

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 132nd Meeting

NATIONAL ADVISORY COUNCIL ON AGING

September 26–27, 2017

**National Institutes of Health
Building 31, C Wing, 6th Floor, Conference Room 10
Bethesda, MD 20892**

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Department of Health and Human Services

Public Health Service
National Institutes of Health
National Institute on Aging

**NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
September 26-27, 2017**

The 132nd meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, September 26, 2017, at 3 p.m. in Building 31, Conference Room 10, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Richard Hodes, 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, September 26, from 3 p.m. 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, September 27, from 8:00 a.m. to 12:45 p.m.

Council Participants:

Dr. David A. Bennett
Dr. Maria Carrillo
Dr. Eileen M. Crimmins
Dr. Steven Ron Cummings
Dr. J. Taylor Harden
Dr. David M. Holtzman
Dr. Raynard S. Kington
Dr. James L. Kirkland
Dr. Stephen B. Kritchevsky
Dr. Richard Mayeux
Dr. Charles P. Mouton
Dr. Anne B. Newman
Dr. Thomas Rando
Dr. Reisa A. Sperling
Dr. Debra Bailey Whitman

Absent Council Participants:

Dr. Terrie E. Moffitt

Ex Officio Participants:

Dr. Jane Tilly, Administration for Community Living

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.

Absent Ex Officio Participants:

Dr. Kenneth G. Pugh, National Naval Medical Center

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:

Dr. John Burch, Center for Scientific Review (CSR)
Dr. Elia Femia, CSR
Dr. Gabriel Fosu, CSR
Dr. Michael Lauer, Deputy Director for Extramural Research, NIH
Dr. Mike McQuestion, CSR
Dr. Sussan Paydar, CSR
Dr. Bruce Reed, CSR
Dr. Elyse Schauwecker, CSR
Dr. Afia Sultana, CSR
Dr. Rebecca Tinker, CSR

Members of the Public Present:

Mr. James Appleby, Gerontological Society of America
Dr. Hillard Kaplan, Chapman University
Ms. Patricia Kobor, American Psychological Association
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Karen Matthews, University of Pittsburgh School of Medicine
Dr. Debra Umberson, University of Texas at Austin
Dr. Meng Wang, Baylor College of Medicine

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).²

A total of **1563** application requesting **\$3,491,414,730** for all years underwent initial review. The Council recommended **887** awards for a total of **\$2,321,627,529** for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

² 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.

II. CALL TO ORDER

Dr. Hodes welcomed members to the open session of the 132nd NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, September 27, 2017.

A. Director's Status Report

Dr. Hodes reported that the FY2017 budget has been finalized and the NIH Budget increased to \$34 billion. This increase includes \$120 million for the Personalized Medicine Initiative/All of Us, \$110 million for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative, \$50 million for research on antibiotic resistance, and \$400 million for Alzheimer's disease (AD) research. The NIA budget has increased to more than \$2 billion, with a \$48 million increase for non-targeted NIA-supported research. With this increase, the NIA budget has doubled since 2013, primarily because of the funds devoted to AD. However, even without that set-aside, the NIA budget has seen a substantial increase since 2013. The President's budget for FY2018 proposes a decrease in funding for all of NIH. However, the Senate appropriations bill proposes an additional \$486 million for NIA (\$414 million for AD research), and the House appropriations bill includes an additional \$410 million (\$400 million for AD research). The President has signed a continuing resolution to continue funding at FY2017 levels through January 19.

The increase in budget has led to substantial improvements in NIA paylines. The payline for general applications ranges from 16th to 19th percentile for established investigators to the 22nd to 25th for new and early-stage investigators. The payline for research on AD and related dementias (ADRD) is even higher, at the 25th to 28th percentile for established investigators and the 28th to 33rd percentile for new and early-stage investigators. Dr. Hodes also noted that NIA is funding first renewals for early-established investigators at the 25th percentile.

Dr. Hodes reported that the establishment of two-tiered review for program projects has succeeded in spreading scores over a wide enough range that NIA can use them to discriminate more effectively among applications. Because this spread results in scoring that differs from that for other funding mechanisms, NIA has set a separate payline for program projects: the 34th percentile for general applications and the 40th percentile for ADRD applications. The paylines for training and career awards range from 22 for general K awards to 40 for ADRD fellowships. In response to questions, Dr. Hodes noted that because behavior in study sections differs between program project applications and R01 applications, it is difficult to align the different scores. He and Dr. Robin Barr committed to providing the Council with success rates at the January 2018 meeting.

Dr. Hodes reminded the Council that Congress requires the NIH Director to submit a bypass budget on NIH initiatives related to the National Alzheimer's Plan. Recommendations are ordered based on categories in the Common AD Research Ontology, and funding and outcomes are tracked through the International AD Research Portfolio. The FY2019 bypass budget, which was released this summer, estimates that NIH will need an additional \$597 million above its base funding for FY2017. Dr. Hodes noted that, with the substantial decrease in the NIH budget requested by the President, the additional amount needed for FY2019 to address the National Alzheimer's Plan would be staggering.

Dr. Hodes then noted that NIA has prioritized expanding its support for small businesses. He noted that legislation requires a percentage of the NIA budget be used to fund Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) applications, but NIA has found it challenging to increase small business involvement at the pace at which the budget has been increasing. General funding announcements related to small businesses include translational research in aging and the development of tools for biomedical and behavioral research. AD-related funding announcements for small businesses include one supporting the development of tools for clinical care and management and one supporting the development of socially assistive robots to engage patients and their caregivers. Dr. Hodes noted that obligations for SBIR/STTR funding have doubled between 2013 and that the success rates for these applications are fairly high. NIA staff can guide prospective applicants on how the process works.

Dr. Hodes also noted the following activities:

- Nine senators from the Senate Appropriations Committee visited NIH in June. This group represented both parties and showed support for NIH. Senator Jerry Moran (R-KS), a longtime supporter, also visited NIH. Dr. Hodes spoke with the Senators about AD/ADRD research and Senator Moran toured an NIA lab during his visit.
- Five Institute and Center (IC) Directors, including Dr. Richard Hodes, Director, NIA, accompanied Dr. Francis Collins, NIH Director, to the Senate Appropriations hearing, also in June.
- In June, several NIH ICs, including NIA, hosted a workshop titled “Inclusion Across the Lifespan,” to explore the best strategies for encouraging older adults to participate in clinical research and for tracking inclusion of older adults. More than 120 individuals participated.
- The 2017 NIA Butler-Williams Scholars program was successful. The deadline for the next round of applications is March 23, 2018.
- The Go4Life campaign developed by NIA, which includes several Federal agencies, aims to translate evidence into recommendations on exercise and lifestyle changes.
- The National Research Summit on Care and Support for Persons with Dementia and Their Caregivers sponsored by NIA and others was held on October 16–17, 2017, at the Natcher Center. The third AD Research Summit sponsored by NIA will be held March 1–2, 2018, and the third ADRD Summit sponsored by NINDS will be held March 14–15, 2018, both in Bethesda.
- The 2017 NIA Directors Regional Meeting was held November 8, 2017, at the University of Colorado. This meeting brings NIA staff together with faculty, trainees, and potential grantees who have not had much experience with NIH research.
- The report from the Agency for Healthcare Research and Quality/National Academies study on interventions and level of evidence for age-related cognitive decline, mild cognitive impairment (MCI), and dementia, which was commissioned by the NIA, is now available. The report notes insufficient evidence to justify a public health campaign. It also finds promising but inconclusive evidence related to the benefit of cognitive training, blood pressure management, and increased physical activity.

Dr. Hodes closed his report by noting a Discovery Channel documentary on the NIH Clinical Center. The documentary, which aired on August 10, 17, and 24, captured the challenges in diagnosing and treating diseases.

B. Future Meeting Dates

January 23–24, 2018 (Tuesday and Wednesday, Building 31)
May 22–23, 2018 (Tuesday and Wednesday, 6001 Executive Blvd)
September 11–12, 2018 (Tuesday and Wednesday, Executive Blvd)
January 29–30, 2019 (Tuesday and Wednesday, Building 31)

C. Consideration of Minutes of the Last Meeting

The minutes of the May 2017 meeting were considered. A motion to approve the minutes was made, seconded, and passed unanimously.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Charles Mouton reported that the Task Force had heard two presentations. The first was given by Dr. Karen Parker, Director of the Sexual and Gender Minority Research Office at NIH, which was established in response to a 2011 Institute of Medicine report calling for more research on lesbian, gay, bisexual, and transgender (LGBT) health issues. Dr. Parker outlined the strategic plan of the Office to expand the knowledge base of sexual and gender minority (SGM) health through NIH-supported research, remove barriers to conducting and reporting research about SGM health and well-being, strengthen the community of researchers and scholars who conduct such research, and evaluate programs on advancing this research. Dr. Parker also discussed the Office's progress, which includes two funding opportunity announcements (FOAs), a Health Disparities Designation, participation in both an HHS research and surveillance working group and a Federal interagency working group, a summer research institute at the National Institute of Minority Health and Health Disparities, and training opportunities.

The second presentation, given by Dr. Debra Umberson of the University of Texas at Austin, focused on marriage health in same-sex and different-sex unions. Dr. Umberson discussed work on how life partners influence and shape each other's health trajectories and health behaviors and how they provide informal care. Through dyadic recruitment, baseline surveys, in-depth interviews, and daily diaries, Dr. Umberson and her colleagues have found that variations in marital dynamics and health outcomes can reflect the gender of the respondent, the gender of the partner, and the gender composition of the dyad.

Dr. Mouton closed his presentation by noting the Butler-Williams Scholars program and the upcoming Directors Regional Outreach Meeting. He also thanked Dr. Carl Hill and the NIH staff for their support.

IV. REPORT: WORKING GROUP ON PROGRAM

A. Clinical Trials Advisory Panel (CTAP)

The Working Group reviewed the CTAP report and recommended that it be forwarded to the Council for approval. A motion to approve the report was made, seconded, and passed unanimously by the Council. **RFA/RFP Concept Clearances**

The Working Group considered nine concepts and recommended that eight of them be forwarded to the Council for approval. A motion to clear the concepts en bloc was made, seconded, and passed unanimously. Dr. Barr noted that the approved concepts would be posted on a website in a few days.

Evolving Implementations for Training Cognition in Aging

This concept proposes a set-aside for up to two planning awards to develop more rigorous protocols for randomized clinical trials in cognitive training. The Working Group suggested the inclusion of biomarkers and other measures to define the study population.

Dementia Care and Caregiver Support Interventions

Promising interventions in dementia care are often “stuck on a cliff” and unable to proceed to pragmatic trials. This concept will support work that will identify what is needed to facilitate the transition between the development of such interventions and the effective implementation of pragmatic trials in the community. The Working Group suggested that the concept also support work to identify barriers to this transition.

Consequences of Amyloid Polymorphisms in AD

Over the past few years, it has become clear that, despite similarities in primary protein sequences for these proteins, the proteins misfold and take on different conformations. Evidence also suggests that amyloid proteins can self-propagate, similar to prions. A better understanding of how these proteins arise and propagate can provide fundamental insights into AD and ADRD. This concept proposes to support work examining key molecular and biochemical steps leading to differences in conformation and toxicity.

Collaboratory on Research Definitions for Cognitive Resilience and Reserve

The prevention of ADRD is a high priority, but approaches and concepts vary among investigators. The proposed collaboratory will develop a uniform nomenclature and standards for resilience and reserve. The Working Group noted that consensus about overarching issues is important, but members also cautioned against developing standards that cannot develop as the field develops.

Sensory and Motor System Changes as Predictors of Preclinical Alzheimer’s Disease

Several sensory and motor changes precede clinical diagnoses of AD, but most of these changes have been considered one at a time. This concept proposes to support work that studies these

changes as a set to identify signals that could serve as a preclinical risk marker. The concept presents several opportunities for technological innovation and new measures for data collection and analysis. However, the Working Group cautioned against “spreading the wealth” too thin across the spectrum of changes.

Sleep Disorders and Circadian Clock Disruption in AD and Other Dementias of Aging

Sleep disruption or disturbance has been associated with advanced disease in individuals with AD and other neurodegenerative diseases. However, evidence suggests a bidirectional relationship between sleep disruption and these diseases. Few studies and investigators have addressed this relationship, current descriptive and mechanistic studies require validation, and more exploration of mechanisms is needed. This concept proposes to support interdisciplinary research to address these gaps.

Samuel Waxman Cancer Research Foundation (SWCRF) Research Collaborations in Aging and Cancer

Aging is an important aspect in the prevalence and incidence of many diseases, including cancer. This concept will support collaborative efforts with the National Cancer Institute (NCI) to explore aging as a risk factor for cancer. Collaboration will take place between the extramural and intramural programs at NIA and NCI, with co-funding from SWCRF.

Immunity in the Elderly

Aging is associated with a decline in immunity and an increase in chronic inflammation. Understanding these phenomena is important because of the increased occurrence of infection with older age and importance of inflammation in age-associated diseases. This concept is a renewal of a request for applications (RFA), co-funded by NIA and the National Institute of Allergy and Infectious Diseases, to support a wide range of studies to explore underlying mechanisms.

B. Statistical Package

Dr. Barr reported that in August, NIA received more than 600 applications in response to RFAs and that awards have just been made. NIA has received 1,120 applications for October.

In response to questions, Dr. Barr noted that SBIR/STTR applications have a fast turn-around between application receipt and award. He also noted that SBIR grants have a more generous appropriation than STTR awards but require principal investigators (PIs) to spend at least 51% of their time on the grant, which can be difficult in some academic institutions. The funding line remains tighter for STTR awards, but academics can serve as PIs and remain in their academic positions. Dr. Barr also noted that for AD, the payline for STTRs is the 40th percentile. He acknowledged that early-stage investigators who apply for R44 awards risk losing early-stage investigator status.

Dr. Hodes noted that practice, policy, and implementation are emerging for the new status of “early-established investigator.” At present, the status includes investigators who apply for their first renewal of an early-stage investigator grant. However, this “renewal” application can be

submitted within 10 years of the initial early-stage investigator award. NIH is also considering the possibility of extending this status to include investigators and laboratories that have only one award and are applying for concurrent support.

In response to questions about the need for more physician-scientists, Dr. Barr noted efforts across NIH to develop a common R25 program.

V. PROGRAM HIGHLIGHTS

A. Division of Neuroscience (DN): The Evolution of Preclinical Alzheimer's Disease: Implications for Prevention Trials

Recognizing that primary prevention of disease is an ultimate goal, Dr. Reisa Sperling discussed the importance of secondary prevention to delay the progression from brain pathology to dementia, which could cut health care costs significantly, and reported on her work on the Anti-Amyloid Treatment in Asymptomatic AD (A4) study.

Accumulation of extracellular amyloid plaques is a hallmark pathology of AD. With positron emission tomography (PET), however, one can visualize amyloid only in its beta-pleated sheet form; it does not measure soluble forms. A β monomers can be detected in spinal fluid, but which forms are toxic is not clear. Up to 85% of individuals diagnosed with AD dementia show detectable amyloid pathology, and about 60% of individuals with mild cognitive impairment (MCI) show elevated amyloid and a higher likelihood of progression to dementia. However, not every diagnosis of clinical AD is AD pathophysiologically. Some individuals who appear normal clinically show evidence of accumulated amyloid in the same anatomic distribution seen at later stages of AD, suggesting preclinical disease. Estimates suggest a gap of 15 to 19 years between the time an individual reaches a sufficient plaque load and the time that individual develops dementia. However, it is not clear how many of these individuals will progress.

The Harvard Aging Brain study found that normal individuals with no amyloid showed a robust practice effect over 5 years, whereas those who were amyloid positive showed a marked decline on several cognitive measures. Data from the Alzheimer's Disease Neuroimaging Initiative showed similar results: individuals negative for amyloid showed a practice effect, whereas amyloid-positive individuals showed a decline that started at 2 years and accelerated over time. Yet the predictive power of amyloid positivity in individuals who are cognitively normal remains controversial, because some individuals have a marked accumulation of amyloid but remain cognitively normal and others decline precipitously.

Another hallmark pathology of AD is the appearance of phosphorylated tau in neurofibrillary tangles. Phosphorylated tau accumulates in the medial temporal lobe in all individuals older than 40 years, but it does not spread into the neocortex. However, the presence of accumulated amyloid increases the likelihood of spreading. This can be seen through tau PET imaging; tau is restricted to the medial temporal lobe in amyloid-negative, cognitively normal individuals, but spread is apparent in amyloid-positive individuals even before they develop MCI.

Although primary prevention of the disease is an ultimate goal, secondary prevention to delay the progression from brain pathology to dementia could cut health care costs significantly.

Several secondary prevention trials are under way. As an example, Dr. Sperling discussed how the A4 phase III trial is assessing solanezumab vs placebo for 240 weeks in clinically normal individuals aged 65 to 85 years with amyloid accumulation as detected by PET imaging. The study also includes an observational cohort of individuals negative for A β . Amyloid status is disclosed to study participants. As of September 21, the trial has brought in 67 sites in the United States, Canada, Australia, and Japan; screened more than 6,900 participants, of whom 14% are from minority groups; randomized 1,092 participants; and enrolled 529 individuals into the observational cohort. Baseline data indicate neocortical spread of tau in approximately half of A4 participants, and preliminary data suggest that memory performance is worse among those with greater tau burden. Dr. Sperling also noted the A5 study, which is assessing a beta secretase inhibitor in participants as young as 60 years, and the A3 study, which is focused on ante-amyloid prevention and is therefore closer to primary prevention.

Council discussion focused on aspects of recruitment. Dr. James Kirkland also suggested the addition of ancillary studies or the collection of samples to determine whether fundamental aging processes are also involved in AD.

B. Division of Behavioral and Social Research (DBSR): Delayed Cardiovascular Aging among Subsistence Populations: Implications and New Questions

Dr. Hillard S. Kaplan, of Chapman University, discussed his work with the Tsimane, a 14,000-person hunter-horticulturalist population living a subsistence lifestyle in the Bolivian Amazon. The lifeway of hunter-gatherers and forager-farmers shares many aspects with our evolutionary past and can therefore shed light on the evolved biology of aging and life expectancy. In addition, comparisons between these societies and modern ones can increase understanding of modern health conditions and the interactions of genes, environments, and lifestyles on health and longevity. For example, little is known about heart aging and heart disease during evolution. It is not clear whether atherosclerosis is a normal part of aging in the modern world, or how pathogen exposure and lifestyle interact to influence the likelihood of atherosclerosis. The study of “traditional” societies could provide new insights about CVD. Early studies suggest that myocardial infarction (MI), cardiac death, diabetes mellitus, and hypertension are rare in this population. Low incidence of coronary artery disease (CAD) has also been reported, but this has been difficult to confirm because this population lives in the rainforest.

Dr. Kaplan presented a study of coronary atherosclerosis, as measured by coronary calcium scoring, among 705 Tsimane adults aged 40 years or older. The study noted a lean diet, high levels of physical activity, and minimal smoking, obesity, or diabetes among this population. However, a higher proportion of Tsimane individuals were at high risk for low high-density lipoprotein cholesterol (HDL) and high levels of inflammation. At age 45, 95% of the Tsimane participants were calcium free, and at age 80, 60% were calcium free. In comparison, only 10% of the Multi-Ethnic Study of Aging (MESA) population was calcium free at 80 years. An increasing proportion of MESA participants were at moderate risk for coronary atherosclerosis by age 70, but by age 80, only 8% of the Tsimane population was at moderate risk, and no one was at high risk. In the MESA population, an exponentially increasing burden of coronary atherosclerosis was apparent at the 75th percentile, whereas in the Tsimane population, the exponential aging process was not apparent even at the 90th percentile.

These differences might arise partly from dietary composition. Only 16% of the Tsimane diet is fat, and only 5% is saturated fat, whereas 34% of the American diet is fat. An even larger driver of these differences is the level of physical activity: Tsimane individuals take an average of 17,000 steps per day, whereas the United States average is 6,500 steps per day. These findings suggest that high levels of physical activity, little to no smoking, and low levels of saturated fat contribute to an average lifetime low-density lipoprotein (LDL) concentration of 70 mg/dL, a mean blood pressure of 116/73 mm Hg, a fasting blood glucose level of 79 mg/dL, and a low body mass index. On the basis of these findings, Dr. Kaplan and his colleagues tentatively conclude that coronary atherosclerosis could be avoided by achieving a lifetime of low blood pressure, LDL, and glucose and high physical activity. They also conclude that urbanization, specialization, and the elimination of the subsistence diet are novel risk factors for CAD.

Dr. Kaplan and his colleagues also looked at atrial fibrillation not only among the Tsimane, but also among other populations. Among a sample of 1,300 Tsimane individuals, only one case of atrial fibrillation was observed and only one new case developed over time. The prevalence of atrial fibrillation in this population is 1/20 of that in the United States. The prevalence is similar among subsistence populations in rural Ghana and rural Tanzania, at 0.07 and 0.08, respectively. Among indigenous populations that have been acculturated, the prevalence of atrial fibrillation is approximately 1.5 times that in the United States. Similar findings were observed with systolic and diastolic function. These findings suggest that differences in CAD are affected not only by differences in lifestyles, but also by differences in other features of heart aging. Dr. Kaplan closed his presentation by suggesting that high inflammation and low HDL alone are insufficient to produce CAD. He also suggested that prevention could work if people could be persuaded to change their lifestyles.

Council discussion focused on other potential hypotheses from Dr. Kaplan's work.

C. Division of Geriatrics and Clinical Gerontology (DGCG): Highlights from the Study of Women's Health across the Nation

Dr. Karen Matthews, of the University of Pittsburgh, discussed the objectives, design, and measures of the Study of Women's Health Across the Nation (SWAN). SWAN is a cohort study that aims to characterize the chronology of biological and psychosocial antecedents and sequelae of the menopausal transition and the effect of that transition on subsequent health and risk factors for age-related diseases. It also aims to extend this information from white women to encompass the perimenopausal women of other racial and ethnic backgrounds. SWAN includes comprehensive data collection in a variety of domains, including cognition, sleep, and lifestyle behaviors and symptoms, in addition to vaginal, urogynecologic, and sexual health.

After 20 years, SWAN has retained more than 70% of its original population. It has published more than 400 journal articles, presented a similar number of abstracts at conferences, spawned 30 ancillary projects, and established an extensive biorepository. Data sets are available to investigators outside the original study team via an application process. SWAN has found that perimenopause is strongly associated with several outcomes, including reproductive hormones, vasomotor symptoms, depression, bone mineral density, and progression of subclinical CVD, and that the trajectories of change, particularly for the reproductive hormones, are not uniform.

Dr. Matthews then focused on data surrounding menopause and lipids. The role of menopause in CVD risk is controversial. Many women who undergo early menopause have higher risk factors such as smoking or obesity, and no large changes in CVD event rates have been observed at the average time of menopause. SWAN data suggest that LDL rises steeply around the time of the final menstrual period, then flattens out and that the extent of LDL changes around the final menstrual period are associated with the extent of plaque in the carotid artery. Obese women with an increase in LDL had the highest carotid intima-media thickness (IMT), suggesting a synergistic effect among risk factors. SWAN data also suggest that HDL might not be as protective in postmenopausal women as it is in premenopausal women. SWAN data also show that HDL increases gradually until the final menstrual period, then declines through the first 5 years post menopause. Elevated HDL before menopause is associated with lower carotid IMT, but with increasing carotid IMT post menopause, consistent with other studies suggesting that HDL is not protective in postmenopausal women.

Thus, SWAN data have challenged traditional ideas about menopause and supported the need for serial observations before and after the final menstrual period. The study is now linking midlife trajectories with health outcomes as the SWAN study population ages into its 70s.

VI. COUNCIL SPEAKER: CLINICAL TRIAL POLICY UPDATE

Dr. Michael Lauer, Deputy Director of Extramural Research, NIH, discussed the Clinical Trial Policy, released in September 2016, to address access to results from NIH-funded research. In January 2012, an analysis published in *BMJ* reported that many NIH-funded trials either failed to publish their main results or did not do so in a timely manner. The authors looked at 635 trials and found that only 45% had published results after 2.5 years. They also noted that the FDA Amendments Act, which includes a provision to reduce the amount of underreporting from clinical trials, did not cover many trials, such as those assessing behavioral interventions or surgical procedures. The authors concluded that no policies existed to ensure that the public had access to results from NIH-funded research.

In response, NIH conducted its own analysis of 274 cardiovascular trials funded by the National Heart, Lung, and Blood Institute (NHLBI) and completed over 10 years. The analysis, published in the *New England Journal of Medicine* in 2013, reported that a good number of trials assessing clinical endpoints had published their results after 1 year and all had published them after 2 years. However, these trials represented only 20% of all NHLBI-funded trials. Among trials assessing surrogate endpoints, only 12% had published their main results after 1 year, and only 40% had done so after 2 years. Yet another analysis by a group of researchers at Yale University looked at trials conducted by major academic medical centers between 2007 and 2010. Although the University of Minnesota had the highest rate of publications, that rate was only 55% after 2 years. Most institutions had publication rates of 35%, and many had rates below 20%.

The authors of the NIH analysis noted that several parties, including funders, investigators, academic medical centers, clinical research organizations, and journals, shared responsibility for this poor performance. This conclusion was echoed by an opinion piece that considered the failure to report research results to be a systemic issue. The opinion piece noted that this failure violates the basic principle of the scientific method, dishonors those who participated in the trials, impedes progress toward scientific breakthroughs, corrupts the medical literature, and

wastes research funding. In addition, the U.S. Government Accountability Office published a report in 2016 noting that NIH invested approximately \$3 billion annually in clinical trials but had not collected enough data to make data-driven decisions or even to know how many trials it supported.

Dr. Lauer indicated that the Clinical Trial Policy states that dissemination of study results is a fundamental premise of all NIH-funded research and that, in research involving human beings, investigators have an ethical obligation to ensure that the study produces meaningful results that help to justify the risk and burden to study participants. It defines clinical trials broadly as studies “in which one or more humans are prospectively assigned to one or more interventions ... to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” The Policy requires registration of all NIH-funded trials within 21 days of enrollment of the first participant and posting of main results on ClinicalTrials.gov within 1 year of study completion. To collect data on the trials it funds, NIH will support clinical trials through designated FOAs, which will serve as labels to alert staff to look for registrations. NIH will withhold funding for a trial if it cannot verify adequate registration and reporting of results.

NIH is providing several resources for investigators, including a web page on clinical trial requirements for grants and contracts and a decision tool for investigators to determine whether their human subjects study is a clinical trial. In addition, Drs. Collins and Lauer, along with Dr. Kathy Hudson, have published an article in *JAMA* on the new clinical trials policy.

Dr. David Bennett noted that the ethical obligation to share study results with the public extends beyond clinical trials to observational and cohort studies. Dr. Lauer acknowledged that some public comments criticized the new NIH policy for being too narrow. However, he also noted challenges to including observational and cohort studies, such as defining the result to be shared. However, more investigators are sharing data from these studies, and the 21st Century Cures Act authorizes the NIH Director to require data-sharing as a condition of the award.

In response to other questions from the Council, Dr. Lauer noted that the NIH definition of clinical trials is deliberately broad because most NIH-funded trials do not focus on clinical endpoints. He reiterated that NIH provides a decision tool to help investigators determine whether their study is a clinical trial, and he provided an email address that investigators can use to ask about their proposed studies. Some applications, such as those for P30 research program projects and centers core grants, might generate future studies that could be defined as a clinical trial, but investigators do not know that yet. In those cases, investigators can click “deferred,” which will alert NIH to look for additional studies arising from that application. Dr. Lauer also noted that ClinicalTrials.gov accepts many kinds of studies, including observational studies and basic science trials. He also noted that NIH is requiring investigators to register trials because it views registration as posting the methods and because investigators will be the ones writing the resulting papers.

Dr. Lauer noted that NIH is considering how to meet ethical obligations to make preclinical data available. In a question, Dr. Bennett pointed out that a major problem in research at the moment is the repeated failure to replicate published results and that is a larger problem than non-reporting of results which is what the new policy addresses. Dr. Lauer responded that not reporting negative results may be an underlying cause of replication failures. In that case a

requirement to report may address the problem of replicability. In response to another question, Dr. Lauer also noted challenges in data-sharing when a company has funded part of the study and does not want to share that data. These issues have been addressed partially by language on data-sharing in the 21st Century Cures Act.

VII. PROGRAM HIGHLIGHTS (CONTINUED)

A. Division of Aging Biology (DAB): Metabolic Drivers in Longevity Regulation

Dr. Meng Wang, of the Baylor College of Medicine, discussed work using the nematode worm *Caenorhabditis elegans* to understand how metabolites mediate intra- and intercellular communications to maintain cell homeostasis and organ fitness. The metabolic regulation of cells depends on the compartmentalization of various metabolic reactions into different organelles. However, the organelles cannot function independently; their activity must be coordinated. At the same time, these cells do not live in a sterile environment; they reside in a space with other microbes, including bacteria, which could be viewed as extracellular organelles.

Dr. Wang and her colleagues have also manipulated the worm system to identify compounds that could promote healthy aging. They have focused on the lysosome, an organelle that is filled with hydrolytic enzymes and carries out phagocytosis and autophagy, and have identified a lysosomal lipase LIPL4, which is barely detectable in wild-type organisms. Worms overexpressing LIPL4 live longer and stay healthier longer. These worms also show an upregulation of the lipid-binding protein LBP-8/FABP, which translocates to the nucleus upon LIPL4 induction. LBP-8 overexpression is sufficient to increase longevity, but only if LBP-8 has an intact nuclear localization sequence. Additional genetic screens in fat storage cells have identified a nuclear hormone complex, which comprises NHR49 and NHR50 and engages in a feedback loop with LBP-8. Dr. Wang and her colleagues have profiled more than 350 metabolites and identified three polyunsaturated fatty acids and one fatty acid derivative that are induced in long-lived *lip14* transgenics. The fatty acid derivative, oteoyl ethanolamide, binds both LBP-8 and the NHR complex and is sufficient to promote longevity on its own. These observations suggest that lysosomes are not just scavengers; they can sense environmental stimuli and produce metabolites that communicate with other organelles within and between cells.

Dr. Wang and her colleagues also have conducted genome-wide screens of all nonessential *E. coli* genes to ascertain how genetic changes in bacteria influences host longevity. They have identified 29 mutants that promote longevity through insulin/IGF-1 or TOR signaling or caloric restriction. Five of these mutants promote longevity by producing colanic acid, a polysaccharide secreted by bacteria when they are stressed. Dr. Wang and her colleagues have purified colanic acid and confirmed that colanic acid supplementation promotes longevity and attenuates age-associated pathologies in *C. elegans* and fruit flies. They have also found that colanic acid targets the mitochondria and regulates their dynamics. The longevity effect induced by colanic acid depends on mitochondrial fragmentation, as well as on the transcription factor ATFS-1 and its cofactor UBL-5. The team is now using functional genomics, metabolomics, and cell imaging to identify additional messengers between cells and bacteria.

Council discussion focused on the potential implications of Dr. Wang's work for promoting human longevity, potential links between these metabolic regulators and other mechanisms

underlying longevity, the balance between evolutionarily conserved metabolites and organism-specific ones, and the protein structure for LPB-8.

VIII. ADJOURNMENT

The open session of the 132nd meeting of the National Advisory Council on Aging adjourned at 12:45 p.m. on September 27, 2017. The next meeting is scheduled for January 23–24, 2018.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.³

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

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

³ These minutes will be approved formally by Council at the next meeting on January 23-24, 2018, and corrections or notations will be stated in the minutes of that meeting.

MEETING ROSTER

National Advisory Council on Aging NATIONAL INSTITUTE ON AGING NACA

Agenda Seq Num - 00319521
09/26/2017 - 09/27/2017

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