DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

MINUTES OF THE ONE HUNDRED FORTIETH MEETING OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

September 10-11, 2013

The National Advisory Environmental Health Sciences Council convened its one hundred fortieth regular meeting on September 10-11, 2013 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 September 10, 2013 from 8:30 a.m. to 3:30 p.m. and on September 11, 2013 from 10:15 a.m. to 3:15 p.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 September 10, 2013 from 3:45 p.m. to 5:00 p.m. and on September 11, 2013 from 8:30 a.m. to 10:00 a.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Council Members Present

Kim Boekelheide, MD, PhD
Kelley Brix, MD, MPH (*ex officio*) (by telephone)
Julia Brody, PhD
Marie-Francoise Chesselet, MD, PhD
Vivian Cheung, MD
Lisa Conti, DVM
David Eaton, PhD
Gary Ellison, PhD, MPH (*ex officio*, substituting for Dr. Winn)
Thomas Gasiewicz, PhD
Jesse Goodman, MD, MPH (*ex officio*)
Tomás Guilarte, PhD
Andrea Hricko, MPH
Howard Hu, MD. MPH, ScD
Norbert Kaminski, PhD
Randall Kramer, PhD
Mary M. Lee, MD
Yvonne Maddox, PhD (*ex-officio*)
Linda McCauley, PhD, RN
Thomas McKone, PhD
Jennifer Orme-Zavaleta, PhD (*ex-officio*)

Edward Postlethwait, PhD
Viola Waghiyi
Deborah Winn, PhD (*ex-officio*) (by video link, September 11)

NIEHS Staff

Joel Abramowitz, PhD
Kathy Ahlmark
Janice Allen, PhD
Beth Anderson
Bruce Androphy, JD
Joellen Austin
John Balbus, MD
Joe Balintfy
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Linda Birnbaum, PhD
Bernard Brown
John Bucher, PhD
Lisa Chadwick, PhD
Kelly Chandler
Jennifer Collins
Gwen Collman, PhD
Donald Cook, PhD
Yuxia Cui
Carolina Dilworth, PhD
Christina Drew, PhD
Dorothy Duke
Paul Ebohon
Benny Encarnacion
Symma Finn, PhD
Christine Flowers
Monica Frazier
Mary Gant
Ryan Gimple
Barbara Gittleman
Kimberly Gray, PhD
Astrid Haugen
Michelle Heacock, PhD
Jerry Heindel, PhD
John House, PhD
Michael Humble, PhD
Laurie Johnson
Helena Kennedy

Heather King, PhD
Annette Kirshner, PhD
Cindy Lawler, PhD
Chris Long
Claire Long
Robin Mackar
J. Patrick Mastin, PhD
Kim McAllister, PhD
Steven McCaw
Rose Anne McGee
Liz McNair
Mark Miller
Geoffrey Mueller, PhD
Sri Nadadur, PhD
Sheila Newton, PhD
Liam O'Fallon
Ted Outwater
Arun Pandiri, PhD
Jerry Phelps
Nicole Popovich
Devin Porter
Molly Puente
Leslie Reinlib, PhD
Elizabeth Ruben
John Schelp
Thad Schug, PhD
Bono Sen, PhD
Wynona Sessoms
Daniel Shaughnessy, PhD
Carol Shreffler, PhD
William A. Suk, PhD, MPH
Claudia Thompson, PhD
Sally Eckert-Tilotta, PhD
Frederick Tyson, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Darryl Zeldin, MD

Members of the Public Present

Phil Agee, Attain
Rich Cohn, SSS
Ernie Hood, Bridport Services
Kyathanahalli Janardhan, PhD, ILS
Carol Kelly, MDB

Grace LeMasters, PhD (former Council member)
Elizabeth Morn-Kensicki, Attain
Terry Wayne Pfeiler, Attain
James Ter Maat, SSS
Bill Wade, Attain

I. Call To Order and Opening Remarks

NIEHS Director of the Division of Extramural Training and Research (DERT) and Designated Federal Official Dr. Gwen Collman welcomed attendees and called the meeting to order. She asked all present in the room to introduce themselves, which they did. She noted that Council member Dr. Kelley Brix would be attending by telephone. She welcomed Dr. Gary Ellison from NCI, who substituted for Dr. Winn, who attended via video link on September 11. She welcomed *ex officio* Council member Dr. Jesse Goodman from FDA to his first Council meeting. She said that Council member Elizabeth Yampierre, J.D., was not present at the meeting.

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 May 2013 Meeting Minutes

Approval of the May 2013 minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Collman noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, DERT

DERT Director Dr. Gwen Collman updated Council on recent accomplishments and activities by DERT.

She reported that the reorganization of DERT she had described at the May 2013 Council meeting has been approved by NIH, has been announced officially to staff members, and will go into effect October 6. The Worker Education and Training, Program Analysis, Scientific Review and Grants Management branches will remain as they are, and four new branches will be created: a Genes, Environment and Health Branch (Cindy Lawler, Branch Chief), an Exposure, Response, and Technology Branch (David Balshaw, acting Branch Chief), a Population Health Branch (Claudia Thompson, Branch Chief), and a Hazardous Substances Research Branch (William Suk, Branch

Chief). These new branches will be composed of staff from the then existing branches. She also welcomed Dr. Alfonso Latoni, the new Chief of the Scientific Review Branch, who comes to NIEHS after five years as Deputy Chief of the Scientific Review Branch at the National Institute on Aging.

Dr. Collman described the recent re-engineering of the Human Subjects Inclusion process. The Planned and Cumulative Enrollment forms have been revised and updated, and the process has been streamlined to enhance efficiency.

Part of the ongoing DERT effort to align the research portfolio with the NIEHS Strategic Plan goals has been an initiative to code the portfolio according to how projects line up with the Strategic Plan (SP). Dr. Collman reported that Phase II of that activity has been completed, which included multi-project and training grants. More than 1800 main project grants have now been coded, allowing enhanced analysis and assessment of DERT investments as they relate to SP goals.

Dr. Gasiewicz asked Dr. Collman how the coding data would help make funding decisions in terms of distribution of future budgets. She noted that the first step was to establish a baseline to see how present distribution lines up with the SP, and using that to evaluate the path toward improved alignment with the SP in the future. She said that looking at the current distribution would help shed light on where the division has heavy or light investments, and would help identify gaps. A somewhat different set of issues is involved in making funding decisions, she noted, but the coding would help identify opportunities to align with the SP, in program development as well.

Dr. Eaton asked Dr. Collman to comment on current trends or directions in funding F31 individual fellowships and F32 postdocs versus institutional training grants. Dr. Collman said that both pools have been fairly stable. As a result of an NIH initiative, approximately 20 slots from T grants have been moved to fund pre-doctoral training grants. She noted that the F grants have been good to help postdocs explore emerging areas of science the institute wishes to encourage.

Regarding the revised enrollment forms, Dr. Hu said that he could not recall having seen any statistics emerge regarding enrollment in NIEHS-funded studies, and felt that it might be a missed opportunity to analyze the full spectrum of NIEHS studies. Dr. Collman noted that the data has been presented to Council, but over the years it has never been analyzed further. She offered to brainstorm with Dr. Hu regarding some ideas for how such analysis might be conducted.

Referring to Dr. Collman's data on subject matter distribution in the Phase II coding, Dr. Hu noted that there seemed to be very little attention to health economics research, which he said was potentially a very fruitful area. Dr. Collman agreed that from a grants perspective, that area has not been targeted by NIEHS. She said that that Strategic

Plan goal represents a very new area that we have not embarked upon in a significant way yet. She suggested that a workshop to discuss how to proceed in that area would be useful, and said that the hope is to develop more programs in that area during the five years of the SP.

Dr. Kaminski asked how content Dr. Collman is in general with the distribution over the various areas, and whether there are any other areas she might see as underfunded. She noted that over the past year there have been several new RFAs that align closely with SP goals, such as the microbiome initiative. She said that over time, it will be possible to fill in some of the details in terms of moving the areas of science being covered. Dr. Kaminski acknowledged that the goal is obviously not to have flat distribution across all of the SP goals, but was curious about the distribution in general. Dr. Collman said that at present, the portfolio generally appears to line up well with the major SP goals, particularly in terms of the fundamental EHS science and individual susceptibility, which comprise much of the work in the field at present. She suggested that exposure science will inevitably grow, as will combined exposures, social issues, and other emerging areas.

Dr. McCauley asked about whether NIH in general has a goal for the proportion of total training awards at each institute, versus research-focused awards. Dr. Collman replied that each year there is a training line in the budget, which has stayed fairly stable over the years, but that there is not a specifically mandated proportion. She noted that there is also much training going on under R01 grants. Dr. McCauley said it was a very discouraging time for training right now, with sequestration and other forms of diminishing funding, causing a "very concerning dynamic taking place in our academic setting."

Dr. Orme-Zavaleta asked whether any NIEHS grants are combined or coordinated with other funding organizations such as NSF or EPA. Dr. Collman cited several examples of such collaborations, including the Children's Environmental Health Centers program, which has been a joint program with EPA since 1998.

Dr. Gasiewicz asked whether data such as the coding information was presented to Washington, and if so, what comments they have. Dr. Collman said that the data has just been completed, and that she would hope that Dr. Birnbaum will wish to use it in her presentations to various Congressional committees, and to present it at the NIH level to different IC directors.

Referring to SP goal #10 on economic impact, Dr. Kramer noted that over the past decade there had been a great deal of collaboration between health economists and environmental health scientists, so if RFAs are developed in that area there would be strong proposals. Regarding that goal, Dr. Boekelheide questioned the inclusion of the

word "minimize" referring to economic impact in Dr. Collman's graphic, in that in many areas such as remediation, the goal is actually to maximize economic impact. She agreed that in future presentations the wording would be done more carefully.

Dr. Postlethwait asked about further analysis of training grants and return on investment. Dr. Collman said that there is a new system called CareerTrac designed to track trainees after they leave their training programs. Dr. Drew mentioned that NIH is also working to develop systems to track trainees as part of the Biomedical Workforce Initiative. Dr. Postlethwait asked whether there had been any analysis of NIEHS training efforts to determine whether there is undertraining or overtraining relative to available job slots in the marketplace. Dr. Collman replied that that type of analysis had not been undertaken, but that the Biomedical Workforce taskforce report contains considerable data about such questions.

Dr. Lee asked how R01s were treated in the portfolio coding analysis; whether they were given one major coding to an SP goal, or otherwise. Dr. Collman answered that every single grant in the portfolio has multiple codes – a primary code and secondary codes. She said that for simplicity, she had only shown the primary codes. Dr. Lee wondered whether the distribution would shift if the secondary codes had been included. Dr. Collman said such a graph had not been composed. She noted from several of the Council comments that the panel is encouraging further analysis of the data.

Responding to prior inquiries about training, Dr. Maddox noted that "essentially, training has been flat for many, many years."

V. TaRGET Program Update

Dr. Frederick Tyson briefed Council on the progress of the Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) I program. TaRGET I is the first of four planned phases of the epigenetics research initiative, which is specifically designed to encourage more research in the area of chromatin structure and transcriptional responses to the environment, aided by the rapid onset of new technologies such as next-gen sequencing, which he said has transformed epigenomics. It involves R01s from an RFA on transcriptional regulation, encompassing epigenetic processes and chromatin dynamics. Dr. Tyson noted that there had been 68 R01 applications, with 65 forwarded to peer review. Of those, 34 were scored while 31 were not discussed. The impact score for the reviewed proposals ranged from 17-54. Programmatic priority was given to applications that demonstrated potential to evaluate the impact of environmental toxicants on events that occur upstream of DNA methylation.

Dr. Tyson said that several high quality grants had been awarded to an impressive cadre of investigators. The studies will use state of the art technologies to explore several aspects of transcriptional regulation upstream of DNA methylation, resulting in state of the art analysis of chromatin biology with exposure contexts. He provided more details about three of the current grants being funded under the RFA.

Dr. Hu said that one of the challenges with human epidemiology in epigenetics is the issue of heterogeneity. He noted that there are huge gaps in knowledge as to how epigenetics could be used from a molecular epidemiology standpoint. He speculated that the National Human Genome Research Institute (NHGRI) might well be interested in the TaRGET Program Research. Dr. Tyson noted that NHGRI had the ENCODE program, although that was not looking at epigenetics in an exposure context. He also alluded to the Common Fund-supported Epigenomics Roadmap. Dr. Birnbaum added that the Epigenomics Roadmap is now its second phase, with many institutes involved, looking at different epigenomic marks.

VI. Report of the Director, NIEHS

Dr. Birnbaum updated Council on institute developments since the May 2013 Council meeting.

She outlined the current situation in terms of appropriations. She stated that the FY2014 budget requests from the President and the Senate "will not happen," nor will the House discussion that includes an 18% cut for NIH. She predicted that the government would continue to operate under more continuing resolutions (CRs).

She presented several data points on the highly positive impact of NIH research on health in the US and on the US economy, and went over information related to the impact of sequestration on NIH, including the fact that the NIH success rate fell to 17% in FY2012, and is expected to continue to decline as long as sequestration remains. This decrease in support has led to fewer RPGs being awarded, and to reduced ability to offer clinical trials to patients and the NIH Clinical Research Centers. She also presented data depicting the fact that there has been a more than 20% decrease in the buying power of NIH funding since 2003.

She shared data showing that the US (-5%) and Canada (-3%) have had declining investments in scientific research and development spending from 2012 to 2013, while China (+15%), Germany (+5%), Japan (+5%), and South Korea (+5%) have increased spending. This threatens US pre-eminence in biomedical research, she noted.

She described recent Congressional activities related to NIH. She predicted that there would not be a government shutdown over the debt ceiling and the effort to defund the Affordable Care Act. She expects a series of CRs, hoping that they will not be one- or

two-day or one-week CRs, but will be at least one or two months in duration as Congress continues to determine how to deal with the budget. She noted that if sequestration continues or expands, FY2014 would be "very, very bleak."

Dr. Birnbaum detailed several recent Congressional meetings she had taken part in, as well as Congressional events and recently introduced bills of interest.

Turning to science advances, she briefly summarized several recent publications by NIEHS/NTP personnel or grantees. One was an update on the CLARITY-BPA research program, a collaboration involving DERT, NTP and FDA scientists. As a new approach to synergize academic and guideline-compliant research, she said "We are very optimistic that this is a new paradigm for how certain kinds of research questions can be addressed."

She updated Council on several different initiatives related to health disparities and vulnerable populations, including recent major meetings at Duke University and at NIEHS.

Dr. Birnbaum introduced and welcomed Dr. Bernard Brown, the new NIEHS Chief Information Officer. She noted that the institute is still interested in hiring a Chief Scientific Information Officer, under the new Office of Scientific Information Management.

She detailed several recent meetings and events, including a community forum held in Detroit on June 18, and provided information about upcoming meetings of interest, including two Congressional briefings on women's cancers and the annual meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM).

She summarized several recent awards and recognitions given to NIEHS personnel and grantees, and related updates on NIH programs, including the Brain Research through Advancing Innovative Technologies (BRAIN) Initiative, the Big Data to Knowledge (BD2K) Centers of Excellence program, and new NIH requirements for individual development plans for trainees that will begin in October 2014.

Dr. Guilarte asked how NIEHS would be involved in the BRAIN Initiative. Dr. Birnbaum said that NIEHS is very interested in the neurosciences and would undoubtedly play some kind of role, focusing on the interaction between the developing or aging nervous system and the environment. She noted that the initiative will not be funded exclusively by government money, but by money donated by private foundations as well.

Referring to Dr. Birnbaum's slide addressing the value of NIH research, Dr. Eaton asked if the $3.2 trillion estimate of the economic benefit of increased longevity included the cost of health care involved with an aging population. Dr. Birnbaum said she did not

know, but that the focus should remain on prevention of major diseases, many of which have an environmental component. Dr. Birnbaum noted that NIH Director Dr. Collins has been doing "a superb job of getting the message out," having met with more than 200 Congress members recently to highlight the importance of biomedical research.

Dr. McCauley expressed concern about the disparate funding of research in the US and Canada compared to other countries. She felt that it would be useful to be provided with more specific data to be able to share with legislators. She said that the information should be "packaged like the moon race" to help the public understand the situation. Dr. Birnbaum noted that "there is no one in the halls of Congress who is opposed to funding biomedical research...the issue is that they are saying there just isn't enough money to fully go around."

Dr. Kaminski posed the possibility of capping indirect costs as a way to free up money for research. Dr. Birnbaum replied that she believes that idea is in legislation, and said that NIEHS would be happy to have lower indirect costs, but that it is not an element that can be controlled without a legislative fix. Dr. Collman said that the idea is being discussed at several different levels of government and academia.

VII. Council of Councils Report

By telephone, former Council member Dr. Grace LeMasters of the University of Cincinnati College of Medicine briefed the panel on her participation in the NIH Council of Councils (CoC), representing NIEHS. CoC members serve two-year terms, with Dr. LeMasters' term expiring in 2014.

For the benefit of the new Council members, she provided some background information about the CoC and how it functions. There are three meetings in Washington, DC per year, along with several conference calls as needed. Typically there is a mix of closed and open sessions at the in-person meetings, with Dr. Collins providing a 15-20 minute report, along with presentations by various other program directors. She said that the closed sessions are comprised mainly of early concurrences related to issues such as equipment requests, early independent awards, and roadmap projects. She described the two most recent CoC meetings, which included review of and voting upon Common Fund ideas, which are projects submitted by multiple ICs. When ideas are approved by the CoC, they go to Dr. Collins and his administrative team to be fleshed out, and the CoC rarely hears more about their fate.

Dr. Birnbaum mentioned that Common Fund proposals for 2015 are now being prepared, although there is not a great deal of money available. She said there were two initiatives from 2014 still to be considered: the three-dimensional structure of nucleosome architecture and characterizing the relationship between exercise and health. Ultimately, she pointed out, Dr. Collins makes the final decisions. Dr.

LeMasters noted that there currently seems to be considerable interest in rare diseases at the Director's level. Dr. Birnbaum pointed out that it would be within the CoC's purview to consider programs at the Office of Rare Diseases, which is within the Office of the Director.

Dr. LeMasters reported that the CoC has also worked on the issue of the use of chimpanzees in NIH research. A CoC working group established requirements and parameters in that area, and then reviewed all NIH grants and NIH sites to assess their compliance with those parameters. Dr. Birnbaum noted that ultimately about 300 chimpanzees will be retired to natural settings, but that Congress has capped the amount of money available to care for the chimpanzees. Dr. LeMasters agreed that that is a major problem.

VIII. Enhancing Reproducibility Initiative

NTP Associate Director John Bucher briefed Council on NIH-level activities related to the reproducibility of published research findings. The problem that has emerged is that there is a lack of reproducibility and transparency in published studies, with increasing concern that most research claims are in fact false. One study from Bayer HealthCare showed that almost two-thirds of 67 in-house projects did not replicate data published by others. There has also been insufficient reporting of methodological approaches in pre-clinical studies, and several challenges to the applicability of animal studies to humans.

Dr. Bucher reported that to address those issues, NIH has convened an ad hoc group that met to develop approaches to counter the problems. The group issued several recommendations for guiding principles to address the underlying issues, including:

- Encourage ICs to discuss the issue with Advisory Councils and BSCs and/or hold workshops to signal attention to the issue of reproducibility to stakeholder communities
- Collaborate further with scientific journals and the scientific community on efforts to improve rigor

He cited several examples of studies where reproducibility would not be possible. He detailed the value of systematic reviews in helping to address issues of transparency and evaluation of study quality.

He noted that study design and quality could be improved by applying systematic review concepts when designing studies, Standard Operating Procedures and/or full GLPs when performing studies, and reporting quality tools in writing manuscripts. He added that submissions to journals could someday be accompanied by a relatively standard,

web-based, publicly available and filled out data extraction form, which would simplify manuscript review and utilization of the findings for many purposes.

Dr. Hugh Tilson, Editor-in-Chief of *Environmental Health Perspectives*, co-moderated the discussion portion of the presentation.

Dr. Postlethwait said that in his experience with animal studies, a variety of elements such as suppliers, strains, housing, etc., make potentially substantial differences in outcomes. Also, he said that many journals are asking for less and less experimental information. These elements render it difficult or impossible to reproduce many experiments. Dr. Birnbaum cited the example of the inapplicability of studies of sepsis in mouse models to humans. Thus, she said, the question is whether the right model is being used to address the specific question. She felt that use of inappropriate models is one of the big problems with pre-clinical studies. Also, asking the right question is vital, she said. Those were among the issues being discussed at NIH, she added, along with the idea that there should be more training in experimental design for pre-clinical work.

Referring to the NTP/NCTR Bisphenol A studies Dr. Bucher had described, Dr. Chesselet discussed the issue of statistical power and multiple comparisons. She said that one solution to the problem would be to allow for a multitude of endpoints, with each one having the proper power of analysis, in exploratory studies, in order to guide replication studies.

Dr. Goodman observed that as more and more data are generated, the whole issue of analysis, with the proper analytic tools, becomes more important. He said that there should be a prospective plan for analysis, beyond just power calculations. That plan could acknowledge that multiple analyses are conducted, and therefore the results may not be conclusive and would need to be repeated. He said that too often scientists observe something in their experiments that they want to believe, and stop there and publish. He agreed that there is a lack of training in study design.

Dr. Eaton asked about the reproducibility issue in the context of animal diets. Dr. Birnbaum agreed that the composition of a diet can make a significant difference in outcomes, with totally different results coming from high-fat diets that more closely mirror human diets.

Dr. Cheung expressed concern about a prescription for how to determine sample size. Dr. Birnbaum said it was unlikely that there would be set programs, but that the issue is to ensure that investigators understand how to ask the question properly. She added that full, transparent reporting of methods and materials is also often lacking. She noted that journals want fewer and fewer words, and all of the information gets shifted to supplemental information, which many people never access.

Dr. Guilarte said that education of young scientists in these areas is important and would help alleviate some of the problems being discussed. Dr. Birnbaum said that NIH agrees, and that it is likely that in the future there will be training program requirements designed to address these issues.

Dr. Tilson added his introductory remarks to the discussion, noting that "as an editor-in-chief, the issue of reproducibility of data is really an important component of our job." He said that conversations at meetings of journal editors have started to focus on the credibility of journals and the credibility of the scientific method and process itself, with studies showing that much of the data published may not be reproducible. He noted that most of the editors he has talked with are very interested in developing processes to ensure the validity of data; processes such as checklists or guidelines. He referred to the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines checklist, which is comprised of 20 items and has been endorsed by 150 journals, although only two were environmental health or toxicology-related. He added the EHP will publish the guidelines soon and will encourage their use, although there are some deficiencies in the application of the guidelines to EHS, such as lack of attention to exposure scenarios or genetic research. He pointed out that journals such as EHP receive many papers related to human or *in vitro* research as well, and that additional guidelines or checklists are needed for submissions in those areas. He said that clearly it will take more than simply journal policy changes to deal with the issue of reproducibility; that it is a multi-faceted issue. Funding agencies, scientific societies, and academia all need to pitch in to address the issue. There is clearly a lack of training in proper journal submission and experimental design, he added, particularly in submissions from developing areas of the world.

Dr. Conti agreed that there is a deficit in the educational process. She asked whether there might be a movement in the future toward a mixed media approach to methods submission, such as the use of videos. Dr. Tilson said he felt that would be helpful, as would with additional information on methods in the bodies of papers. Word limits are an ongoing problem, with methods often going into supplemental materials, but such papers are sent back by EHP with instruction to put methods into the main section, with some leeway on word limit.

Dr. Hu pointed out that the issue of reproducibility and validity in animal studies has a counterpoint in human epidemiology studies. One approach to that problem has been the establishment of central data repositories where all methods are stored for later reference. He suggested that such an approach may be useful in EHS studies. Dr. Tilson felt that that was a good idea for animal and *in vitro* studies. He noted that accessibility of raw data is another problem.

Dr. Boekelheide noted that many journals now require a raw data dump into a repository, even though at times the underlying methodology that generated the data may be "squishy," raising questions about validity. Dr. Tilson said that there is little a journal like EHP could do about that problem on the back end, but perhaps much it could do on the front end.

Dr. Postlethwait posited an up-front gatekeeper in the NIH application process, with reviewers drilling down and determining whether the appropriate methods are being used to answer the research question at hand. Presently, he said, reviewers often have to simply take applicants' word that their methods are sound and appropriate. That is a string that runs all the way through journal publication. Dr. Tilson agreed that if funding agencies did their due diligence early, it would make the journals' jobs easier.

Dr. Birnbaum brought up the issue of biosketches, and asked whether there may be another way to approach them. She also discussed the issue of papers with many, many authors, and the issue of pressure to publish in one-word journals such as *Science* and *Nature*. She said these issues were also being discussed at NIH in the framework of reproducibility.

Dr. Goodman said the whole issue is critical to the credibility of science, but cautioned against thinking that education is the only solution. He felt that the problem is amenable to the use of checklists, as has been done in medical care. Dr. Birnbaum agreed.

IX. Children's Centers Update

NIEHS Scientific Program Administrator Kimberly Gray reported to Council about the Children's Centers for Environmental Health and Disease Prevention Research (Children's Centers, CEHC) program, which is celebrating its 15th year in existence.

She detailed the background of the joint NIEHS/EPA program's goals, establishment, milestones and funding rounds. Most recently, 2013 saw the funding of eight 5-year centers. Total funding of all of the centers to date has been $160 million.

Dr. Gray focused on several key scientific findings that have emerged from the CEHC program in areas such as obesity, air pollution, lead exposure, pesticide exposure, autism, and flame retardants exposure. She also described several key highlights from centers' community outreach efforts, which are a required element under Center funding. They included meetings, workshops, and community forums based on topics relevant to the centers' surrounding communities and stakeholders.

She reported on several notable successes by CEHC faculty members, including several prominent awards and recognitions.

She described the program's objectives and required components as contained in the most recent funding opportunity. She also shared highlights and a brief overview of each of the eight current centers.

Dr. Gray described communication and collaboration efforts, including a monthly EPA/NIEHS Children's Centers webinar series. A virtual forum on childhood obesity and the environment was held November 29, 2012. A similar forum on autism is tentatively scheduled for April, 2014. The next CEHC annual meeting will be October 29-30 in Washington, DC.

Dr. Hricko took note of the array of talented women involved in the Centers program, and suggested to Dr. Gray that her presentation should be given to women scientists groups across the country.

Dr. Birnbaum said that the Children's Centers are "pretty amazing." Dr. Gray noted that although she concentrated on the Centers program, much of the science is leveraged from other R01-supported research grants.

Dr. Birnbaum added that the program, which from its inception has been conducted in conjunction with EPA, is another good example of NIEHS working across the government.

X. Finding the molecular links between house dust and asthma

Newly tenured intramural scientist Dr. Donald Cook, who leads the Immunogenetics Group within the Laboratory of Respiratory Biology, described for Council his group's discoveries in characterizing the molecular links between house dust and asthma.

Asthma and its underlying allergic reactions are heterogeneous. Thus, not all asthmatics respond to the standard of care, inhaled corticosteroids. Allergic responses to specific environmental stimuli in the lung involve many different types of immune cells, including dendritic cells, airway epithelial cells, and various types of T cells, as well as inflammatory cells called neutrophils and eosinophils. An improved understanding of these cells and the signaling pathways they participate in offers the potential to develop improved therapeutic strategies that target specific types of asthma, including steroid-resistant asthma.

Allergic sensitization, which is the biological basis for allergic asthma, is caused by both allergens themselves such as plants, insects, and animals, and by adjuvants such as air pollution and microbial products – ingredients that exacerbate the immune response similar to how a catalyst triggers a chemical reaction.

House dust, Dr. Cook noted, contains several adjuvants, including dead bacteria and their products, which are particularly efficient adjuvants. The research honed in on one

particular bacterial product called flagellin, which turned out to be especially potent in inducing allergic responses that bring eosinophils to the airways. The researchers found that asthmatics had considerably higher titers of anti-flagellin antibodies than did controls with healthy airways, a finding consistent with the hypothesis that exposure to environmental flagellin predisposes a person to development of allergic asthma.

Further exploring the cellular and molecular mechanisms that give rise to flagellin signaling and hence to allergic sensitization, the team identified a signaling molecule called Myd88 that appears to play a key role in the process, working in conjunction with toll-like receptors in both epithelial and dendritic cells in the lung. That role varies according to cell type, however. It is complicated by the fact that there appears to be cross-talk between epithelial cells and dendritic cells, so Myd88 functions differently in the different cells.

Dr. Cook also explained that apparently there are two different arms of the immune response involved in the different types of allergic asthma, involving the T helper cells Th2 and Th17. This helps to explain some of the heterogeneity seen in asthma, and may offer opportunities for new therapeutic strategies that could prevent or reverse the molecular course of events that gives rise to asthma.

Dr. Postlethwait asked Dr. Cook for his opinion on a paradox he had observed - that oxidant gases such as ozone can activate dendritic cells, but infant primate model animals exposed to ozone as infants display eosinophilic inflammation, unlike the mouse or adult human, who get neutrophilic inflammation. Dr. Cook said that it appears that two specific types of dendritic cells, acting synergistically, work better at T cell differentiation than any one single type. He also cited evidence that as one ages, the migratory capacity of dendritic cells changes, and that the ratio of these different types of dendritic cells is different in the newborn than in the adult.

Dr. Hu asked how Dr. Cook would relate his work to the hygiene hypothesis, which alleges that exposure to certain microbes early in life will actually desensitize an individual. He further inquired whether there may be interaction between viral infections and certain types of dendritic cells. Dr. Cook said that the hygiene hypothesis may be related to the impact of regulatory T cells. He added that clearly viral infections are an exacerbating factor in asthma, but that he did not know whether such infections change the number or type of dendritic cells.

Dr. Maddox mentioned that she would like to reproduce Dr. Cook's results, which clearly rely on the quality of house dust samples. She asked how his lab looks at the quality of the flagellin in the samples. Dr. Cook described where the flagellin-containing samples had come from – inner city homes in the Raleigh area. Those samples also contained more cockroaches than samples from other areas.

Dr. Cheung commented that next-gen sequencing might be of value to characterize the house dust samples. She asked whether Dr. Cook's results align with GWAS results in asthma. He replied that that is one of the reasons he is looking at IL-33 as a candidate gene for asthma – it had emerged as one of the candidate genes identified by a large GWAS study.

Dr. Conti suggested that working with feline veterinarians might help inform Dr. Cook's work, in terms of cats being a model with similar pathways of allergenicity. Dr. Cook said it was an interesting idea.

Dr. Goodman asked whether in these models a sensitizer like house dust or flagellin sensitizes to itself. Dr. Cook replied that that type of cross-reactivity does appear to happen, noting that flagellin itself if not an allergen, but an adjuvant. Dr. Goodman suggested that it might be interesting for Dr. Cook to collaborate with someone conducting experiments related to the indoor microbiome.

Dr. Brody was curious about the dust in terms of its composition. Dr. Cook explained the methods his team employs to make house dust extract, which is a complex mixture. He said that is a disadvantage, but the advantage is that it is truly environmental.

XI. Adjourn Open Session

The September 10 open session portion of the meeting adjourned at 3:30 pm.

XII. Consideration of Grant Applications

This portion of the meeting (3:45 pm – 5:00 pm, September 10, 2013) 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).

XIII. Adjourn for the day

The meeting adjourned for the day at 5:00 pm.

XIV. Consideration of Grant Applications (continued)

This portion of the meeting (8:30 – 10:00 am, September 11, 2013) 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).

XV. Discussions on Council Operations

Council *ex officio* member Dr. Deborah Winn joined the proceedings via video link.

The balance of the Day Two activities was comprised of a general discussion among Council members and NIEHS/NTP officials that was billed as a "Council Retreat." Following introductory remarks by Dr. Birnbaum related to the goals of the meeting and the NAEHSC charter, the session was split into three sections, each focusing on a specific question (and sub-questions) posed beforehand to Council members. They were:

1. Is NIEHS getting what they need from Council? (Lisa Conti, discussion leader)

- Group discussion of council meeting operations and logistics
- NIEHS staff presentations to Council
- Scientific lectures
- Closed session
- Open discussions
- Topics of interest to Council members

2. How can Council engage in the implementation of the NIEHS Strategic Plan? (Julia Brody, discussion leader)

- How have Council members promoted the Strategic Plan to date?
- Are there other ways for Council to help?
- What does success look like? How can we measure our success?

3. Council input on strategies for funding the best quality science in the current fiscal reality. (Howard Hu, discussion leader)

- Maintaining impact in an "Age of Anxiety"
- Balance of solicited vs. unsolicited grants
- Cuts to grants
- Non-RPG portfolio
- How to prioritize science
- How to use portfolio evaluations to make priority decisions

To lay the groundwork for the discussion, Dr. Birnbaum first read from the NAEHSC charter: "This body is charged with advising, assisting, consulting with, and making recommendations to [me] on matters related to the activities carried out and by and through our policies about the activities." She noted that it is a broad and not very restrictive mandate.

She noted that she has made it a point during her directorship to present information to Council about all parts of the Institute, asking for feedback and new directions in many areas, not just the extramural program. She discussed the importance of the other advisory boards that provide her with insight, including the Board of Scientific

Counselors (BSC) and the NTP BSC. To ensure that Council is aware of all parts of NIEHS, she asked all of the Institute's senior leadership to participate in the discussion. She thanked Council for putting forward the idea of conducting the discussion session, and said she looked forward to hearing Council's comments, criticisms, and ideas about good ways to work together productively.

During the first discussion session led by Dr. Conti, it was brought up that at times it seems that some of the most important Council conversations never actually get back to NIEHS; that there should be a mechanism or process by which the "parking lot conversations" where many ideas are spawned are communicated to NIEHS. There was also an impression that much time is spent listening in Council meetings, with precious face-to-face time being taken up by passive receipt of information by Council members. The suggestion was that much of that material could be read and absorbed by Council members ahead of time, leaving more time for valuable Council input to be formulated and communicated, with a less formal agenda leaving more time for discussion. The scientific talks and some of the reports could be expendable, for example, creating more time for discussion of new developments and emerging technologies. It was also suggested that the materials provided before meetings include clear delineations of what is being asked of Council in any given area; key questions rather than just blanket information.

Along the same line, it was suggested that there should be more effort to solicit programmatic input and direction from Council, beyond efforts to simply inform, taking more advantage of the diversity of expertise offered by Council members.

NIEHS leadership agreed that their primary need from Council is robust discussion, comments and suggestions. It was felt that the updates provided should be followed by more questions and discussion points.

One Council member suggested the idea of focusing on one key program area (or proposed concept) during each meeting, with specific questions for Council to address, and with background materials such as slides provided in advance to allow preparation. Council members agreed that seeing slides and having specific questions in advance would be useful, and would perhaps cut down on the length of presentations during the meetings and would facilitate "question-driven discussions."

Council members also discussed at length the issue of inadequate follow-up from robust discussions and critical votes at Council meetings – there is much curiosity about what happens to ideas and suggestions. Closing the circle would be valuable, it was felt.

There was much discussion about the idea of NIEHS expanding partnerships, particularly to include foundations such as the Bill and Melinda Gates Foundation, to help identify and leverage new resources in this resource-constrained environment. It

was suggested that the Global Burden of Disease report that appeared in December, 2012 in *The Lancet* would be a good source to link with foundations and to drive environmental health research opportunities via partnerships.

The impression emerged that there should be more advocacy from Council, with less of a passive role and more input in the hard decisions facing NIEHS. One way to do so would be to form subcommittees teaming Council members and staff members to focus on specific policies, it was suggested.

Regarding closed sessions, Council was concerned about so many grant applications being discussed with few Council members present due to conflict of interest recusals. The idea was proposed that there should be a mechanism by which the entire Council could participate in programmatic discussions separated from discussions of individual grants. Dr. Collman noted that there were no conflicts at the concept stage, and that it is a critical element in collecting treasured Council feedback, as is post-award discussion, when programs' progress is updated to Council. Council discussed the issue of conflicts of interest at length, with the suggestion posed that perhaps there might be an intermediate state in which a conflict could be disclosed but the individual could still participate in initial discussions, while being recused for final discussion and voting. It was noted that there are complex, deep delineations of conflicts facing Council members, which occasionally can be waived, but must be adhered to.

In the second discussion session led by Dr. Brody, Council members focused on how the body can help implement the NIEHS Strategic Plan (SP). Introducing the session, Dr. Brody noted that many of the routine functions and actions of the Council work to help promote the SP, and that Council members could all do things at their home institutions or the wider world beyond Council meetings to assist in aiding the success of the SP. "We should think seriously about whether we as a Council have some outward-facing responsibilities that could help in various ways," she said, noting that all Council members have their own constituencies where they wield influence, with numerous opportunities to discuss and promote elements of the SP.

The suggestion was made that NIEHS should make sure that SP topics are on the agenda at scientific conferences and similar events, with there being many such opportunities, including commentaries and editorials. Council members noted that NIEHS has gotten into new areas (e.g., health disparities and global health) as evidenced by the elements of the SP despite the tight budgetary times, presenting challenges for prioritization. One approach might be to work with funding sources outside the US to help support some of the new areas being pursued. Dr. Birnbaum mentioned that there are several initiatives underway to pursue those opportunities.

The question was raised about activities that may fall outside the SP, and how resources may be shifted as a result. Dr. Birnbaum said that those questions are under active consideration, noting that NTP as a multi-agency program has some responsibilities that go beyond the NIEHS SP (e.g., research on herbals).

There was also considerable discussion about how NIEHS plans to prioritize according to the elements that do fall within the SP, particularly in the face of diminishing resources – will resources be targeted to specific areas, or are across-the-board cuts being contemplated? Dr. Birnbaum responded that Council input on those questions is desired, but that generally the focus is on the cross-cutting SP themes, which are "absolutely essential," as well as the eight identified areas of multi-divisional interest. Dr. Zeldin noted that in DIR, the focus is on depth vs. breadth. The panelists also discussed the question of which areas may be deemed less important as science marches on and priorities inevitably shift. Dr. Birnbaum and Dr. Collman asked Council members to consider those questions and provide their input back to NIEHS leadership as part of the ongoing process of implementing the SP and identifying criteria for those decisions.

Although it may appear that the resources devoted to the SP goals are out of balance, it was noted that all of the goals are cross-cutting, and that it is necessary to assess that balance beyond just the assignment of R01s. It was suggested that the assessment of the resources devoted to the SP goals be broken down into endpoints to help see how the institute is changing over time. Dr. Birnbaum emphasized the need to look at the entire institution to fairly judge its priorities and resource expenditures, particularly since there is such a broad charge to NIEHS, unlike the other, more disease-focused ICs. Dr. Zeldin added that it is important to take into account the concept that the institute (especially DIR) must be willing to support high-risk, high-reward research. Council members were particularly concerned that high-risk, high-reward, transformative research should continue to be encouraged and developed, and discussed several potential models for doing so.

Dr. Hu moderated the third discussion session, devoted to strategies for funding the best quality science in an age of dwindling fiscal resources. In his introductory remarks, he noted that the discussion would focus on three areas: ideas that can be executed now, bigger process considerations such as entire NIH policy, and bigger ideas that transcend the first two areas, all within the current constraints. He said that one idea that had been floated in prior discussion among Council members was to randomly select grants that fall within the fifth and fifteenth percentiles. Also, it was suggested that investigators whose grants had been denied might be offered the option of converting their R01s to R03s. Another thought was to subject existing programs to "stress tests" to ensure their ongoing viability and importance per the NIEHS mission. Also, there was a concept that there should be more nimbleness in training grants. Dr.

Hu reported that there had been a "spirited discussion" of the issue of indirect costs. One idea along those lines was to let particular institutions serve as "core centers" to offer specific resources to other centers, such as bioinformatics, in order to provide efficiencies and eliminate redundancies. Other Council members agreed that that concept would be one way to leverage resources in these tight budgetary times. There was also a suggestion that there should be more sharing of animal tissues among investigators, which would also facilitate reproducibility.

Council members discussed at length the concept of random selection of high-scoring grants. They generally agreed that the upper 5% should be automatically funded, but had widely varying opinions regarding random selection beyond that. Some members felt that funding of grants in the 5%-20% range should be fit to institute priorities, while others felt that that would be a dangerous concept, since it is important to applicants to know up front what is expected or sought. Dr. Collman said that applications in the "gray zone" from 15-35% might be looked at by Council to help prioritize them in terms of high vs. low program priorities, in an advisory capacity, and that in fact the whole concept of a gray zone may be outmoded and could be replaced by a priority-based process. Dr. Hu noted that such a process would need to be transparent and forward-shifted so that applicants would be aware of the priorities up front. It was pointed out that random selection could lead to clustering and the loss of ability to focus on priorities. At the same time, focusing on priorities could lead to the process becoming more like RFAs and could potentially stifle innovation.

The suggestion arose that a second level of review/assessment be considered, focusing on the concept of innovation. Dr. Brody pointed out that the Department of Defense has two levels of review, a process she felt works very poorly. Dr. Birnbaum said that innovation is one of the criteria used in the existing review process, which is generally broad. She opposed the idea of random selection, but added that NIH is considering other models and options for the grant review process.

There was discussion regarding the amount of time investigators spend writing grant applications. Dr. Birnbaum noted that most NIH grantees have less than two funded grants per PI, and that most PI's grants come from a variety of funding sources. There is always pressure for funding at the academic level as careers are starting or tenure is being sought. Dr. Collman floated the idea that since the top universities get up to 80% of NIH grants, perhaps they should receive block grants, to take the competition out of the hands of NIH and put it at the local level. Council members were generally opposed to the concept, in part because it would circumvent the peer review process. Dr. Hu noted that the Canadian system requires collaboration in all grants programs, "spreading the pot even as the entire pot shrinks a bit."

The utility of various funding mechanisms was discussed in the context of tight budgetary times, including the SBIR and consortia, which are seen as a way to keep people working together in specific, focused areas. They are rich opportunities for building collaborations and increasing the output of the program, Dr. Collman observed, although they require more expenditure of time by investigators and NIEHS staff alike.

Council discussed the issue of solicited vs. unsolicited grants. The question was raised as to whether there is a way for the institute to evaluate the relative value of RFA vs. investigator-initiated grants. There is better control of the review process with RFAs due to in-house SEP review, it was noted. Dr. Birnbaum mentioned that the institute pays for in-house panels, which can represent substantial expense as opposed to the more minimal payments required to support CSR reviews. Dr. Postlethwait noted that there is implicit bias in study sections, making it difficult for worthy studies to be reviewed positively in same cases. Dr. Kaminski said that both funding methods are important, because they result in a diversity of grants. Moving to a more RFA-oriented approach would drive much of the research direction, which may not be the best scenario, he added. Dr. Birnbaum observed that the issue of study section bias is being looked at within NIH, and Dr. Collman noted that CSR has been receptive to researching the issue and taking steps to ameliorate the situation. She also said that the mix of solicited vs. unsolicited grants is changing due to budgetary pressures, with less funding going to RFAs as the budget tightens. She asked Council for its input on that trend going forward.

Dr. Birnbaum thanked Council for a stimulating and valuable discussion session, and proposed that it should potentially become a regular feature of Council meetings in the future. She said it would help to "complete the circle" in terms of Council being more consistently updated on the progress of various topics it has previously considered.

XVI. Adjournment

The meeting was officially adjourned at 3:15 pm on September 11, 2013.

CERTIFICATION:

/s/

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

/s/

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

Attachment:
Council Roster