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 19-20, 2011

The National Advisory Environmental Health Sciences Council convened its one hundred thirty-third regular meeting on May 19, 2011 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. Dr. Linda Birnbaum presided as Chair.

The meeting was open to the public on May 19, 2011 from 8:30 a.m. to 4:30 p.m. and on May 20, 2011 from 8:30 a.m. to 9:45 a.m. In accordance with the provisions set forth in Section 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), the meeting was closed to the public on May 20, 2011 from 10:00 a.m. to 12:00 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register.*

Council Members Present

Stephen Baylin, MD
Chris Bradfield, PhD
Julia Brody, PhD
Marie-Francoise Chesselet, MD, PhD
Steve Dearwent, PhD
Robert Dyer, PhD
Richard Finnell, PhD
Thomas Gasiewicz, PhD
Mary M. Lee, MD
Grace LeMasters, PhD
R. Stephen Lloyd, PhD
Yvonne Maddox, PhD
Sem Phan, MD, PhD
Jerald Schnoor, PhD
Nsedu Obot Witherspoon, MPH

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD
John Balbus, MD, MPH
Eddy Ball, PhD
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
John Bucher, PhD

Janet Cakir
Pamela Clark
Jennifer Collins
Gwen Collman, PhD
Helena Davis
Caroline Dilworth, PhD
Christina Drew, PhD
Dorothy Duke
Sally Eckert-Tilotta, PhD
Lisa Edwards
Don Ellis
Yolanda Eskridge-Nyass
Christine Flowers
Mary Gant
Barbara Gittleman
Astrid Haugen
Michael Humble, PhD
Laurie Johnson
Paul Jung, MD, MPH
Ed Kang
Annette Kirshner, PhD
Cindy Lawler, PhD
Chris Long
Robin Mackar
J. Patrick Mastin, PhD
Elizabeth Maull, PhD
Kimberly McAllister, PhD
Rose Anne McGee
Liz McNair
Aubrey Miller, MD MPH
David Miller, PhD
Sri Nadadur, PhD
Teresa Nesbitt, DVM, PhD
Sheila Newton, PhD
Liam O'Fallon
Michelle Owens
Joan Packenham, PhD
Linh Pham, PhD
Jerry Phelps
Scott Redman
Leslie Reinlib, PhD
Margarita Roque
Ramendra Saha, PhD
John Schelp
William Schrader, PhD
Daniel Shaughnessy, PhD
Carol Shreffler, PhD
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD
Claudia Thompson, PhD
Frederick Tyson, PhD

Craig Wladyka
Mary Wolfe, PhD
Rick Woychik, PhD
Darryl Zeldin, MD

Members of the Public Present

Ernie Hood, Scribe
Betty Mekdeci, Public Interest Partners
Pamela Schwingl, PhD, Social and Scientific Systems, Inc.
Branka Sekis, SSS Social and Scientific Systems, Inc.
Deborah Wales, EPA

I. Call To Order and Opening Remarks

Dr. Linda Birnbaum, Director of NIEHS and NTP, welcomed attendees and called the meeting to order. She noted absent Council members Dr. Kim Boekelheide, Dr. Palmer Taylor, Ms. Elizabeth Yeampierre, Ms. Andrea Hricko and Dr. Thomas McKone. She welcomed new Council *ex officio* member Dr. Yvonne Maddox. She noted that public member Dr. Robert Pestronk had declined service to Council at this time. She then asked all present in the room to introduce themselves, which they did.

II. Review of Confidentiality and Conflict of Interest

Dr. Collman reviewed the Conflict of Interest and Confidentiality procedures, which had been provided earlier to Council members in written form, and went over various other administrative matters.

III. Consideration of February 2011 Meeting Minutes

Approval of the February 2011 minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Collman also noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Dr. Birnbaum welcomed the *ex officio* Council members from sister agencies, present at the meeting, and thanked them for their service.

She updated Council on staff changes: Joellen Austen has been selected as Associate Director for Management, Dr. J. Patrick Mastin is now the permanent Deputy Director of the Division of Extramural Research and Training (DERT), Dr. Claudia Thompson is now the permanent Chief of the DERT Susceptibility and Population Health Branch, and Dr. Anton Jetton is now the permanent Chief of the NIEHS Laboratory of Respiratory Biology. The announcement for Scientific Director closed on March 31, and interviews will be held in late June/early July. The hope is for at least a tentative candidate by September. The search for a Clinical Director is open, with the announcement being open until June 13.

Dr. Birnbaum noted the passing of Dr. James Fouts, a pioneering environmental health scientist and former NIEHS Scientific Director.

Dr. Birnbaum noted that the institute now has a working budget in the form of a year-long continuing resolution, which will last until September 30th. There has been a 1% cut in the NIH budget, which, in actuality is closer to a 3-4% decrease due to inflation. She said that although the President's request was for a 3% increase in the NIH budget for FY 2012, it is unrealistic to expect that to happen, and that a flat budget is likely the best to be hoped for. She pointed out that the Superfund was only cut 0.2%.

She updated Council on legislative developments. In April, she participated in a Congressional staff briefing held by Friends of NIEHS, attended by approximately 50 staffers. Asthma, breast cancer, and autism were among the topics discussed. Another briefing on developments related to the Gulf oil spill was to be held the week of May 23. Congress is currently considering a 3-year reauthorization of the Small Business Innovative Research/Small Business Technology Transfer (SBIR/STTR) programs. Also under consideration are the Lung Cancer Mortality Reduction Act of 2011, the Gulf Coast Health Monitoring and Research Program Act of 2011, and the Radiation Exposure Compensation Act, all of which are unlikely to pass this year. Each involves potential unfunded authorizations. There has been a proposal to reinstate the Superfund Tax, which is also unlikely to pass.

Recounting recent scientific advances, Dr. Birnbaum mentioned a publication in *Environmental Health Perspectives* by Dr. Steven Kleeberger from NIEHS, Dr. David Peden from UNC and colleagues describing the key role of IL-10 in protection against ozone-induced pulmonary inflammation. That research has implications for development of therapeutic interventions. She noted an investigation led by Dr. Doug Bell of the NIEHS Intramural program, which showed that human SNPs modulate cellular stress response. Grantee Dr. Rebecca Rugo from MIT and colleagues published a paper describing the mechanism of cell memory of genotoxic insult, describing an epigenetic effect. Grantee Dr. Isaac Wirgin from NYU and colleagues published a study describing the mechanistic basis of resistance to PCBs in Atlantic tomcod from the Hudson River, illustrating rapid evolution in the face of an environmental stressor. Two NTP groups had significant publications as well. Frawley *et al* (including Dr. Dori Germolec) reported on gene expression alterations in immune system pathways in the thymus after exposure to immunosuppressive chemicals, and Tokar *et al* (including Dr. Michael Waalkes) described the interplay of arsenic and stem cells in the developmental basis of adult cancer.

Turning to institute highlights, Dr. Birnbaum updated Council on ongoing Gulf oil spill works. The GuLF STUDY is currently in the field, recruiting subjects from all Gulf Coast states. Dr. Birnbaum conducted community forums in New Orleans and the nearby bayou country February 23 and 24. Chip Hughes, head of the NIEHS Worker Education and Training Program (WETP), and his staff recently held a two-day workshop in Mobile, Alabama to discuss lessons learned in worker training from the Gulf oil spill experience.

There has been an effort in recent months to bring sister institute directors to NIEHS. Visits have included Dr. Thomas Insel of the National Institute of Mental Health, who spoke at NIEHS on March 1, and Dr. Eric Green, Director of the National Human Genome Research Institute, who visited NIEHS April 11.

After eighteen months of effort, the NTP is now officially its own division within NIEHS. The Secretary of HHS has signed the reorganization, and it appeared in the Federal Register on April 28. Dr. John Bucher is now Director of the Division of the National Toxicology Program (DNTP) and remains Associate Director of the larger NTP, which is still associated with NIOSH and FDA.

In other NTP news, the Tox21 high-speed robot screening system was unveiled March 10 at the NIH Chemical Genomics Center. The Comparative Toxicogenomics Database (CTD) has now become part of ToxNet. In late March, NICEATM (the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods) held a peer review panel on *in vitro* assays for endocrine-disrupting chemicals, and the Republic of Korea signed on to the International Cooperation on Alternative Test Methods agreement. Also in March, scientists from NTP and the extramural program were involved with an effort promoting green chemistry in environmental health sciences, looking to design endocrine-disrupting chemicals out of consumer products.

In outreach developments, *Environmental Health Perspectives* is expanding the reach of its Science Education Program with the launch of a new website and redesigned lessons, and has also launched an iPhone app that gives readers of the journal access to research and news as soon as it is published on line.

Important recent meetings and events for the Institute have included a March 29 Spirit Lecture by Dr. Nancy Andrews, dean of the Duke University School of Medicine, substantial NIEHS/NTP involvement with the 50th anniversary annual meeting of the Society of Toxicology in Washington, DC (more than 75 poster presentations and 30 scientific talks, among other activities), the final GEI Exposure Biology Program grantee meeting at NIEHS on April 14, and the April 27-28 conference held at NIEHS by the NRC Committee on Emerging Science for Environmental Health Decisions, "Interplay of the Microbiome, Environmental Stressors, and Human Health."

New AAAS Fellows include Dr. James Mason of NIEHS, grantees Dr. Marie-France Chesselet, Dr. Barbara Turpin, and Dr. Agnes Kane. A recent paper by Dr. Ken Korach of NIEHS earned a Faculty of 1000 award, and a paper by Superfund Research Program grantee Dr. Barry Dellinger earned Editor's Choice recognition as one of *ES&T*'s Best Papers of 2010. In other recognitions, half of the ten 2011 Science Communications Fellows announced by Environmental Health Sciences were from NIEHS.

Dr. Birnbaum delivered the opening lecture at the recent Pew Workshop entitled "Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food Are Safe." She showed Council members a copy of the latest issue of the prestigious policy-oriented journal, *Health Affairs*, which this month for the first time is entirely devoted to articles regarding environmental health. The edition includes a lead article co-authored by

Dr. Birnbaum and Chief of Staff Paul Jung, as well as articles by former NIEHS Director Dr. Kenneth Olden, and several NIEHS grantees.

Dr. Birnbaum shared news about the NIH Director's Awards, which had just been awarded. NIEHS won two science awards; one for the Deep Water Horizon/Gulf oil spill effort, and another for the initiators of the GuLF STUDY. The Patient-Reported Outcomes Measurement Information System (PROMIS) Working Group, with NIEHS represented by DERT program analyst Martha Barnes, also won a Director's Award. The awards ceremony will take place August 2.

Updating NIH developments, Dr. Birnbaum noted new Common Fund Awards in Global Health devoted to training health care researchers and physicians in Africa. She also mentioned an important discrepancy in grant title field lengths between Grants.gov and IMPAC II. Also, NIH is updating its reporting on its Government Performance and Results Act (GPRA) products.

Dr. Birnbaum updated Council briefly on the NIEHS Strategic Planning Process, noting that invitations had gone out to the 200 people invited to the July workshop. She asked Council members to be sure to visit the website (www.niehs.nih.gov/strategicplan) and input their ideas.

V. Strategic Plan Process

NIEHS Deputy Director Dr. Richard Woychik updated Council on the status of the institute's Strategic Planning Process, which he leads. He reminded the Council members that the process is slated to take a total of 15 months, and that at the May 2012 Council meeting, they should be presented with new mission and vision statements, as well as strategic goals and implementation strategies. He said it will be an 8-10 page document succinctly describing the institute's direction over the next five years. It is a three-phase process, currently in Phase One, gathering broad-based stakeholder input, including the Visionary Ideas that have been solicited on the web, and the Stakeholder Community Workshop planned for July. Phase Two, beginning at the end of July, will involve initially drafting the mission, vision and strategic goals statements, which will then be posted on the web for comment. During Phase Three, commencing in November, implementation strategies will be developed, and a draft of the plan will be posted on the web for comment.

The first portion of Phase One, gathering web-based input, has just been completed. Dr. Woychik reported that it was "wildly successful." The site received 231 Visionary Ideas, 491 comments, and had 2,983 registered users who cast more than 10,000 votes. The ideas received were organized into 11 categories, and are available at www.niehs.gov/strategicplan.

He said that plans are well underway for the July 12-14 Stakeholder Community Workshop, which will be designed to access input from the broad-based environmental health sciences community. Two hundred individuals representing a broad-based cross-section of the community will be selected to be invited. Open Space technology will be

used during the meeting, which requires an experienced facilitator. Dr. Woychik described the search process used to identify a facilitator, and announced that an excellent facilitator has been selected. A multi-step process was used to create the invitation list, starting with the nearly 600 nominations received on the web site. A team was put together at NIEHS to be sorted into representative categories, including scientists and non-scientists, with junior, mid-career and senior investigators and professionals. The target categories for the 200 invitations were 100 scientists, 25 public health, policy or regulatory experts, 50 people involved with research management, 5 communications experts, and 20 "other" NIEHS staff and non-scientific leadership. After consideration of all of the nominations, initial invitations were emailed May 9, and 133 acceptances had been received. The final list of participants is expected to be compiled by the end of May.

Dr. Woychik concluded by thanking his team for their hard and highly efficient work on the various aspects of the process.

Dr. LeMasters asked Dr. Woychik to explain the Open Space technology a bit more. He said that Open Space is a powerful way to get large groups together, as a self-assembling technology. Visionary ideas are shared and posted on a wall. Then the participants engage in breakout discussions, selecting which group to attend on their own. A person who is passionate about the given idea will lead individual discussions, with another attendee designated to take notes. At the end of that process, there are report-back sessions, with the key points from the notes shared with the broader-based group. There will ultimately be brief written summaries of the discussions, which will be made available to the participants and posted on the web.

Dr. LeMasters explained that she was wondering how the web-based comments would be integrated into the meeting, or whether they were two separate entities. Dr. Woychik confirmed that the thinking is that the two are separate.

Dr. Gasiewicz asked whether there would be international representatives, given the involvement of NIEHS in global issues. Dr. Woychik replied that global connections and collaborations were certainly a consideration during the selection process. Dr. Birnbaum added that budgetary concerns were an issue limiting the possibility of inviting a great many international participants.

Betty Mekdeci of Public Interest Partners asked whether all of the submitted Visionary Ideas would be part of the stakeholder meeting. Dr. Woychik clarified the fact that the Stakeholder Workshop is being looked at as being a complementary means of bringing in ideas, in addition to the electronic forum. Ideas from both sources will be considered in Phase II of the process, he said.

Dr. Lee asked whether there would be pre-identified champions for various ideas at the stakeholder meeting, which would help define how the group would be broken up. Dr. Woychik replied that there would be no preconceived notions of who was doing what, and that the definitions of the breakout groups would be identified at the meeting itself by the participants as part of the Open Space process. He said that the meeting begins with everyone gathered in concentric circles. Leadership introduces the proceedings and then

steps aside, and the group poses visionary ideas for about two hours, eventually forming the foci of the breakout sessions. He said that the expectation is that about 50 Visionary Ideas would emerge, which number could be accommodated in the subsequent breakout groups.

VI. The NIEHS Human Research Protection Program

Dr. Joan Packenham, Director of the NIEHS Office of Human Research Compliance (OHRC), briefed Council on the OHRC and the Human Research Protection Program (HRPP).

She began by providing a historical perspective of the programs. In 2006 and 2007, in anticipation of the building and opening of the NIEHS Clinical Research Unit, the Institutional Review Board (IRB) at the time was evaluated and a plan was formulated to ensure that the resources would be in place to handle the anticipated increased workload the IRB would be facing. The process included a "friendly" audit by the NIH Office of Human Subjects Research Protections (OHSRP), a professional outside audit, meetings with various officials and observation of other IRBs, both within and outside NIH. Also, a contractor was hired to perform a gap analysis regarding IRB processes. The evaluation showed that the single IRB was inadequate, and that the NIEHS would need entities working on regulatory compliance, human research protection, and clinical research support. The plan was made to institute an integrated, multi-component approach, to yield the best possible human research protection and the best possible clinical research and investigator support. In 2008, the OHRC was established to implement and administer the new processes and components, and to establish and maintain a culture of protecting human research subjects. It works under the Clinical Research Program, with the appropriate level of staff, space, and contract support to carry out its mission. Its goals are to:

- Improve the systems that protect participants in clinical research
- Provide professional advice for all who conduct clinical research at NIEHS
- Ensure compliance with federal, state and local laws and regulations
- Improve the quality of research
- Improve risk management
- Improve education and training for all involved in clinical research
- Work collaboratively with clinical investigators and study staff
- Improve consistency and efficiency of review processes
- Serve as liaison with the NIH OHSRP, the DHHS OHRP, and the FDA
- Prepare and guide NIEHS through accreditation
- Increase communication to the public in an effort to build public trust

Dr. Packenham pointed out that although there are several entities involved in the process, ultimately a study's principle investigator is legally responsible for human subjects protection. She noted that NIEHS has three components with different responsibilities to support clinical research and protect human subjects: the OHRC, the IRB, and the Protocol Service Center (PSC). The PSC assists investigators with the

preparation of their study protocols. The IRB reviews research involving human subjects. The OHRC provides leadership, oversight and management of the NIEHS HRPP.

The OHRC provides guidance during protocol development and pre-IRB management, in a process involving several steps that ultimately lead to a protocol being ready for IRB review. The process includes concept review by the Clinical Advisory Committee, clinical resource review, and scientific and statistical reviews. Once a protocol has been approved through OHRC, it is ready to be submitted to the IRB.

Dr. Packenham reported that NIEHS currently has 61 active protocols, 52 of which were reviewed by the NIEHS IRB, and 9 of which were reviewed by other NIH IC IRBs. The IRB currently has 16 active members, 11 of whom are NIEHS personnel.

She described the rigorous education and training program for all personnel involved in clinical research, including mandatory NIH investigator and study staff training, as well as mandatory IRB member training. OHRC also presents a wide variety of educational and training opportunities on an ongoing basis, including outreach activities.

The OHRC quality assurance and quality improvement program is also rigorous, and has been a model for NIH. There is continuous monitoring of clinical research, including due diligence auditing, routine quality assurance reviews, and for-cause auditing. For ongoing quality improvement, OHRC conducts an annual survey of investigators, offers continuous education and training, employs a best practices tool for corrective and preventive action, and checks on PI responses to audits and reviews. The office has also developed a web-based Sharepoint site to provide a source for information for all involved in clinical research at NIEHS, as well as a customized Protocol Tracking and Management System (PTMS) to support protocol submission, approval, and monitoring of the protocol review process.

Dr. Packenham summarized the important accomplishments of the OHRC:

- Development of the NIEHS HRPP
- Implementation of the PTMS
- Implementation of an Electronic IRB
- Digitization of all IRB protocol study files and administrative files
- Decrease in average time from IRB submission to IRB approval from 5.8 months (2004-2007) to 1.7 months (present)
- Developed and implemented a rigorous QA/QI program
- Established collaborative relationships with PIs and Clinical Research staff
- Model compliance program for NIH

The OHRP is currently seeking accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP), which is the gold standard for such programs. The AAHRPP promotes high-quality research through an accreditation process that helps organizations strengthen their human research protection program. The accreditation is important to NIEHS and NIH because many institutions around the country are now AAHRPP-accredited and will not collaborate with institutions lacking that

accreditation. The effort to be accredited is NIH-wide, with the process having begun in 2008. A site visit to NIEHS will take place in 2011, and the NIH application for accreditation should be submitted this year as well. The hope is that full AAHRPP accreditation will be awarded in 2012, or certainly by 2013.

Dr. Packenham reported that NIEHS will be hosting an important meeting March 21-22, 2012 at the Raleigh Convention Center, "Ethical Considerations Surrounding Community-Engaged Research."

Dr. Brody asked whether the program described by Dr. Packenham applied strictly to the NIEHS clinical research program, or is broader. Dr. Packenham replied that it is in fact broader, as it works with some epidemiological and basic science clinical studies that are not under the clinical research program. Dr. Brody asked Dr. Packenham to elaborate on how community interests are represented. Dr. Packenham said that several of the epidemiology studies are community-based, and that the IRB has two lay community members. Dr. Brody said that there are many community-based organizations around the country conducting clinical research and facing difficulties accessing the appropriate IRB services, and wondered if NIEHS might be able to provide resources to help solve that problem. Dr. Packenham said that budget issues would make that difficult, but that it would be a good topic for the 2012 conference.

Dr. Chesselet noted the "remarkable" decrease in IRB approval time, but wondered how long the protocol development process takes. Dr. Packenham replied that the protocol timeline depends on the nature of the individual study.

Dr. Lloyd wondered where AAHRPP authority to provide accreditation comes from. Dr. Packenham replied that AAHRPP is an accrediting body similar to others in the field, and has captured that authority by accrediting hospitals and universities around the country.

VII. Report of the Director, DERT

DERT Director Dr. Gwen Collman updated Council on DERT developments and activities, beginning with staff changes. In addition to those already mentioned by Dr Birnbaum, she recognized the hiring of Ms. Yolanda Eskridge-Nyass and Ms. Kindra Morrison, and a DERT internship by Dr. Linh Pham, a DIR post-doctoral fellow.

DERT is working to meet the budget challenges posed by the FY 2011 Continuing Resolution (CR). Dr. Collman reported that competing R01 grants have been cut between 10% and 20%, depending on direct costs—the same policy as was used in FY 2010. Changes have occurred in the non-competing grants category. For modular grants (<$250,000 direct costs), there will be a 1% reduction in FY 2011, with no increases allowed for the years FY 2012 and beyond. For the non-modular grants (>$250,000), FY 2011 will see a 1% reduction and 3% inflation cuts, or a total of 4% cut. For FY 2012 and beyond, 2% increases for recurring costs will be allowed.

Dr. Collman summarized the trends in extramural research supported by NIEHS. She pointed out to the Council the existence of the publicly searchable "Who We Fund" database page on the NIEHS website. She illustrated how DERT codes science projects

by showing the "By Topic" page on the Who We Fund site. The codes are organized mainly by disease, with some topics such as Centers coded individually. This generates a one-dimensional look at the portfolio, which actually helps to understand its range. The codes focus on biological pathways and disease, with none currently assigned to public health or exposure. There are 100 codes available, of which 85 are currently in use. Each grant is also given a code for its (current) Strategic Plan topic, which is used primarily for Congressional justification.

Dr. Collman shared a series of bar graphs with the Council, which illustrated NIEHS investments over the 2006-2010 period in various key areas, which allows analysis of funding trends. In basic research, investments have increased significantly in the individual areas of nanotechnology, DNA repair, epigenetics, and genetic regulation/gene expression. Investment in signal transduction studies has decreased slightly over the five-year period. NIEHS investment in organ systems research covers a wide range of biology, toxicology, epidemiology, and clinical science. The bar graph data in this area illustrated investments in Partnerships for Environmental Public Health, and portfolio representation of studies involving the endocrine system, cancer, the reproductive system, respiratory organs, and neuroscience. In neuroscience specifically, she presented data illustrating investment trends in CNS Centers, Parkinson's disease, neurodegeneration, neurobehavioral research, neurodevelopment, and the nervous system. Another "long-term investment in a high-priority area" has been children's environmental health, as indicated by the data presented illustrating portfolio presence in Children's Centers, neurodevelopment, neurobehavioral research, development, and teratogenesis research. Dr. Collman completed this portion of her presentation with a bar graph illustrating the trends in NIEHS investment in Centers, including a large portfolio of Core Centers.

She displayed a line graph illustrating the trends in budget authority by program, which depicts the changes brought about by the shifting priorities within the current Strategic Plan. For example, investment in basic mechanisms research declined, while investments in clinical and translational research rose sharply. Training and career development, and exposure science investments remained roughly the same over the period.

Dr. Collman described the three upcoming workshops planned for the summer of 2011.

The first is "Engineered 3-Dimensional Tissue Models for Environmental Health Sciences Research: Symposium and Workshop," scheduled for NIEHS June 27-28. It will highlight efforts in the development and use of engineered tissue models, both 3-dimensional multi-cellular and computational. A working group meeting on June 28 will formulate recommendations for an NIEHS research agenda to enhance utility of the model systems.

On September 8-9, there will be an "NIEHS Workshop to Examine the Interactions between Environmental Exposures and Infectious Agents in the Etiology of Human Disease." It will bring together experts in the field to discuss the relationship and interaction between environmental exposures and infectious vectors such as viruses, bacteria, fungi, parasites, etc. Topics will include toxicant modification of responses to pathogens and pathogen modification of responses to toxicants, One Health and

emergence/re-emergence of disease, and toxicant and pathogen synergy in disease etiology.

September 26-27 will see a workshop entitled "An Integrated Strategy for Advancing NIEHS Mixtures Research." The meeting will be designed to identify and prioritize advances, knowledge gaps and roadblocks in mixtures research conducted in epidemiology, statistics, biology, exposure, and risk assessment, and will provide recommendations for research to address critical topics in mixtures.

VIII. New NIH Appeals Process

Dr. J. Patrick Mastin, DERT Deputy Director, presented the new NIH-wide appeals process for initial peer review ("study section") to Council. The policy is effective for applications received for the January 25, 2011 receipt date and after. The NIH Guide Notice for more details is NOT-OD-11-064 ("Appeals of NIH Initial Peer Review"). The first step of the process is for the applicant with concerns about the review to contact the Program Officer (PO). The PO answers questions and describes the appeals process -- without attempting to talk the applicant out of filing an appeal. If the applicant wants to continue with the appeal the PO has preliminary discussions with the Scientific Review Officer (SRO).

The SRO is then to: 1.) review the summary statement, reviewer assignments and notes from the meeting to determine if the appeal is warranted, 2.) if warranted, contact the original reviewers for clarification without indicating that an appeal has been submitted, 3.) discuss the basis of the appeal with the Integrated Review Group (IRG) chief, and 4.) provide the PO with a written response to the applicant's concerns. If the review group agrees that there is cause, it can elect to re-review.

If the PO and the SRO do not agree with the applicant that re-review is warranted, the applicant has three options: submit a new application, submit a revised application, or insist on the appeal. If the applicant opts to have the appeal taken to Council, it must be done. An applicant can request an appeal up to 30 days after the relevant council meeting has taken place. At any point in the process, if the IC agrees with the applicant that re-review is warranted, it can be granted. Also, at any point in the process the applicant can withdraw the review.

The process must be conducted formally, including the requirement of a formal appeal letter to be submitted by the Authorized Organization Representative (AOR), or at least indication of concurrence by the AOR. All formal appeals must be taken to Council unless withdrawn or deferred for re-review prior to Council. Council or IC staff decide which appeals require formal discussion by Council. Letters that fail to meet criteria for an appeal or lack the AOR endorsement will be treated as grievances.

There are some issues that do not go to Council, including issues involving potential violation of ethical conduct rules by an NIH staff member or other federal employee or and concerns about referral assignments. The latter concern constitutes a "dispute" under the new terminology. A "grievance" is an applicant's concern about issues that are not

appeals or a communication that is not filed as a formal appeal. An "appeal" is a written, formal communication from an applicant, endorsed by the AOR, which disputes the outcome of an initial review and is based on the allowable grounds for an appeal.

There are just four allowable grounds for an appeal:

- reviewer bias
- conflict of interest among the reviewers
- lack of appropriate expertise in the study section
- substantial and significant factual errors that could have substantially altered the outcome of the review.

Difference of scientific opinion is not a basis for appeal.

The appeals process applies to grant review, not contract review, and does not apply to funding decisions.

The NIEHS Appeals Officer (currently Dr. Mastin) is responsible for determining that the PO has worked with the PI and SRO but has been unable to resolve issues; ensures that the PO has prepared the appeals package; and informs the IC Director and Council's Executive Secretary of the appeal. The IC staff cannot deny a PI the opportunity to have the appeal available to Council. The staff may decide which appeals receive formal discussion, but Council members may elect to discuss an appeal at their discretion. The minimal information that is required to be made available to Council includes a list of the formal appeals, relevant summary statements, appeal letters, and responses from POs and SROs.

The only outcome of a successful review is a re-review of the original application; otherwise the original review outcome stands. Council's recommendation is final. If Council does agree to a re-review, the original application, without modification or update, must be re-reviewed by the same or a different SRG, depending on the review flaw that led to the appeal. The outcome of the re-review is final and not subject to further appeal.

After Council has deliberated, the Council Executive Secretary informs the PI of the Council's recommendation, with a copy to the AOR. The SRO also receives a copy. At that point, the PO should discuss next steps, as appropriate, with the PI.

Letters that fail to meet the criteria for an appeal are treated as grievances. Disagreement with a budget recommendation is also an example of a grievance.

The individual ICs develop procedures and time lines for handling appeals and grievances, within the provisions of the OER guidance.

Dr. Lloyd asked Dr. Mastin how many calls or requests are being received per funding cycle, and whether there is a mechanism for specific appeals to be assigned to a sub-set of Council members with particular expertise. Dr. Mastin said the procedures are still being worked out, but that he would envision a similar mechanism as is employed with concepts, that is, some specific Council members would be asked to lead the discussion,

although all would participate in a vote. Dr. Lloyd said that would be a good idea. Dr. Mastin added that it was difficult to predict the number of appeals that would result from this new policy.

Dr. Gasiewicz asked whether the processes would be consistent across all institutes. Dr. Mastin said that they would, and that that had been part of the idea for starting the new policy.

Referring back to Dr. Collman's presentation, Dr. Lloyd asked her whether the growth in translational funding she had depicted reflected growth in SBIR/STTR funding. Dr. Collman replied that it was her recollection that the SBIR/STTR funding spanned a number of the bins she had shown.

Dr. Lloyd asked Dr. Collman about the use of the number of publications as a metric for the success of grants, in that publications emanating from Centers may be less reported. Dr. Collman said that NIEHS had encouraged grantees to acknowledge funding sources in their articles, and that that practice was increasing, which would help make the necessary links. She said that for program evaluation, NIEHS also uses the Scientific Publication Information Retrieval & Evaluation System (SPIRES), which was developed at NIEHS and later adopted across NIH.

Ms. Witherspoon asked Dr. Collman whether any particular area would be hit harder by the upcoming budget cuts, or whether they would go across the board. Dr. Collman replied that for the most part it would be across the board, except for some small areas of discretionary decision-making. She said that in terms of priority setting, it was difficult to make those decisions as long as the Institute is in the midst of formulating a new strategic plan. With the new strategic plan in place by this time next year, she said, it would then be appropriate to make investment decisions based on the priority areas identified in the plan.

IX. Permanent Reprogramming of Gene Expression in Response to Neonatal Phytoestrogen Exposure: Implications for Female Reproductive Tract Function and Pathology

Acting Scientific Director Dr. David Miller introduced the meeting's scientific speaker, Dr. Carmen Williams from the intramural Laboratory of Reproductive and Developmental Toxicology.

Dr. Williams said she would present work that has built upon work that began at NIEHS more than ten years ago by Retha Newbold and John McLachlan, studying the effect of estrogens on female reproductive tract development. She reviewed some basic facts about development and the environment, citing the well-known example of the harmful effects of prenatal exposure to diethylstilbestrol (DES) as a phenomenon that has led to increasing concern about developmental exposure to a number of environmental substances with estrogenic activity. She illustrated the concept with a timeline of the development of the female CD-1 mouse reproductive tract, which showed that major organogenesis takes place from prenatal day 9 to 16, during which time, upon DES

exposure, there will be a low incidence of cancer later in life, but a very high incidence of reproductive tract malformations. Conversely, upon DES exposure during neonatal days 1 to 5, when cellular differentiation of the reproductive tract is still occurring, later in life there will be a high incidence of cancer (>90%), but a low incidence of malformation. This demonstrates that the timing of sensitivity to estrogenic compounds differs depending on the outcome.

She focuses on phytoestrogens, because soy is very prevalent in use, including widespread use of soy-based infant formulas. Soy protein contains isoflavones, which have estrogenic activity. In particular, she is studying the major soy isoflavone called genistein. The oral form in soy products, called genistin, is quickly hydrolyzed in the digestive system into genistein. In mouse model systems of human infant soy formula exposures, genistein is introduced via subcutaneous injection or oral exposure. Dr. Williams pointed out that it is the circulating level of genistein in the bloodstream that drives its biological impact, as opposed to the exposure dose. She showed data indicating that the genistein levels seen in her experimental rodent model was the same as those seen in human children being fed soy infant formula.

Approximately 30% of the mice given genistein (50 mg/kg subcutaneously) once per day on neonatal days 1-5 develop uterine cancer by the time they are 12-18 months old. One hundred percent of those animals turn out to be infertile. They can often achieve pregnancy, but many of the embryos are lost in transit through the oviduct, and no embryos are successfully implanted in the uterus. Additional studies using a range of genistein doses have shown that neonatal genistein alters ovulation, with the higher-dose animals showing no ovulation at 4 months. However, superovulation is effective; therefore anovulation is due to problems with the hypothalamic-pituitary-ovarian axis. The experiments also showed that neonatal genistein reduces fertility, with no live pups delivered by the higher-dose group, and the average number of pups decreased in the lower-dose groups. Examination showed that pregnancies were actually achieved in the higher-dose animals, but the implantation sites were fewer and smaller than in controls.

There were no differences in levels of steroid hormones among the groups; thus the infertility could not be explained by the hormonal environment, leaving egg quality, oviductal environment, or uterine environment as potential explanations. Studies examining egg developmental competence showed that it appeared normal even in the high genistein dose group. Embryos developed in vitro appeared to grow normally, for the most part. Thus, egg quality did not appear to be the source of the problem.
Studies examining the role of the oviduct environment suggested that substantial loss of embryos in the genistein groups occurred between day 2 and day 3 of pregnancy. Experiments also showed that uterine receptivity (to control blastocysts) was reduced in genistein-treated mice. Thus, it appears that there are adverse effects in both the oviduct and uterus of the treated animals.

To learn more about the mechanisms driving the effects, oviducts were collected from genistein-treated animals at 48 hours into pregnancy, to examine their morphology. Dr. Williams depicted several histological examples, both normal and treated. As she

summarized the results, "There's clearly a problem a problem with the morphology, but why is that? What is it about the five days of genistein treatment that is going to lead to these cellular changes in the oviduct as an adult, six or eight weeks later?"

To potentially answer those questions, the researchers examined Hox gene patterning. Hox genes are important to reproductive tract development. The oviduct is high in Hoxa9, the uterus in Hoxa10 and Hoxa11, and the cervix and vagina in Hoxa13. Dr. Williams also showed a list of several other genes believed to be involved in female reproductive tract development.

The team elected to take a candidate gene approach, collecting oviducts on day 1 and day 5 of treatment, looking at candidate genes using real-time PCR. The experiments showed that many of the genes anticipated to be involved with disruption of reproductive tract development in fact were, including Wnt genes, hedgehog signaling pathway genes, Foxa2 and several of the Hox genes. The process called "posteriorization" was illustrated by the altered gene patterning after neonatal genistein treatment.

To assess the long-term impact of neonatal genistein treatment on oviduct gene expression, the researchers collected oviducts and ran them through microarray analysis. In the genistein group, the most up-regulated genes were homeobox transcription factors. Several serpins were also highly altered, as were immune response genes. Ingenuity analysis of enriched biological functions showed that immune response, metabolism, hematological development, cell proliferation, cell interaction, and development were all significantly altered. Further analysis showed that 34 of 35 immunoglobulin genes were up-regulated more than two-fold. Thus, the investigators think there is a huge difference in immune response and inflammatory pathways in the neonatally genistein-treated animals on day 2 of pregnancy. That is important because the reproductive tract is a mucosal membrane exposed to the outside world, and its normal function allows for down-regulation of the immune response to accommodate the embryo, which is not recognized as self. With the immune response skewed by the genistein exposure, the theory is that this process is altered.

Further real-time PCR analysis of oviducts collected as late as 6 months after birth showed that the Pitx1 and Six1 genes, both homeobox transcription factors, were up-regulated permanently, as was protein expression. The posteriorization effect was observed in the altered gene expression of the adult oviduct in the treated animals. The oviduct genes altered by neonatal genistein were shown to be normally expressed in the posterior female reproductive tract in controls. Also, immune response genes were seen to be expressed in the oviduct during pregnancy in the treated animals.
The next step was to assess the impact of the genetic changes on the embryo, since the question was actually why the treated animals were infertile. It was known there was a slight delay in fertilization, and that by day 3, half of the embryos were lost. Examining blastocysts, it was seen that in the treated animals there was a significantly decreased ratio in cell counts between the outer layers, which would form the placenta, and the inner

layers, which would form the pup. However, there was no difference in litter size when the blastocysts were transferred into pseudopregnant control mice.

Dr. Williams said that the conclusions from the mouse model were:

Neonatal exposure to environmentally relevant doses of genistein causes permanent alterations in morphology and gene expression in the oviduct and uterus

The oviduct becomes posteriorized and has alterations in mucosal immune function during pregnancy

These abnormalities alter fertilization and embryo development

Long-term consequences for surviving embryos are unknown

Dr. Williams then related her results to human health. She said that approximately 10% of couples undergoing in vitro fertilization have "unexplained" infertility, with no grossly apparent reason for the infertility. Failed fertilization and failed implantation are both potential explanations. She said there is a possibility, then, that the types of insults she had described, in neonates, could lead to fertility problems in adult women, based on oviductal or fertilization problems due to issues with the oviduct.
Studies have also shown a greater risk of early fibroid diagnosis being associated with soy formula during infancy. Returning to the subject of cancer, she noted that the Six1 gene has been associated with human breast, ovarian and several other cancer types, and that there is higher Six1 expression in higher grade and stage cervical cancer. Another question to be addressed is the possible association of early phytoestrogen exposure, Six1 expression and endometrial cancer.

Dr. Lee asked Dr. Williams about the parallels between the mouse model and soy feeding in infancy, particularly in terms of early uterine development and cell differentiation. Dr. Williams noted that the cell differentiation starts earlier but goes on longer in the human than in the mouse, even up to age 7 or 8. Thus, the mouse model genistein exposure is clearly happening when human cell differentiation is happening, in terms of the relevancy of the timing of the exposure.

Dr. Baylin asked whether the epigenetics had been examined. Dr. Williams said that was precisely the direction in which her lab is heading, based on other work in her lab on neonatal DES exposure.

Dr. Woychik asked about whether the Hox genes dysregulated in the oviduct are expressed elsewhere in the neonate. Dr. Williams said that expression in the external genitalia may be different, but that she is unaware of any other changes in Hox gene expression.

Dr. Birnbaum asked if any such abnormalities in external genitalia had been reported in women. Dr. Williams did not believe it had been reported in DES women; however, women with müllerian anomalies have a high incidence of ureteral system abnormalities, although she did not know how tight an association is there with the Hox genes.

Reflecting on the potential public health impact, Dr. Maddox wondered about the effects of genistein exposure in males. Dr. Williams said that they did not see any impact at all on fertility in male mice. She speculated that the problem area in males might be effects on the hypothalamic-pituitary axis, but she had no data to support that, and said it was "a wide-open area for study."

Dr. Gasiewicz asked whether the activity observed by Dr. Williams was exclusively mediated through estrogenic activity, or whether something else might be contributing. She said that gene expression analysis following pre-genistein administration of an estrogenic inhibitor showed that it is certainly possible that there is an alternate mechanism being triggered that does not go through the estrogenic receptor.

Conversely, Dr. Lee asked if they had looked at a pure estrogen such as estradiol to see whether it might have similar effects. Dr. Williams said they had conducted PCR on DES-exposed uteri, and the same gene expression patterns were seen.

Dr. Woychik asked whether genistein appears to have effects in early development. Dr. Williams said that she imagined it would, since the amount of estrogen dictates the phenotype, but has not tested that.

X. Environmental Epigenetics/Epigenomics: NIEHS Extramural Investment – an Update

Dr. Frederick Tyson of the DERT Cellular, Organ, and Systems Pathobiology Branch provided Council with an update on NIEHS activities and investments related to epigenetics and epigenomics.

He began with a brief overview of epigenetics. He defined the term and briefly discussed its importance in biology, including the fact that each cell type in the human body has its own gene expression profile, which is greatly influenced by the cell's epigenome. Epigenetic modifications can, for instance, regulate gene expression by controlling the openness of DNA: genes in areas of open chromatin (less densely coiled) tend to be activated, while those in more closed areas (more densely coilded) tend to be repressed. Epigenetics plays its most important role during development, but is sensitive to perturbations throughout life. He described the three mechanisms of epigenetic gene regulation that are most commonly studied: histone tail modification, DNA methylation, and non-coding RNAs.

Dr. Tyson said that the key message of his presentation would be the fact that the epigenome serves as the interface between the genome and the environment in common complex human diseases.

He outlined the NIEHS extramural investments in epigenetics. They include targeted solicitations starting in 1998 such as RFAs and PARs involving genomic imprinting, the fetal basis of adult disease, environmental epigenetic regulation, and chromatin, environment and transcription, as well as a transgenerational RFA. The latter two are still in development and have not yet been released. There is also a growing portfolio of investigator-initiated grants. NIEHS also has invested in the Roadmap Epigenomics Program, which includes Reference Epigenome Mapping Centers and Epigenomics in Human Health and Disease R01s. He also recounted NIEHS support for, and organization of, several international scientific meetings since 1998, the most recent of which was the Keystone Symposium on Environmental Epigenomics, which was held in March, 2011.

The goals of the environmental epigenetics program are:

- To understand the biology of normal epigenetic regulatory pathways
    - The role of epigenetics in normal biology across the lifespan
    - Tissue-specific changes in epigenetic marks
    - Mechanisms controlling epigenetic changes
        - Readers, writers, and erasers of epigenetic code
- To develop bioinformatics tools and resources
- To determine the role and mechanism whereby the epigenetic regulatory system interacts with and interprets the environment, focusing on environmental exposures
    - The role of epigenetics in the action of environmental exposures across the lifespan
        - Windows of susceptibility
        - Mechanisms

In terms of the importance of epigenetics in the environmental health sciences, Dr. Tyson said that exposure-induced epigenetic reprogramming is associated with disease and with increased disease susceptibility, with particular vulnerability during gestation or early childhood, through puberty. Resulting diseases can manifest themselves at any later point in the life course. Environmental exposures during critical windows of susceptibility can alter the development of a target organ, with altered epigenetic programming of somatic cells, which can lead to increased susceptibility to disease. Thus, the potential disease outcome is related to the nature, site and mechanism of action of the environmental exposure, as well as the genetic background.

To illustrate some of the concepts he was describing, Dr. Tyson shared some of the work of Dr. Cheryl Walker, showing that exposure to endocrine-disrupting compounds such as DES, BPA, and genistein led to development of leiomyomas, or uterine fibroid tumors, in

the Eker rat model. In that model, 60% of the animals will develop leiomyomas without treatment, but exposing them to—in the case he depicted—DES during gestation, 100% of the animals will develop the tumors, which also grow much faster and are much larger than in the untreated animals. This shows an altered response to normal physiologic signals leading to increased susceptibility to adult disease. Dr. Tyson showed a graphic representing the pathway activity altered by the DES exposure, leading to epigenetic reprogramming of gene expression.

He shared another example, this one illustrating epigenetic reprogramming by carcinogens, using immortalized human bronchial epithelial cells. When the cells are treated with carcinogenic byproducts of tobacco smoke, they are transformed from epithelial cells to mesenchymal cells, and become tumorigenic. The process is mediated by the reprogrammed expression of specific miRNAs.

Dr. Tyson cited another example of funded research, in which the investigators, using T lymphocytes, are screening for alterations in the chromatin landscape near double-strand breaks, and are elucidating how histone modifications are involved in the DNA repair of double-strand breaks. This is an example of NIEHS-funded research into the interaction of epigenetic alterations with the genome.

He also provided an update on the NIH Roadmap Epigenomics Program. NIEHS is involved with the Reference Epigenome Mapping Centers and the Epigenomics in Health and Human Disease initiatives under the program. In the Mapping Centers, the goal is to define the epigenome of a variety of normal cells, to provide a starting point for understanding the epigenomes of diseased cells. Also, the intent is to establish a community resource for the scientists around the world examining epigenomic questions. In the Health and Human Disease Program, the goal is to understand the role of epigenetic changes in disease, including environmentally induced diseases.

The Mapping Centers are working on establishing reference maps of epigenetic changes, including DNA methylation, a core set of histone modifications, and chromatin accessibility. There are currently over 100 partial sets of epigenomic data available, from both adult and fetal tissues, and including both embryonic stem (ES) cells and induced pluripotent stem (iPS) cells. So far, a grand total of 34 reference epigenomes have been completed. Significant advances that have emerged from the Mapping Centers include:

- Generation of first complete human methylomes
- Comparisons of epigenomes of ES, iPS and lineage-committed cells
- Comparison of assays and analysis methods for genome-wide investigation of DNA methylation patterns
- Detailed quality assessment of commercially available histone modification antibodies used for ChIP (in collaboration with ENCODE)
- Improved protocols for epigenetic mapping in clinical samples

Dr. Tyson noted that the Epigenomics of Health and Disease RFA has funded 22 investigators studying a variety of human diseases.

Summarizing what has been learned, Dr. Tyson noted that:

- The epigenetic regulatory system is very complex.
- Development is the most sensitive window for epigenetic programming and is sensitive to environmental exposures, nutrition, stress, drugs and infections.
- Epigenetic programming is responsible for both maintaining pluripotent stem cells and transmittal to terminally differentiated cells.
- Epigenetics and genetics work together to influence our disease and health status.
- Epigenetic marks may be useful as biomarkers of disease susceptibility.
- Epigenetic marks are plastic and abnormalities may be changed, and thus protect against disease.

In the future, said Dr. Tyson, environmental epigenetics needs to move from descriptive to more mechanistic studies, including more emphasis on looking at the role of non-coding RNAs. Analysis of genomics and epigenomics needs to be more integrated, and there needs to be determination of potential epigenomic mechanisms in transgenerational inheritance.

Dr. Schnoor asked Dr. Tyson whether there should be examination of nutritional alterations of epigenetic status as a potential source of new therapies. Dr. Tyson said that such studies are already in process, but therapeutics is "down the road for us."

Dr. Chesselet asked about knowledge of methylation patterns in blood cells. Dr. Tyson said that there were several studies addressing blood cells in the Mapping Centers program.

XI. Update on NIEHS Autism Activities

Dr. Cindy Lawler of the DERT Cellular, Organ, and Systems Pathobiology Branch updated Council on NIEHS activities and investments related to autism.

She reviewed some of the basic facts about autism and autism spectrum disorders (ASD). ASDs are recognized as a group of syndromes, with diagnosis based on behavior. The severity of these disorders can range from mild to disabling, and many people with an ASD have other medical conditions, such as GI difficulties or epilepsy. It is known that as many as four times more boys than girls are affected. Symptoms must be evident by age 3, although diagnosis often occurs much later. The 'gold standard' diagnosis requires a carefully structured interview with the caregiver and the child to elicit and measure social and communicative behaviors.

Part of the public health urgency surrounding autism is related to the dramatic increase in its prevalence in a relatively short period of time—the past 30 years. The most recent

accepted figure has been 1 in 100 children, although a study conducted in Korea that has just been published calculated prevalence at 1 in 38 children. Many factors are likely to contribute to the increased prevalence. For example, changes in diagnostic criteria account for some of the increase, as do extrinsic factors such as increasing identification of cases and awareness of the condition. The possibility of an increase in underlying biologic risk from environmental exposures is of great interest to this institute.

Since autism and ASDs were first described in the 1940s, suspected causes have evolved from the now-discredited idea that parents were to blame to understanding that genetics are at least part of the etiology, since twin studies in the early 1980s showed that the condition has a heritable element. Consensus is emerging regarding the complexity of autism, and the fact that there is not just one, but many forms of autism, with a wide variety of causes, stemming from genetic factors and environmental factors and their interactions.

Dr. Lawler cited the establishment in 2006 of the Interagency Autism Coordinating Committee (IACC) as a major step forward in autism research. Its membership includes federal officials and public members, whose responsibilities are to:

- Provide advice to the Secretary of Health and Human Services
- Coordinate all efforts within the DHHS concerning ASD
- Develop and update a Strategic Plan for ASD research
- Develop and update a summary of advances in ASD
- Monitor federal activities related to autism

The IACC has met 51 times in the past three years, Dr. Lawler noted. She described the 2011 Strategic Plan for ASD Research released by the committee, which is written from the perspective of addressing questions that might be posed by a family member of a person with ASD. She said that the NIEHS mission related to autism falls most readily under Question #3 in the plan, "What caused this to happen and how can it be prevented?"

Over the past 10 years, NIEHS funding for autism-related research has grown from 0 in the year 2000 to a current base funding level of more than $5 million. Additional funds were made available in 2009 and 2010 through the American Recovery and Reinvestment Act. All in all, it is "a very healthy and non-trivial investment," according to Dr. Lawler. She noted as well that total NIH funding for autism research in FY 2009 was more than $132 million, with NIEHS investment totaling about 3% of that amount, making it important to leverage the other NIH investments and work closely with other NIH partners to ensure that NIEHS research is part of the core mission of the overall NIH activity.

A significant portion of the NIEHS research portfolio related to autism is embedded within the NIEHS/EPA partnership in the Children's Environmental Health and Disease Prevention Research Centers. Two of the Centers first established in 2001 were devoted

to autism research—at the University of California (UC), Davis, and at the University of Medicine and Dentistry in New Jersey. The New Jersey center was focused on the potential role of oxidative stress in autism etiology, and several notable findings were published. The UC Davis Center, funded continuously since 2001, is conducting the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, a case/control study involving more than 1500 families. Last year, preliminary data from CHARGE were published in JAMA; these data suggested that children with autism may be more likely to have mitochondrial dysfunction. Dr. Lawler also described one of the more provocative immunological findings from the CHARGE study—the result that 12% of mothers of children with autism produce specific antibodies to fetal brain tissue, and the suspicion that maternal autoantibodies may contribute to autism risk. Many other CHARGE findings also point to immune alterations in ASDs, and preliminary studies are underway to determine whether immune abnormalities in autism have consequences for environmental exposures. Another study published from CHARGE showed that autism risk is associated with distance of maternal residence near the time of birth from freeways and major roadways; distance was used as surrogate measure of air pollution. Another CHARGE publication showed that children with ASDs have reduced blood mercury concentrations, apparently due to lower fish consumption.

Another noteworthy study published last year looked at the relationship between exposure to benzo[a]pyrene, a common component of combustion byproducts, and expression levels of a recognized autism gene in an animal model. The researchers found that exposure to the chemical had significant effects on the timing and levels of expression of the gene, and noted concomitant behavioral changes in the offspring.

Dr. Lawler reported on a study exploring association between prenatal exposure to endocrine disruptors and childhood social impairment. Higher phthalate levels in the pregnant mothers were positively associated with increased social impairment in their children, as measured 7-9 years later.

She outlined another important autism study that was recently launched, called the Early Autism Risk Longitudinal Investigation (EARLI). It is a 4-site study funded as part of the NIEHS Autism Centers of Excellence program, with NIEHS as the lead institute, partnering with NIMH, NICHD, and NINDS. Mothers with at least one child with autism who are planning to become pregnant or are in the early stages of a subsequent pregnancy will form the study cohort. This enriched risk design is based on knowledge that siblings of children with autism are at greatly elevated risk of developing the condition as well. Prospective, real time data collection during critical periods of early development will take place, avoiding the need to assess exposures retrospectively. Enrollment for the study began in Spring 2009. The goal is enroll up to 1000 mothers. A wide array of data and biological specimens will be collected throughout pregnancy and during the first three years of the new baby's life.

Dr. Lawler briefly alluded to NIEHS investments in epigenetics/epigenomics research related to autism, including several NIEHS-supported studies.

She described the National Database for Autism Research (NDAR), to which NIEHS contributes along with several other NIH ICs. It combines the functions of data repository and scientific community platform. NIH-funded autism researchers are expected to contribute their data regularly to NDAR. The first data release from over 10,000 ASD study participants occurred in November 2010. Now, clinical data on over 22,000 subjects from 45-50 studies are available.

Recognizing the importance of collaboration in autism research, NIEHS, in partnership with Autism Speaks, launched in 2010 the Epidemiology of Autism Environmental Risks Network (EEARN), which so far has brought together more than 30 scientists from 15 different epidemiologic studies in a workgroup focused on opportunities to study gene-environment interplay in autism using existing large-scale epidemiologic studies. The group is currently considering a range of collaborative network activities.

In another collaborative effort, NIEHS, other NIH institutes and Autism Speaks are looking at whether there is an increased prevalence of autism among Somali immigrants in Minneapolis.

In addition to research, NIEHS also frequently funds meetings in the autism area, designed to bring together a diverse group of stakeholders to build partnerships, share ideas, educate, and develop recommendations for future initiatives.

In summary, Dr. Lawler noted that:

- NIEHS investments in autism research have grown considerably over the past 10 years
- Infrastructure for large-scale human studies (CHARGE, EARLI) is now in place
- Provocative initial findings identifying potential environmental risk factors and gene-environment interactions have been generated
- NIEHS support for basic research in neurotoxicology and exposure science will be essential for understanding and informing human studies in autism

She identified the priorities for future NIEHS autism activities as:

- The opportunities outlined in the IACC Strategic Plan
- Coordination with other federal agencies
- Meaningful involvement of affected communities
- Translation of findings to public health and prevention

Dr. Lloyd asked whether enough time had elapsed since the early diagnoses to conduct progression analyses related to autism. Dr. Lawler noted that there is an expected "tsunami" of adults with autism as the children diagnosed in recent years grow into adulthood. She said there is great interest in studying disease trajectories. She said the

data is not available currently, but that that type of research is a big part of the IACC Strategic Plan.

Dr. Lloyd asked if there was perhaps an overlap in documentation of children with autism and children with attention deficit hyperactivity disorder (ADHD). Dr. Lawler said there is certainly such an overlap in clinical features, but that it is unclear whether such overlap may be part of the increase in autism prevalence.

Dr. Lee said she is troubled by the wide criteria used in some of the large autism studies, and wondered whether there was any idea of limiting analysis to more severe subjects, with more clear diagnoses. She also wondered whether some people were working to receive benefits based on a diagnosis of autism, and whether that phenomenon might skew research results. Dr. Lawler replied that the diagnostic criteria for ASDs are going to change soon, which will constitute another challenge. She said Dr. Lee made a great point, and that everyone in the autism research community is very interested in the issue of heterogeneity in the population.

Dr. Brody asked Dr. Lawler to elaborate on what exposures were being pursued in the EARLI Study. Dr. Lawler said that it is meant to be a 10-year study, and during the second five years, such issues as immune biomarkers during pregnancy, nutritional exposures, pesticide exposures will be studied, along with many more that the investigators are interested in. Right now, while the study is still in its early phase, the main concentration is proof of principle studies. Approximately 150 families have been enrolled so far, she added.

Dr. Winn asked about diagnosis of impairment, and whether very slight effects are being detected that would not cause a person a lifelong problem. Dr. Lawler said that the diagnosis does in fact require a significant impairment. She added that the recent Korean study was getting much attention in the community, since it appeared to be rigorously conducted, and uncovered a great many children who met the criteria for autism but had not been previously diagnosed.

Dr. Schnoor asked about the presence of vaccine as a cause of autism studies in the NIEHS portfolio. Dr. Lawler noted that there had been a number of studies looking at a potential association, none of which were funded by NIEHS. She said that the weight of evidence from well-designed studies did not support the assertion that thimerisol exposure from vaccines could explain the increase in autism prevalence.

Dr. Dearwent asked how the prospective cohort would fit in with the National Children's Study (NCS). Dr. Lawler said that the NCS involves an unselected sample population (as opposed to the EARLI study, which is a selected population), and autism is one of the endpoints the researchers are particularly interested in. Given the selection involved with EARLI, the same type of study can be conducted with much smaller numbers in the cohort, because of the high expected recurrence rate. She felt that the different study designs would complement one another. Dr. Birnbaum added that the EARLI study was designed so that a smaller number of women could be involved to acquire the information being sought. Dr. Lawler observed that it was likely that some of the EARLI children who

may not meet the autism diagnostic threshold may still exhibit developmental issues, and that the study would be able to capture that along with exposures, thus making the sample size of the study larger and increasing its power.

Dr. Maddox agreed with Dr. Lawler's comments regarding the EARLI study and its value in light of the NCS. She said that it should allow the identification of differences between autistic and non-autistic children that perhaps would not be detected by the NCS.

Dr. Lloyd asked whether the concept that many autistic children have a compensatory ability in a single area has been analyzed in terms of a percentage. Dr. Lawler said that was an area of interest to some researchers, but that she was unaware of any data on that question.

XII. Climate Change and Sustainability: NIEHS Efforts to Integrate Human Health

NIEHS Senior Advisor for Public Health Dr. John Balbus updated Council on NIEHS efforts to integrate human health with climate change and sustainability science.

Dr. Balbus reminded Council that it was the one-year anniversary of its approval of the concept regarding the first Human Health Impacts on Climate Change (HHICC) program within NIH. He said he would inform Council about translation of the science emerging from NIEHS grants and application of the science in a number of different settings, as well as how the climate change research is relevant to a suite of larger ongoing activities.

He began by depicting data from NASA from December 2009 showing the "average monthly temperature anomaly"—how far off normal the monthly temperature was compared to the prior 30 years. The striking abnormality was that much of the northern hemisphere was above average by 20 degrees Fahrenheit. The warmer Arctic was (and is) associated with altered wind patterns around the world. As Dr. Balbus put it, "Despite whatever the political climate in Washington is, it's kind of irrelevant, because the real climate is telling us that this is a real phenomenon, it is underway, we know that it's much more of a phenomenon going on in the Arctic, where there's tremendous coastal erosion and melting of permafrost, and literally, people's lives are being upended." He showed that the '00s were our hottest decade, with 2005 and 2010 as the hottest years. He said that 98% of climate scientists are unequivocal as to what is going on.

Dr. Balbus shared the key messages for climate change and human health, many of which were developed under NIEHS leadership:

- Changes occurring in the world's climate are affecting our health and will have even greater impacts in the future.
- Climate change also makes many existing diseases and conditions worse, although it may also lessen some cold-weather diseases.
- The most vulnerable among us—children, elderly people, those living in poverty, with underlying health conditions, or in certain geographic areas—are likely to have less ability to cope or adapt.

- Climate change places stress on our health care systems, public health infrastructure, and ability to deliver and receive health services.
- We can take steps now to prepare for changes in our climate that will protect our health, the health of our children, and that of future generations.
- Many actions to address and prepare for climate change will yield extra benefits for our health, our environment, our economy, and our society.

The goals of the NIEHS HHICC Program are to provide a structure to coordinate and support a variety of NIEHS-sponsored research and mission-related activities to better understand how climate change will directly and indirectly affect human health risks, and to coordinate collaborative research initiatives within NIEHS, across the NIH, and with other federal agencies. The research is applied in public health protection through general preparedness and awareness, monitoring, surveillance and early warning and interventions, as well as in decision-making outside of traditional public health but in related areas such as impact modeling and energy, transportation, agriculture, etc.

Dr. Balbus depicted the central leadership role that NIEHS is playing outside its own boundaries regarding climate change and human health. This includes co-chairing the trans-NIH working group on climate change and human health. Other groups in which NIEHS is involved include the US Global Change Research Program (USGCRP), the President's Climate Adaptation Task Force, the DHHS Council on Environmental Quality, the UN Framework Convention on Climate Change, and the Intergovernmental Panel on Climate Change (IPCC). Two years ago, the USGCRP created an Interagency Group on Climate Change and Human Health, which is co-chaired by NIEHS. The working group is charged with research prioritization, with monitoring, early warning, data integration and surveillance (inventorying relevant databases), with education and engagement, and with coordinating international activities. The group is also working on adaptation, working with the President's Climate Adaptation Task Force, and is supporting the ongoing National Climate Assessment.

One of President Obama's first acts as president was to sign an executive order directing all federal agencies to incorporate sustainability and climate change adaptation planning into their work. The working group co-chaired by NIEHS within the interagency task force provided health information to the President's Climate Adaptation Task Force. Currently a series of white papers and workshops is being prepared to inform other federal agencies about how their decisions in the climate change area have health implications, and how they can assess those health impacts.

Within DHHS, NIEHS is assisting the Assistant Secretary for Health in projecting the integration of health within climate change across federal agencies, as well as working to project that concept within DHHS itself. NIEHS is also helping DHHS to write the climate justice portion of a new interagency environmental justice strategy.

Dr. Balbus showed Council a flyer that had been prepared for a meeting in 2010 in Cancun, "Climate Change and Human Health: New Developments." It was the 16th

conference of the parties to the UN Framework Convention on Climate Change, and the first that featured a speaker representing the US DHHS (Dr. Balbus).

NIEHS is also working with several other international organizations such as the IPCC, the World Health Organization, and the Pan American Health Organization, partnering to support international workshops, including preparation for the Rio+20 summit and COP17.

Dr. Balbus cited cookstoves as an area where global health, climate change and sustainability meet. The prior week, there had been a workshop where approximately 150 scientists from around the world gathered to assess research needs in the context of a large international alliance on cookstoves that is aiming to replace 100 million cookstoves around the world by 2020. Cookstoves are responsible for approximately 2 million deaths annually, primarily in developing countries from conditions such as childhood pneumonia and COPD in adult women. There are strong associations between indoor air pollution from cookstoves and the four leading non-communicable diseases. Also, black carbon emitted from cookstoves is a potent warming agent in the atmosphere, but it can be relatively quickly and easily removed from the atmosphere. Biomass accumulation for cooking is also contributing to deforestation. Ultimately, he said, the frame of looking at environmental health aspects of sustainable development is a major theme of the translation of the work of the NIEHS moving forward.

On the institutional scale, that commitment to sustainability is exemplified by the practices of the NIEHS itself, which won a Green Champion Award from DHHS in 2009. Dr. Balbus read a quote from the 2009 NIEHS Sustainability Report: "As a public health entity, the NIEHS is naturally poised to take on a leadership role in sustainability. In our laboratories as well as through research grants and contracts, we study the effects on human health of environmental pollutants, chemical substances and phenomena such as climate change to create a scientific basis for informed public policy. Understanding that there is a critical balance between ecology, the built environment and human health helps establish a foundation for sustainability."

Several parts of the Institute represent strengths and capacity areas related to global health and sustainability efforts in addition to the climate change program. They include work on air pollution impacts and modeling, both indoor and outdoor, basic science research related to pulmonary physiology, research on health effects from changes in fate and transport of toxic chemicals, high-throughput screening of new chemical compounds, community-based research partnerships, and international collaborative research and outreach efforts.

Looking at future directions in the climate change and human health area, Dr. Balbus said that NIEHS grant-making is a major step toward building a community of climate health researchers, who will ultimately inform policy in the US and around the world. Interagency and international efforts will continue to help translate the science of health impacts of climate change. Interagency cooperative research efforts will continue to be examined to work toward filling knowledge gaps. Work will also continue with international partners to

integrate health science into sustainability summits, the very high-level policy discussions going on around the world.

Dr. LeMasters asked whether there was going to be another RFA in this area. Dr. Birnbaum said that the present RFA is a 3-year PAR (Program Announcement with a special review, and in this case set aside funding as well), with further opportunities for applications to be submitted. Dr. Collman added that through the partnerships and workshops Dr. Balbus had discussed, planning for future directions by NIEHS would continue. Also, the other NIH partners are being encouraged to plan and fund their own activities in the area, so that NIEHS is not the only source of funding.

Dr. Brody asked Dr. Balbus what he felt were "the big unanswered questions" in the area. He said there were many gaps, including "virtually all of the infectious diseases," particularly seasonal variability in water-borne diseases and food-borne diseases, vector-borne diseases, and emergent and novel infectious diseases. He said there is also huge gap in knowledge on the fate and transport of chemicals.

Dr. Brody noted that with the science of climate change, it seemed that there had been a need to "prove the same thing" repeatedly. She wondered whether NIEHS was going to need to do the same thing in terms of human health and climate change. Dr. Balbus said that if that happens, it would be more due to investigator interest and the orthodoxy of the NIH review process than anything political. He pointed out that much of the research in the area was more about climate variability, which is always present, than climate change per se.

Dr. Brody asked Dr. Balbus about the NIEHS agenda fitting with some of the larger sustainability issues such as fuel extraction and economic development. He answered that the focus is on providing science to inform policy, but outside of the political framework. Dr. Birnbaum added that NIEHS is beginning to look at how to assess the potential health impacts of fracking.

Dr. Schnoor wondered whether NIEHS has a leadership role in looking at climate change-related increases in pollen, mold and other allergens. Dr. Balbus said that is an understudied gap at this point. He said those topics would certainly fit within the purview of the current PAR, which could be tweaked accordingly for year 3.

Dr. Dearwent asked whether NIEHS would also consider oil sands. Dr. Birnbaum said that looking at other kinds of energy extraction was currently under discussion.

Dr. Dearwent asked what the cookstoves being replaced would be replaced with. Dr. Balbus replied that for the most part they would be replaced with improved biomass stoves. Dr. Birnbaum added that it was not a situation of "one stove fits all," that there are issues surrounding what is being burned, where it is being burned, and cultural issues.

XIII. "In Small Doses: Arsenic" (Dartmouth video)

Introducing the video from Dartmouth, Dr. William Suk noted to Council that the Superfund Research Program (SRP) requires translation of research findings to a larger community.

Many of the grantees do so in the form of producing videos, and at the last annual meeting up to 20 were shown. Dr. Suk chose to share the Dartmouth video designed to communicate why private well water tainted with arsenic is a health hazard.

Following the ten-minute video, Dr. Birnbaum noted that the problem with arsenic in well water is not restricted to New England, but is present in the American Southwest and in many other parts of the world.

Ms. Witherspoon praised the video, and hoped that other grantees would be encouraged to produce such works. Dr. Suk noted that each SRP grantee program has its own website, and that there are approximately 12-15 other videos available on those sites.

XIV. Concept Clearance: An Integrated, Multi-institute Plan to Facilitate Gene-Environment Interaction Studies

Dr. David Balshaw presented the concept clearance to Council on behalf of the GEI Signature Projects Development Committee.

As he explained, funding for the NIH Genes, Environment and Health Initiative (GEI) has come to an end. The concept being presented represents a series of initiatives designed to follow up on the work of the GEI—an integrated plan for next steps in enabling gene-environment studies. He noted that the plan is truly multi-institute, having been designed by a committee with representation from 10 NIH institutes, and that funding will not all be from NIEHS.

He reviewed the GEI, which began in 2005. The vision behind Phase I of the initiative arose from the premise that the vast majority of human disease emanates from some variation in both genes and environment, with individual risk determined by individual genetic makeup and individual environment. Implementation saw the development of two parallel programs—the Exposure Biology Program, which was intended to develop technology and biomarkers, and the Genetics Program, which was designed to identify genetic variants, focusing on genome-wide association studies (GWAS).

Dr. Balshaw said that although the programs had been "incredibly productive," they had largely moved in parallel, and that genes and environment had not been integrated as successfully as had been hoped for. He said the Exposure Biology Program had published 90 papers in the past year, including several high-visibility publications. However, he said, the real success of the program has been the development of new tools, such as devices with the ability to measure air levels of ultra-fine particles and hydrocarbons in real time. He mentioned that the recent grantees' annual meeting gathered 32 awardees who presented 53 posters, almost all of which were demonstrating new devices.

Dr. Balshaw said that "the reality is we're probably still not there to be able to propose a very large, globally based assessment of genetic variation and environmental variation at the individual level." With that in mind, he said, the time had come to return to the vision of the GEI by supporting initiatives for continued improvement of exposure assessment,

continued improvement of statistical methods, continued proof-of-principle studies, and enhanced ability to identify the mechanisms of interaction.

He pointed out that preparations for the next phase of the GEI had been in the works over the entire past four years of the program, including many sessions at relevant workshops and meetings, and internal planning retreats and working groups. He summarized several ongoing activities designed to continue the GEI's momentum, including two validation RFAs for testing new tools and biomarkers led by NIEHS. NIEHS also led a PAR for statistical methods and approaches to detect gene-environment interactions. The NHGRI issued administrative supplements to standardize measures used in its PhenX Toolkit, and NCI is leading a forthcoming program announcement supporting research on spatial uncertainty.

The proposed activities fall within three broad domains, each with its own set of initiatives:

- Continued development of tools for exposure biology
  - Validation and field testing of prototype tools and candidate markers
  - Integration of tools for multi-component analysis of exposure
  - Development of technologies for biomonitoring
- Proof of principle studies
  - Adding genomic information to "E" studies
  - Adding new environmental measures to "G" studies
  - Secondary analysis of existing GWAS data
- Functional analyses of candidate GxE interactions
  - Mechanistic underpinnings of GxE interactions
  - Consortia of existing studies on a focused environmental exposure

The continued development of tools for exposure biology involves refinement of technologies for characterization of the personal environment. The goal of the validation and field testing of prototypes element is to continue the program announced in 2010, to scale the new tools up and get them into epidemiological studies. This will be done by documenting the utility of the prototype or candidate biomarker in terms of validity, usability, and scientific value. The format will still require a partnership between the tool developers or biomarker discoverers and epidemiologists. In the solicitation, the language will be strengthened to clarify the goals of the program, and its design will be modified to allow more rigorous testing, addressing the question of value.

Integration of developed tools for multi-component analysis of exposure goes to the heart of the Exposure Biology concept, addressing the personal environment, which is comprised of chemical exposures, dietary intake, physical activity, psychosocial stress, and other elements. There were some small success in this area in Phase I of the GEI, but continued support of integration and "productization" of existing measures is required. These efforts will support both the academic and small business communities.

New tools for biomonitoring are in the works, including devices for multi-analyte detection, using *in vitro* diagnostics technologies to analyze small sample volumes of blood, saliva or urine, whether fresh or banked.

To present the second and third domains covered by the concept, Dr. Balshaw turned the podium over the Dr. Kim McAllister.

She said that one element of establishing proof of principle for gene-environment interplay is to leverage existing studies from both sides of Phase I of the GEI. Ultimately, the goal is to demonstrate the value of integrating the genetics and environmental factors for disease risk. She pointed out that most of the major, common, complex diseases (cancers, diabetes, heart disease, mental illnesses, etc.) are multi-factorial, with many genetic variants combining with many environmental exposures.

She described the initiative to conduct secondary analyses of GWAS data, looking for gene-environment interactions. It would leverage the considerable investment made in GWAS studies during Phase I of the GEI. Despite the successes of those studies (which focused on main effects) in identifying SNPs, much of the heritability of common complex diseases is still unaccounted for, suggesting that re-analysis looking for GxE interactions would be fruitful.

Dr. McAllister said that adding a genetic component ("G") to environmental studies ("E") could entail several different approaches, such as combining GWAS data with human population studies focused on exposure or environmental data collection, when there are shared phenotypic outcomes examined. Data from birth defects registries or cohorts could also be integrated with exposure data. Also, smaller environmental studies could be combined to generate sufficient power to conduct GWAS studies.

On the other hand, she noted, existing environmental data could be added to genomic studies, adding the "E" to "G". One aspect of this would involve adding environmental measures to ongoing GWAS or other large human population studies. It would require standardization of environmental exposure measurements and improvement of questionnaire data. In some cases, "E" data could be added retrospectively, such as GIS data. Also, epigenomic data reflecting the impacts of exposures could be overlaid onto human genomic data.

The third broad domain of the program will be to promote understanding the functional consequences of replicated genetic variants and the mechanism of interaction between genes and environment. This would follow up on a small part of the GEI Phase I genetics program, which looked at a small number of SNPs pulled from various GWAS studies. This initiative would take some of the SNPs found in Phase I and investigate them in model organisms including rodents, zebrafish, *c. elegans*, and yeast, among others. This would involve the development of improved functional assays and medium-throughput screens. The studies would be looking at functional elements in different genetic backgrounds and following different exposures, eventually taking the information into human populations. She mentioned that NIDA is particularly interested in this area, and will take the lead in this initiative.

She summarized by reiterating that the goal is to enable large-scale GxE studies by filling three major gaps:

- The need for improved measures of environmental exposure, moving beyond external point of contact to internal dose and from single factor to multi-component definition of environment
- The proof-of-principle that a comprehensive analysis of genetic variation and environmental exposure is feasible and provides insight into disease etiology and progression
- The investigation of the mechanistic underpinnings of the interaction between genetic and environmental information

She emphasized that NIEHS would not be taking the lead on many of the proposed initiatives, but will continue to work in concert with the other NIH ICs that were partners in GEI Phase I.

Dr. Lloyd was the first Council discussant. He acknowledged the magnitude of the challenge that had been presented by the concept, in that it is trying to capture an enormous problem in that at the outset (of the GEI) there had been little appreciation for how complex the issues would turn out to be. He appreciated the forthrightness and candor in the presentation in recognizing that the problems are large. He said there had clearly been much progress and outstanding science, but that a great deal of work remains to provide satisfactory answers to the major questions. He felt that the concept represented a long-term but extraordinarily worthwhile commitment by NIEHS, and that without NIEHS taking the lead, the effort would not take place. He wondered whether there were plans to involve 3-D organ systems as an intermediate, "third angle" from which to approach the problem. Overall, he said, the challenges are still quite significant, and the plan and diversification of funding responsibility have been well thought out. Despite the fact that it is not an inexpensive project, he felt that it is so integral and germane to the NIEHS mission that "it's something we can't possibly punt on." Dr. Balshaw agreed with Dr. Lloyd's idea to utilize 3-D modeling.

Dr. Lee, the second discussant, agreed with Dr. Lloyd that the concept is a very broad proposal encompassing the whole philosophy of environmental research. She felt that the next step still did not quite accomplish a true meeting of exposure and genetics. She wondered whether the NIEHS initiatives might be expanded further to come closer to achieving that integration. She thought that the newly developed tools in exposure biology might need to be more widely circulated among the genetics researchers, to further develop the necessary partnerships. Dr. Lloyd interjected that perhaps Dr. Lee's idea could be implemented through P30 Centers or Superfund Centers. Dr. Lee wondered whether there was enough information available in GWAS studies to allow meaningful secondary analyses. Dr. McAllister provided some examples of studies with environmental information included, in which secondary analyses had been performed. Given budgetary constraints, she added, the approach has been to look at getting investigators to add environmental epidemiology elements to existing studies, rather than attempting to establish new cohorts. She said the group is trying to convince GWAS investigators of the added value of including an environmental component, allowing the elevation of risk ratios. Dr. Balshaw added that the integration of the environmental side

was a subject "we've struggled with a lot." He said that success is more likely if efforts are focused, identifying the particular gap to be addressed.

Dr. Chesselet said there is a case to be made for a well-defined population in terms of environmental factors leading to higher power in genetics, and that it is important for NIEHS to convey that message to the other institutes and study sections. Dr. McAllister agreed, and said that was being pursued.

Dr. LeMasters described her experience in working on the development of a personal exposure monitor. It was an extensive process, she said, which started with just an idea and led to patented devices. She added that many of the prototypes developed under GEI are now ready for real-time application to measure and assess various environmental exposures.

Dr. Finnell asked Dr. McAllister about the effort to add "G" to "E," particularly the idea to incorporate information from the National Birth Defects Prevention Study. He said he had been involved with that study over the course of ten years, and that several GxE studies emanating from the project had been published. Dr. McAllister said there had been a meeting last year at which participants discussed next steps for the study, including the idea of the NIH funding further GxE studies. However, so far that funding has not been allocated.

Dr. Maddox asked Dr. McAllister if thought had been given as to how to engage the community in the early stages of the concept's initiatives, soliciting information from the affected communities and the investigators already working with those populations. Dr. McAllister said that a community involvement component had been considered, but had not been included in this particular proposal. However, she added, it makes sense for NIEHS to take the lead in such efforts due to its past record of pioneering community-based participatory research. Dr. Balshaw agreed that more efforts in that area should be undertaken in the future.

Dr. Brody said that although getting the "G" and the "E" together is a good goal, the "E" end has lagged behind, and there is much work to be done on the environmental side alone.

Dr. Collman said that there were two compelling points—that when the GEI was started, it was too ambitious to be accomplished in just four years, and that the current proposals probably represent a five-to-ten-year span of activities, spread out over time so that one builds upon the other, creating continued momentum. She said she saw it as the job of NIEHS to define the target and keep investigators, wherever they are, focused on the GxE and providing many different programs and vehicles for them to do so. She praised staff efforts in particular, and recognized their importance moving forward as well.

Dr. Collman called for a vote from Council on the concept. Dr. Lloyd moved to approve it, with Dr. Lee seconding. Council voted unanimously in favor of the proposal.

XV. Consideration of Grant Applications

This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 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).

XVI. Adjournment

Following the closed portion of the meeting, Dr. Birnbaum thanked Council for its efforts and officially adjourned the meeting.

The meeting was adjourned at 11:30 a.m. on May 20, 2011.

CERTIFICATION:

Linda S. Birnbaum, PhD, DABT, ATS
Chairperson
National Advisory Environmental
Health Sciences Council

Gwen W. Collman, PhD
Executive Secretary
National Advisory Environmental
Health Sciences Council

Attachment:
Council Roster