgery which removes only the fibroids but leaves the uterus intact) in the treatment of symptomatic and asymptomatic fibroids?

There is limited data on the long-term benefits of myomectomy on symptom

relief. Two-year follow-up of several cohorts suggests that long-term outcomes for women undergoing hysterectomy are favorable. Differences in short-term outcomes such as in-hospital complications may reflect differences in fibroid and uterine anatomy rather than differences in the procedures themselves. There is no literature to support a benefit to either hysterectomy or myomectomy in women with asymptomatic fibroids.

**Question 2:** What are the risks of myomectomy in women with a single fibroid compared to women with multiple fibroids? Short-term complication rates appear to increase as the number of fibroids increase based on case-series. Women with only a single fibroid detectable and removed appear to have a lower risk of recurrence and need for subsequent therapy, based on case-series. This may represent underlying differences in biology rather than surgical efficacy.

**Question 3:** Who are appropriate candidates for each available procedure or treatment available for fibroids? Hysterectomy is inappropriate for women wishing to retain fertility. We were unable to reach any other conclusions based on the available literature.

**Question 4:** How often do women undergoing conservative therapy require additional treatment? Data are severely limited for most treatments. For women undergoing myomectomy, reported need for subsequent conservative surgery ranges from 3-76%, with 2-12% receiving hysterectomy.

**Question 5:** Does subsequent treatment after conservative therapy result in increased morbidity compared to immediate definitive therapy? We found no evidence which could be used to address this question.

**Question 6:** What are the risks and benefits of non-surgical treatment of uterine fibroids? The only treatment for which randomized trial data exists is the use of gonadotropin-releasing hormone agonists as preoperative therapy. These agents result in reduced blood loss during surgery and may allow alternative surgical approaches with less perioperative morbidity. The long-term clinical significance of these effects is unclear.

**Question 7:** What are the costs associated with effective surgical and nonsurgical treatments? Data on the outpatient costs, or the nonmedical costs (time lost from work, etc) associated with symptomatic fibroids were not available. Analysis of the Nationwide Inpatient Sample, a dataset maintained by AHRQ, resulted in an estimated hospital cost of over \$2 billion annually for treatment of fibroids. Cesarean section, performed on twice as many women, and coronary artery bypass surgery, which costs 6 times more, are the only surgical procedures performed in women which result in more costs.

**Question 8:** Do risks and benefits differ for women of different race, ethnicity, age, or interest in future child-bearing? Black women are more likely to undergo myomectomy or hysterectomy than white women, at younger ages; at the time of surgery, they appear to have larger and more numerous fibroids, and are more anemic. These differences explain the observation that black women are more likely to experience complications of surgical management of fibroids. Conservative treatments such as myomectomy, gonadotropin-releasing hormone agonists, and uterine artery embolization may be more effective in perimenopausal women. Data on the effect of fibroids on fertility and pregnancy outcomes are inconsistent; reported associations between fibroids and infertility and adverse pregnancy outcomes may be the result of flaws in study design or interpretation rather than true causation.

**Question 9:** What are the effects of treatments for fibroids, especially hysterectomy, on the aging process? Data are inconclusive.

Given that fibroids affect a third of women in their reproductive years, show significant variation in incidence and outcome among racial groups, and result in considerable costs to society, it is surprising and disappointing that our knowledge about the most appropriate and effective therapies is so limited. Additional research into the natural history, biology, epidemiology, and treatment of fibroids is urgently needed.