

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 122nd Meeting

NATIONAL ADVISORY COUNCIL ON AGING

May 20–21, 2014

**National Institutes of Health
Building 45, P2 Level, Conference Room E1/E2
Bethesda, MD 20892**

CONTENTS

I.	REVIEW OF APPLICATIONS.....	4
II.	CALL TO ORDER.....	4
III.	REPORT: Task Force on Minority Aging Research	6
IV.	REPORT: Working Group on Program	7
V.	COUNCIL SPEAKER: Strategies for Expanding Scientific Workforce Diversity	9
VI.	PROGRAM HIGHLIGHTS	12
VII.	ADJOURNMENT	17
VIII.	CERTIFICATION	17

Attachment A: Roster of the National Advisory Council on Aging

Attachment B: Director’s Status Report to Council

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging

**NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
May 20–21, 2014**

The 122nd meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, May 20, 2014, at 3 p.m. in Building 45, Conference Room E1/E2, National Institutes of Health (NIH), Bethesda, MD. Richard J. Hodes, M.D., director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92–463, the meeting was closed to the public on Tuesday, May 20, from 3 to 5 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Public Law 92–463.¹ The meeting was open to the public on Wednesday, May 21, from 8 a.m. to 12:45 p.m.

Council Participants:

Dr. Kimberly Acquaviva
Dr. Norman Anderson
Dr. Laura Carstensen²
Dr. Ana M. Cuervo
Jennie C. Hansen²
Dr. Kevin P. High
Dr. Bradley T. Hyman
Dr. Richard Mayeux
Dr. Richard Morimoto
Dr. Charles P. Mouton
Dr. Eliseo Perez-Stable
Dr. Thomas A. Rando
Dr. Jonathan Skinner²
Dr. Reisa A. Sperling
Dr. Debra Bailey Whitman²

Absent Council Participants:

Dr. Steven R. Cummings

¹ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applied to applications that were discussed individually, not to “en bloc” actions.

² Drs. Carstensen, Hansen, Skinner, and Whitman were present on Tuesday, May 20, 2014, but not at the open session on Wednesday, May 21, 2014.

Ex Officio Participants:

Dr. Richard M. Allman, Veterans Health Administration
Dr. Jane Tilly, Administration for Community Living, Department of Health and Human Services

Absent Ex Officio Participants:

Dr. Kenneth G. Pugh, National Naval Medical Center
Edwin Walker, Administration on Aging

The Council Roster, which gives titles, affiliations, and terms of appointment, is appended to these minutes as attachment A.

In Addition to NIA Staff, Other Federal Employees Present:

Ms. Amy Mistretta, Office of Research on Women's Health
Dr. Raya Mandler, Centers for Scientific Review, NIH
Dr. Hannah Valantine, Scientific Workforce Diversity, NIH

Members of the Public Present:

Mr. James Appleby, Gerontological Society of America
Ms. Cynthia Bens, Alliance for Aging Research
Dr. J. Taylor Harden, Gerontological Society of America
Dr. Hadine Joffe, Harvard Medical School and Dana Farber Cancer Institute
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Frances McFarland Horne, Rose Li and Associates, Inc.
Dr. Brent W. Roberts, University of Illinois, Urbana-Champaign
Dr. Norman E. Sharpless, UNC Lineberger Comprehensive Cancer Center

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).³

A total of **1,419** applications requesting **\$590,535,177** for all years underwent initial review. The Council recommended **802** awards for a total of **\$387,535,698** for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

Dr. Hodes welcomed members to the open session of the 122nd NACA meeting and called the meeting to order at 8 a.m. on Wednesday, May 21, 2014.

³ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to "en bloc" actions.

A. Director's Status Report

Dr. Hodes reported that the FY 2014 appropriations legislation passed by Congress includes an overall increase of \$1 billion above the post-sequester funding level of FY 2013 for the NIH. This represents a partial restoration to pre-sequester levels. NIA has received a 12% increase, or \$130 million, including \$100 million to support an increased focus on Alzheimer's Disease (AD) research. This increase brings the NIA budget close to what it was in FY 2012. Dr. Hodes considered this to be good news but he also reminded the Council that the President's proposed budget for FY 2015 represents a drop in constant dollars, or real purchasing power, to a historical low.

The distribution of the NIA budget remains the same as it was in 2013, with about two-thirds going to research project grants. Likewise, the paylines publicized by NIA are the same as they were in 2013. However, for FY 2014, NIA is able to achieve these paylines without substantially cutting commitments in non-competing grants. Thus non-competing awards will receive their pre-sequester commitment in FY 2014 non-competing awards.

Aging research continues to be of interest to Congress, as illustrated in hearings on AD and on the Accelerated Medicines Partnership in which NIA participates. Francis Collins, Ph.D., NIH director, also has discussed NIA-supported research on his blog. Dr. Hodes reported on several other events that have occurred since the last Council meeting:

- Applications responding to a request for applications (RFA) on falls prevention are being considered for funding. This RFA represents collaboration between NIA and the Patient Centered Outcomes Research Institute (PCORI), with \$30 million in funding provided by PCORI. An announcement of awards is expected soon.
- Several new RFAs and program announcements (PAs) for AD research initiatives, including basic studies in human cell reprogramming and neural systems, continuation of genome sequencing efforts, and planning grants for AD Translational Centers for Predictive Drug Development.
- Newly-funded clinical trials on dominantly inherited AD, AD prevention, and anti-amyloid treatment.

Dr. Hodes also provided a sample of research findings supported by NIA. One study reported that the effects of a low-protein diet on overall cancer or diabetes associated mortality vary by age. In humans and in rodent models low protein reduced mortality at younger ages but not at older ages. The Healthy Aging in Neighborhoods of Diversity across the Life Span study has demonstrated that well-known lower total vitamin D levels in African Americans misrepresent bioavailable vitamin D in these individuals. The study found no difference in bioavailable vitamin D between African Americans and European Americans. The study was able to attribute the difference in total Vitamin D to differences in Vitamin D binding protein which were largely (79%) associated with genetic polymorphisms. Another study on nudging, or the use of environmental cues to influence behavior, has demonstrated that simply adding a poster-sized pre-

commitment letter to examination rooms reduces the inappropriate use of antibiotics. Other studies have found that circulating factors in younger animals promote rejuvenation in older animals and have isolated a protein (GDF-11) present in young but not old animals, that recapitulates the effect of youthful circulating blood. Work in the Intramural Research Program on the DNA repair disorder xeroderma pigmentosum has revealed previously unknown connections between DNA repair and mitochondrial function

Dr. Hodes reminded the Council that NIH has changed its resubmission policy such that new applications can be submitted after an unsuccessful A1, without any requirement that that application be substantially different. NIA is waiting to see how this change will affect the number of applications. In addition, the NIH Geroscience Interest Group continues to move forward with post-Summit activities and another summit is planned for February 2015. Dr. Hodes closed by thanking Linda Harootyan for her service as chair of Friends of the NIA.

B. Future Meeting Dates

Sept. 16–17, 2014 (Tuesday and Wednesday, Natcher Building)
Jan. 27–28, 2015 (Tuesday and Wednesday, Natcher Building)
May 12–13, 2015 (Tuesday and Wednesday, Natcher Building)
Sept. 16–17 2015 (Tuesday and Wednesday, Building 31)

C. Consideration of Minutes of the Last Meeting

The minutes of the February 2014 meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Eliseo Perez-Stable, M.D., reported that the Task Force focused on three topics during the previous day. The first was a presentation by Angela Bates, of the NIH Office of Research on Women's Health, on NIH policies for inclusion of women and minorities. This presentation allowed the Task Force an opportunity to review policies and how NIH and NIA use inclusion reports. Dr. Perez-Stable reminded the Council that the current reporting system includes both U.S. - and non-U.S.-based studies and those large studies, for example in East Asia, can skew the numbers. In her presentation, Bates noted that a new inclusion management system will roll out in Fall 2014. This system will change how study participation is reported and allow investigators to input data directly. At present, the system will include data on race/ethnicity and gender, but other elements, such as socioeconomic status, could be added at a later date.

The second topic involved a presentation, given by Kimberly Johnson, M.D., an associate professor at Duke University, on African Americans' use of hospice services. Traditionally, use among African American individuals has been lower than that among white individuals. This gap persists and is even growing, even though the number of African American individuals using hospice has almost tripled. Dr. Johnson's presentation provided a framework of potential causes for this gap, including less

knowledge and more unfavorable beliefs. Dr. Johnson is now focusing on systems and ways to involve organizations in interventions to overcome some barriers.

The third topic focused on a health disparities research framework, which was recommended in a review of NIA's portfolio on disparities and diversity. The framework is still in draft form and will be circulated at some point. Richard Morimoto, Ph.D., suggested that the draft be sent to directors at Resource Centers for Minority Aging Research (RCMARs), AD Research Centers (ADRCs), and other NIA-supported centers.

Dr. Perez-Stable also reported that NIA has received more than 200 applications to the 2014 Butler-Williams Scholars Program. These applications are under review. Dr. Perez-Stable also noted that the RCMAR program held its annual meeting on March 31, 2014. A meeting between RCMAR investigators and ADRC investigators is planned for November at the annual Gerontological Society of America conference. A possible joint meeting with the Pepper Centers program is under discussion.

Robin Barr, D.Phil., added that the new inclusion reporting system is tied to the Form C application that was introduced in September 2013 and that applications submitted since October 2013 will be compatible with the new system. He noted that data, which were presented previously as PDFs, will be easier to manipulate. Thus Research Condition and Disease Categorization terms can be added, Institutes and Centers (ICs) can identify clinical or survey research studies, and investigators can create more useful tables for meaningful questions. In the long term, investigators might be able to pool populations for analyses across studies.

In response to questions about adding age groups to the new reporting system, Dr. Barr noted that Bates had raised the same point during her presentation. However, he also pointed out that the 1995 legislation requiring inclusion reporting only specified gender and race and ethnicity. Thus NIH cannot require investigators to report data by other categories. Marie Bernard, M.D., deputy director of NIA, also commented that looking at age categories alone does not capture everything, for example comorbidities, in which NIA might be interested. Richard Allman, M.D., noted that NIH needs to know what proportion of study participants are older than 65 years, or even older than 75 years, because this is the fastest growing population. He and Dr. Perez-Stable pointed out that NIH expects applications to include many items that are not mandated by law.

IV. REPORT: WORKING GROUP ON PROGRAM

The Working Group on Program considered five concept clearances and one program project grant renewal.

A. RFA Concept Clearances

Sarcopenia Phase II: Validation of Criteria for Clinically Relevant Muscle Weakness and Low Lean Mass in Older Adults with Substantial Physical Limitation

This RFA aims to fund additional work to support the utility of measures for muscle mass and muscle weakness. Existing definitions for cut points were derived from studies in younger populations and set arbitrarily at two standard deviations below the mean. These cut points were not examined in studies on older adults or diverse populations. Whereas a previous concept proposal sought to support validation studies, the current revised proposal seeks to clarify markers for stratification in study participant selection, with the goal of preparing a receiver operating characteristic curve to look at performance, sensitivity, and specificity at different cut points. The Working Group recommended that this concept be approved by Council. The motion to approve the revised concept for the Sarcopenia Phase II study was approved unanimously.

DN Translational Concept Clearance

This RFA concept seeks to fund two AD Translation Centers for Predictive Drug Development. These centers will employ an integrated approach including genomics, proteomics, structural biology, mathematical modeling, and cellular and animal models to move beyond the current state of knowledge in drug discovery. All the compounds discovered through the existing state of knowledge have failed in further development. In presenting this proposal, NIA staff highlighted reasons for failures, including incorrect pathophysiological mechanisms, drugs that do not engage intended targets, intervention at incorrect stages, lack of translatable pharmacodynamic models, and poor predictive power of models in preclinical efficacy studies. The Working Group expressed great enthusiasm for the proposed Centers and recommended that Council approve it. The concept for Centers for Predictive Drug Development for Alzheimer's Disease was unanimously approved by Council.

Biomarkers of AD in Down Syndrome

This RFA concept aims to support studies to obtain biomarkers in this population. Triplication of chromosome 21 affects amyloid precursor protein and individuals with Down Syndrome develop AD pathology beginning in their 30s. Studies supported by this RFA will collect existing biomarkers that have been collected in other populations and include cognitive measures to link these biomarkers with cognitive changes. The Working Group noted that this RFA will serve as an extraordinary opportunity to collaborate with the Eunice Kennedy Shriver National Institute of Child Health and Human Development and with the National Institute of Neurological Diseases and Stroke. The RFA also complements existing NIA-supported efforts in autosomal dominant disease. The Working Group recommended that Council approve the concept. Council approved the concept for an initiative to identify biomarkers of Alzheimer's Disease in Down Syndrome unanimously.

Interdisciplinary Research to Understand the Vascular Etiology of AD and Related Dementias

Evidence of the interplay between vascular disease and AD has been observed in several cohorts, but the mechanisms underlying this interplay are not known. This RFA will support studies exploring such mechanisms. The Working Group agreed that this is an important aspect of study and recommended that the concept be approved. Council approved the initiative on the vascular etiology of Alzheimer's Disease and related dementias unanimously.

Immune and Inflammatory Mechanisms in AD

Aging has been associated with inflammation and recent evidence suggests that the immune system facilitates communication between the brain and other systems. This RFA concept proposes to support studies exploring the contribution of inflammation to AD. The Working Group expressed a large amount of enthusiasm for this concept and recommended that it be approved. Council approved the Immune and Inflammatory Mechanisms in Alzheimer's Disease initiative unanimously.

B. Program Project Grant

Dr. Barr reminded the Council that NIA policy for large, collaborative program projects limits them to \$1.5 million in direct costs. Exceptions to this policy are allowed but they must be approved by senior NIA staff. A large survey, the National Survey of Midlife in the United States (MIDUS II), was approved 5 years ago with a budget of \$3 million. This application was submitted for renewal, and NIA sought the advice of an outside group of consultants. This group recommended that this project be moved to a cooperative agreement mechanism, which will allow continued involvement by program staff, the development of a steering committee, and input from more investigators. The Working Group recommended that this program project be approved as a cooperative agreement.

Dr. Perez-Stable noted the importance of this cohort study in light of the current focus on reversible and modifiable factors that influence late-life effects. He suggested increasing minority participation in this study, which has the potential to be a hallmark study similar to the Health and Retirement Study. The motion to accept the MIDUS study as a cooperative agreement was passed unanimously by the Council.

C. Statistical Data Package

Dr. Barr reminded the Council that the number of applications to NIA increased by 30% from 2012 to 2013. Even after correcting for the number of applications submitted in response to RFAs, there was still an increase of 20%. The number of applications in 2014 has remained elevated at a level similar to that of 2013.

V. COUNCIL SPEAKER: STRATEGIES FOR EXPANDING SCIENTIFIC WORKFORCE DIVERSITY: A FOCUS ON FACULTY

Hannah Valentine, M.D., Chief Officer for Scientific Workforce Diversity, NIH, noted that most would agree to the notion of equal access and opportunity for all Americans with respect to education and the ability to contribute to society. She further argued that

recruiting, retaining, and advancing the entire intellectual capital of the United States is imperative to the country retaining its competitive edge. A diverse workforce is needed to solve the complex challenges of human health and disease, to address health disparities, and to train and develop the next generation of talent. Research evidence indicates that diversity in research teams, when managed properly, leads to better and more creative solutions. However, the research career pipeline has several leaks and the small pool of researchers from underrepresented minority groups grows smaller at higher levels. Likewise, almost half of the individuals graduating with Ph.D.s are women, but the percentage of women at advanced career stages is much smaller.

Dr. Valantine described approaches taken at Stanford University, where she was senior associate dean for Diversity and Leadership in the School of Medicine. She emphasized that Stanford implemented programs targeting every transition point to increase diversity across the entire pipeline. These include a program to provide mentoring and laboratory experience to high school juniors; a faculty recruitment process that has evolved to include women and minorities on search committees, provide these committees with the tools to identify talented women and minorities, and evaluate leadership ability among these individuals; and policies to support faculty retention and a sense of belonging. Evaluation has been a core aspect of these approaches.

Although these strategies have increased representation among the faculty at Stanford, the pace of change remains too slow. Thus the approaches Stanford has taken have moved it in the right direction but they are not sufficient. Dr. Valantine noted the need for approaches that address cultural issues. One such issue is unconscious bias, or implicit bias arising from stereotypes everyone has. For example, in a study by Dr. Valantine and colleagues, half of kindergarten students drew a white male when asked to draw a scientist. This percentage increased with older students. In another study, scientists presented with identical curriculum vitae were more likely to select the candidate with a male name. Yet another study suggests that a short intervention in the form of a talk can decrease the level of unconscious bias. Another cultural issue is stereotype threat, or fear of becoming associated with a negative stereotype, which affects performance. At the core of this issue is a sense of not belonging. Studies by Dr. Valantine and colleagues have found substantial differences between male and female faculty members with respect to belief in one's potential, belief in career advancement, and feelings of isolation. Investigation is under way to determine whether interventions directed at stereotype threat will narrow these gaps.

The Transformative Diversity Initiative, which NIH has undertaken in response to reports of low success rates among grant applicants from underrepresented minority groups, comprises several approaches. Among these are:

- Strategies to enhance diversity in the NIH-funded workforce, including the NIH Building Infrastructure Leading to Diversity (BUILD) program, a National Research Mentoring Network, and a coordination and evaluation center to track success in these programs and make changes where needed.

- Strategies to ensure fairness in peer review, including pilot programs focused on blinded review.
- Increased engagement by NIH leadership, including the establishment of an NIH Steering Committee Working Group on Diversity and the appointment of a chief officer for Scientific Workforce Diversity, who will coordinate NIH initiatives in both the intramural and extramural research community, oversee a rigorous prospective evaluation, and work as a practicing scientist in the intramural research program.

Dr. Valentine described her vision for building a scientific workforce at NIH that serves as a model for capturing the most talented individuals for scientific research. She is meeting with IC directors to understand current status, existing challenges, and opportunities for early success. Dr. Valentine aims to implement strategies similar to those she oversaw at Stanford: expanding diversity in the intramural research program; creating a climate of inclusion; facilitating diversity at NIH-funded institutions; establishing a coordinated system for prototyping, evaluating, and disseminating successful programs; and establishing a robust and coordinated research agenda to implement a science of diversity.

Council members discussed NIH diversity supplements to existing research awards, which allow investigators to recruit and mentor individuals from underrepresented groups. These awards have shown mixed results. Dr. Valentine did a scan of such supplements at Stanford and found that they were rarely used. However, Dr. Perez-Stable pointed out that the review of NIA's diversity and disparities portfolio found the diversity supplements to be one of the most successful aspects of that portfolio. He also pointed to RCMAR as another model for supporting diversity in the scientific workforce.

Reisa Sperling, M.D., noted that, in her experience, individuals from underrepresented minority groups want to serve their communities and seldom see research as a way to do so. Dr. Valentine pointed to this issue as one of culture: trainees look around their institutions and see that community-oriented research, particularly that focused on health disparities or minority health, is not valued. She also noted research isolation among underrepresented minorities as another reason for attrition.

Charles Mouton, M.D., suggested a program that allows medical students to take a year off from medical school to work in an NIH laboratory, as well as an exchange program that allows faculty from institutions that predominantly serve underrepresented groups to work in an NIH laboratory to develop research skills, to energize the pipeline. He noted programs at Meharry Medical College, the NIH summer research programs, and Howard Hughes research programs as models.

In response to questions from Norman Anderson, M.D., about evidence-based approaches to the design and implementation of programs, Dr. Valentine noted that her office will include at least two or three social scientists who are interested in diversity in education and the sociopsychological issues she described during her presentation. These social scientists will be adept at study design. Her office also is collecting information from surveys and meetings with IC directors to identify priority areas and

key questions, determine where those priorities align with sociopsychological theory, and design experimental interventions.

Dr. Morimoto emphasized the importance of building relationships and promoting communication not only between students or junior faculty and mentors, but also among higher career levels. For example, he noted a workshop that had brought together training directors from the National Institute of General Medical Sciences (NIGMS) and program directors from historically black colleges and universities and predominantly Hispanic universities. None of the institution directors knew the NIGMS training directors, even though NIGMS is a major supporter of training programs. Dr. Morimoto remarked that faculty members need to know who the training directors are at institutions to which they might send their trainees.

VI. PROGRAM HIGHLIGHTS

A. Division of Aging Biology (DAB): Measuring Molecular Aging

Norman Sharpless, M.D., of the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill presented data on senescence; its relation to aging, and on the genetics of senescence that regulate aging. The p16 gene locus encodes three proteins: CDKN2a and CDKN2b (INK4A), two differentially regulated proteins that inhibit CDK4/6; and ARF, a differentially spliced variant of INK4A that regulates p53. Activation of the entire locus leads to cellular senescence, a permanent state in which cells stop dividing. Tumor suppressor mechanisms such as senescence are necessary throughout life and play a role in successful mammalian aging. Mice deficient in p16INK4A exhibit a high tumor burden, whereas those heterozygous for p16 die from cancer at a young age, mice doubly deficient in p16INK4A and p53 die before they can breed. p16INK4A and ARF increase with age in almost every tissue, whereas lack of p16INK4A expression keeps cells “young,” even in chronologically older mice. Although suppression of p16INK4A is associated with resistance to age-related diseases such as diabetes, the mice die from cancer. Similar results have been observed in humans.

Dr. Sharpless pointed out that many but not all stem cells show declines in the ability to renew with increasing age. He looked at all regulators of expression in the cell cycle to identify regulators whose expression changes with age and that might explain the age-related changes in proliferation. The only ones that did change were p16^{ink4a} and ARF. He maintained that if declines in replicative capacity are critical to aging then these two candidates are the critical drivers. Using pancreatic beta cells as a model he showed in mice a very strong relationship between p16^{ink4a} expression and age. Mice with over-expression of p16^{ink4a} show “old” beta cells even when young, and mice who are p16^{ink4a} null show forever “young” beta cells but die young of cancer. Other investigators established a similar pattern for neural and for muscle stem cells. P16^{ink4a} is linked to age-related changes in all these tissues.

He then described a model in which senescence – driven by age-related increases in p16^{ink4a} – both contributes to age-related loss of function in tissue and generates

increased vulnerability to cancer through changes in the composition of senescent cells. The model also predicts age-related “hot spots” in the genome. In other words cross-individual variability in the production of p16^{ink4a} will lead to differential susceptibility to age-associated diseases and conditions. In an analysis across the genome his group found hot spots for senescence particularly, at enhancer locations for p16^{ink4a} and for ARF, and for several locations associated with immune function. Diseases associated with the INK4/ARF locus included several cancers, aortic aneurysm, glaucoma, Type II diabetes, stroke, and myocardial infarction. Some of these associations (particularly atherosclerosis) are surprising.

The model also predicts that molecular aging may be measured by tracking the increasing prevalence of senescent cells in the body with a marker for the presence of p16^{ink4a}. Using a light-sensitive reporter attached to p16 he showed exponential growth in the presence of the reporter in mice as they grew older. His group then looked for “gerontogens”. These are environmental triggers that accelerate or decelerate the pace of molecular aging. In his mice his group found that a high fat diet was not a gerontogen but even a modest exposure to cigarette smoke led to a lifelong increase in senescent cells. In humans, his group has tracked the presence of p16^{ink4a} in T cells. P16^{ink4a} did show a consistent and continuous age-related increase in p16^{ink4a} with age. In a study involving breast cancer patients given chemotherapy the group found that the chemotherapy was gerontogenic – almost all of the patients showed a noticeable increase in p16^{ink4a} as measured in their T cells.

Questions included whether his lab had looked for anti-gerontogenic treatments – such as exercise, whether the growth of senescent cells shows a change in slope at puberty, and whether the heterogeneity of expression across animals also leads to consistent mortality differences among the animals. Dr. Sharpless indicated that his lab is looking at anti-gerontogenic treatments and showed some earlier success with caloric restriction in rats although the effect varied by tissue-type. He indicated that p16^{ink4a} is very difficult to measure in juvenile animals. On heterogeneity he indicated that as cancer deaths are the major contributor to mortality in mice it is difficult to explore the effects in that model. Nevertheless his lab is making his reporter model widely available and he hopes that some work will identify these kinds of relationships.

B. Division of Neuroscience (DN): Genetic Analyses of AD in Hispanics and African Americans

AD is a medically complex disease. The AD phenotype is not precise: there is a long period with no symptoms and manifestation varies across patients. The genetics of AD is also complex. Families with a rare autosomal dominant form of AD have been identified, as well as families with late-onset AD (LOAD) that does not follow Mendelian genetic patterns. Although families showing recessive forms of AD have not been identified, evidence suggests that some exist. Richard Mayeux, M.D., discussed his work with the Washington Heights, Hamilton Heights, Inwood, and Columbia Aging Project (WHICAP), which includes a cohort of 6,000 African American patients. He also presented unpublished work from the Estudio Familia Influenza Genetica de Alzheimer

(EFIGA), which follows 700 families of Hispanic WHICAP patients, who originate primarily from the Dominican Republic.

Using GWAS, Dr. Mayeux together with a European consortium and his colleagues have identified 11 new susceptibility loci and observed that APOE and ABCA7 are strong players among African American patients. Though APOE4 showed a risk ratio similar to Caucasian patients, ABCA7 showed a substantially higher risk ratio in the African-American sample than in Caucasians. A TREM2 variant identified by whole exome sequencing in the NIA-LOAD Family Study does not appear to play a role among the African American cohort, but Dr. Mayeux and colleagues have identified a locus within the same linkage disequilibrium block and are investigating further. They also have done biological assessments of NIA-LOAD variants, looked further at whole genome and whole exome sequencing data from the AD Sequencing Project, and conducted linkage analyses between GWAS and whole genome sequencing to identify candidate regions among the Caribbean Hispanic cohort. Dr. Mayeux stressed that the sample sizes of 6,000 African Americans and 6,000 Caribbean Hispanics were insufficient to identify all Alzheimer's related genes in those groups.

On the basis of this work, there are likely to be multiple gene variants that increase the risk for AD and while some variants do appear across all ethnic and racial groups enough variation is evident that the importance of including different ethnic and racial group becomes clear. Although functional analysis is incomplete, variants indicate alterations in amyloid processing and in the intracellular Golgi-endoplasmic reticulum transport system. Moreover, mutations typically related to early-onset disease might appear in families multiply affected by LOAD and pathogenic mutations related to frontotemporal lobar degeneration might appear in some families affected by AD. Dr. Mayeux concluded his presentation by noting genetic and molecular characterization of AD as the most important step in identifying new targets for treatment and prevention.

In response to questions from Dr. Perez-Stable, Dr. Mayeux noted data suggesting that incidence rates have increased among African American and Hispanic individuals over a 25-year period, whereas those among white individuals appear to be flattening. He also noted that AD incidence among African American individuals is about twice as high as that among white individuals and that incidence among Hispanic individuals is slightly higher. Council members also discussed algorithms that can predict the effects of mutations on protein structure and the availability of materials for further study.

C. Division of Geriatrics and Clinical Gerontology (DGCG): MsFLASH Trial 03 Results: Low-Dose Estradiol and the Serotonin-Norepinephrine Reuptake Inhibitor Venlafaxine for Vasomotor Symptoms

Hadine Joffe, M.D., of the Harvard Medical School and Dana Farber Cancer Institute, discussed three randomized clinical trials conducted by the MsFLASH Network, a multisite research network conducting studies of interventions for vasomotor symptoms associated with menopause. Hot flashes are the leading reason for women seeking medical treatment: up to 88% of women will experience hot flashes during the menopausal transition. They are highly disruptive to women's lives and they have been

correlated with markers of other health outcomes such as coronary artery disease. Following reports from the Women's Health Initiative, use of hormone therapy, the primary treatment for hot flashes, declined considerably. However, studies of non-hormonal treatments have not demonstrated consistent evidence to guide clinical practice. African American women are known to experience hot flashes more than Caucasian women. All trials described below included large samples of African-American women.

The first trial, which was published in *The Journal of the American Medical Association*, found that the number of hot flashes reported each day was reduced more with the selective serotonin reuptake inhibitor (SSRI) escitalopram than with placebo and that women using escitalopram were more likely to experience a reduction of 50% from baseline. There were no differences by race/ethnicity or other demographic factors. The second trial, a 3 x 2 factorial crossover design of yoga, aerobic exercise, and omega 3-fatty acid supplementation, found that none of these interventions were effective in reducing vasomotor symptoms.

Dr. Joffe devoted the bulk of her presentation to the third trial, which investigated the effects of low-dose estradiol or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine on the severity of hot flashes and the bother and interference associated with them. The trial also assessed whether baseline characteristics predict response to these treatments. More than 330 women aged 40 to 62 years who experience at least two symptoms per day were randomized to low-dose estradiol, venlafaxine, or placebo for 8 weeks. The study found that estradiol and venlafaxine were similarly effective in reducing hot flashes compared with placebo. Both interventions also conferred a benefit with respect to the bother and interference associated with hot flashes, although women on estradiol expressed more satisfaction with their treatment. Tolerability was high for both groups. No differences by baseline characteristics were observed.

The MsFLASH Network also has completed a pilot study of objective hot flash monitors and two ancillary studies of correlates with heart rate variability and bone turnover markers. Ongoing pilot studies are investigating cognitive behavioral therapy for menopausal insomnia and nighttime-only dosing of gabapentin for vasomotor symptoms.

Questions focused on when in the day the treatments were administered (morning) on effects on sleep disturbance (small effect, paper under review) and on whether there were cognitive changes (there were none).

D. Division of Behavioral and Social Research (DBSR): Evidence and Implications for Conscientiousness as a Marker of Health and Longevity

Conscientiousness comprises impulse control, responsibility, orderliness, industriousness, conventionality, and punctuality. Since the 1993 report by Friedman and colleagues correlating childhood conscientiousness with longevity, several studies and three non-overlapping meta-analyses have been conducted. Brent Roberts, Ph.D., of the University of Illinois, Urbana-Champaign, described work by an NIA Working

Group to assess developmental antecedents of conscientiousness, mechanisms that might explain the relationship between conscientiousness and longevity, and how these patterns might be moderated by age and context. He pointed out that different dispositions within conscientiousness might have different relationships to different outcomes and that a “family approach” helps to keep track of the research.

Like all psychological phenotypes, conscientiousness includes genetic and environmental components. For example, individuals born into families with secure attachment tend to show higher levels of conscientiousness, whereas those born into families with a lot of conflict tend to show lower levels. Individuals with higher levels of conscientiousness tend to build different life structures, with different health consequences, than those with lower levels of conscientiousness, and these structures are associated with later differences in patterns of growing older. For example, one study found that children with higher self-control were more likely to be in higher-income jobs and planning for retirement. They also were more likely to avoid typical snares that can occur in adolescence. Another study found that the level of conscientiousness at the age of 26 years could predict self-reported health and objective health measures at age 38.

A meta-analysis of more than 100 longitudinal studies suggests that conscientiousness is changeable, with conscientiousness increasing in young adulthood and more so through midlife and older age. Several studies have investigated why conscientiousness might change. One study found a positive relationship between social support and increased conscientiousness and another study found an inverse relationship between stress levels and conscientiousness over time. Dr. Roberts noted that clinicians have been changing conscientiousness for some time. For example, findings from one meta-analysis show that clinical interventions can increase extraversion, agreeableness, conscientiousness, and emotional stability. When to intervene, on whom to intervene, how best to intervene, and social environments that might preclude changeability are unclear.

Dr. Roberts concluded his presentation by highlighting recommendations from the Working Group:

- Improve measurement of conscientiousness.
- Identify the endophenotypes of conscientiousness and the biologic and cognitive substrates associated with them.
- Identify the developmental antecedents and biologic substrates of conscientiousness.
- Identify the age- and context-specific nature of development for the family of conscientiousness dispositions.
- Assess the potential public health significance of changes in conscientiousness.
- Identify scenarios where too much conscientiousness is bad.

Discussion involved questions about the influence of socioeconomic status and the relationship between conscientiousness and anxiety.

VII. ADJOURNMENT

The open session of the 122nd meeting of the National Advisory Council on Aging adjourned at 12:45 p.m. on May 21, 2014. The next meeting is scheduled for Sept. 16–17, 2014.

VIII. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.⁴

Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Robin Barr, D. Phil
With assistance from Rose Li and Associates, Inc.

⁴ These minutes will be approved formally by Council at the next meeting on September 16–17, 2014, and corrections or notations will be stated in the minutes of that meeting.