**NATIONAL INSTITUTES OF HEALTH**

**NATIONAL INSTITUTE ON AGING**

Summary Minutes

The Seventy-Eighth Meeting

NATIONAL ADVISORY COUNCIL ON AGING

September 23-24, 1999

National Institutes of Health
Building 1, Wilson Hall
Bethesda, Maryland 20892

## CONTENTS

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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 23-24, 1999

The 78th meeting of the National Advisory Council on Aging (NACA) was convened on Thursday, September 23, at 1:00 p.m. in Building 1, Wilson Hall, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Richard J. Hodes, Director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public on Thursday, September 23, from 1:00 to 5:30 p.m. and again on Friday, September 24, from 8:00 to 10:30 a.m. The meeting was closed to the public on Friday, September 24 from 10:30 a.m. until 12:30 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 Public Law 92-463.[1]

**Council Participants:**

Dr. Helen M. Blau
Dr. Jeffrey Bluestone
Dr. Judith Campisi
Dr. Rose Dobrof
Dr. Fred H. Gage
Dr. Patricia S. Goldman-Rakic
Dr. Mary S. Harper
Dr. James S. Jackson
Dr. Dennis Selkoe
Dr. James W. Vaupel
Dr. Jeanne Y. Wei
Dr. Myron Weisfeldt
Dr. David A. Wise

**Ex-Officio Participants:**

Dr. Saadia Greenburg

**Absent:**

Dr. Elizabeth Barrett-Connor
Dr. Richard Goldsby
Senator Mark Hatfield
Dr. William Hazzard
Dr. John Rowe
Dr. George Fuller
Dr. Judith Salerno

[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.

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

**Members of the Public Present**:
Normandy Brangan, American Association of Retired Persons
Dr. Shirley Brown, Gerontological Society of America
Dr. Larry Crecy, National Caucus and Center on Black Aged, Inc.
Dr. Harold Freeman, North General Hospital; Columbia Univ. College of Physicians & Surgeons
Linda Harootyan, Gerontological Society of America
Dr. Harrison-Clark, Population Association of America/APC
Gail Hunt, National Alliance for Caregiving
Dr. Sylvia Johnson
Dr. Raynard Kington, National Center for Health Statistics
Pat Kobor, American Psychological Association
Pam Moore, Capitol Publications
Deloris B. Mouege, Center for Drug Abuse Research
Jane Otano, Howard University
Dr. William L. West, Howard University
Allen B. Williams, University of Maryland Eastern Shore
Jean Moody Williams, Emergency Medical Services for Children

**In addition to NIA Staff, other Federal employees attending were:**
Diane Adams, Agency for Health Care Policy and Research
Patty Austin, OER/OD/NIH
Dr. Lula Beatty, OD/NIDA
Dr. John D. Chah, NCCAM
Dr. Mary Custer, CSR/RRB/NIH
Dr. Bernard Driscoll, CSR/RRB/NIH
Dr. Eugene Hayunga, NCCAM
Dionne Jones, NIDA
Dr. Matthew Kinnard, OER/OD/NIH
Dr. Daniel McDonald, CSR/RRB/NIH
John Medina III, OEO/OD/NIH
Dr. Ramesh Nayak, CSR/RRB/NIH
Dr. Robert Nussbaum, NHGRI
Denise Manouelian, NIDDK
Dr. Jeanette Bevelt Miles, SAMHSA
Josephine Pelham, CSR/RRB/NIH
Dr. Lawrence Prograis, NIAID
Dr. Don Schneider, CSR/RRB/NIH
Dr. Paula Skedswald, OBSSR/OD/NIH
Dr. Lorrita Watson, ORMH/OD/NIH
Dr. Charles Wells, OEO/OD/NIH

## I. CALL TO ORDER

Dr. Hodes welcomed members and introduced staff member Dr. Barbara Mittleman who has joined the Biology of Aging Program as an HSA to develop the Immunology and Aging portfolio. Introductions of Council members were made.

**Director's Status Report**

Dr. Hodes noted that budget information for FY 2000 was not yet available. (Later in the meeting, information became available that the House Appropriations Subcommittee on Labor, Health and Human Services, and Education recommended an 8-9 percent increase for NIH. The final bill included a 15 percent increase for NIH.)

He reported that as NIA continues to develop research initiatives specific to its own mission, the Institute is increasingly developing initiatives in areas of shared interests with other Institutes and organizations.

Examples of new initiatives being developed are:

1. Infrastructure for microarray analysis will enable investigators to purchase use of new methodologic resources. Specifically, microarray resources produced within the NIA Intramural Program by intramural scientists would be made available more broadly for application by the extramural community.
2. Clinical research initiatives in conjunction with the Food and Drug Administration (FDA), the Veterans Administration (VA), and the private sector. Examples are: (a) an NIA-National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)-FDA-private sector partnership to develop bio- or surrogate markers of osteoarthritis to trace the natural history of the disease and for use in facilitating the development of therapies; (b) a collaborative initiative with the private sector in the Alzheimer's disease area for development of diagnostic markers and therapeutics, (c) a collaborative study with the VA involving use of the VA clinical trials infrastructure to conduct jointly-funded studies, and (d) collaborations between NIA and the National Cancer Institute (NCI) for studies of aging and cancer that would take advantage of the Cancer Therapy Evaluation Program (CTEP) infrastructure.

Dr. Hodes noted that the Institute has been working on a strategic plan that is to be posted on the internet for public comment and that is slated for completion by the end of the year. (Council discussion of the plan is addressed on page 13 of these Minutes.)

Dr. Hodes observed that the review of NIA's minority aging research programs by Council is a historic attempt to look comprehensively at minority aging research to understand the nature of the Institute's current investment and the opportunities and degree to which NIA ought to focus this program in the future. He indicated that this review would be presented to the Council in full later that day. (The review is addressed on page 6 of these Minutes.)

Finally, Dr. Hodes commented on the Office of Management and Budget (OMB) Circular A-110 which relates to regulations being promulgated to provide public access to research data used in developing an agency action that has the force and effect of law. The rule is implementation of the Shelby amendment to the FY 99 Appropriations bill. The Council was provided with a copy of the letter from Senator Shelby, the sponsor of the original amendment, in which he responded to OMB's proposed guidelines for implementation of A-110.

The Director's Status Report is appended to these minutes as Attachment B.

**Future Meeting Dates**

February 8-9, 2000 (Tuesday-Wednesday)
May 25-26, 2000 (Thursday-Friday)
September 27-28, 2000 (Wednesday-Thursday)
February 6-7, 2001 (Tuesday-Wednesday)
May 22-23, 2001 (Tuesday-Wednesday)
September 25-26, 2001 (Tuesday-Wednesday)

**Consideration of Minutes of Last Meeting**

The minutes of the May 27-28, 1999 meeting were approved as submitted.

## II. PRESENTATION: RACE AND RACIALISM IN SCIENCE AND SOCIETY

Dr. James Jackson, moderator, introduced the presentation, "Race and Racialism in Science and Society." He noted that scientific literature documents a role for race and ethnic issues in health behaviors and outcomes. He also acknowledged that life style and cultural factors may transcend racial and socioeconomic (SES) differences. Therefore, models of health behavior and interventions are needed that include cultural heterogeneity as a major variable. Dr. Jackson introduced the guest speaker, Dr. Harold Freeman, and the respondent, Dr. Raynard Kington. Dr. Freeman is President of North General Hospital, Director of the Department of Surgery at the North General Hospital in New York City, Professor of Clinical Surgery at Columbia University College of Physicians and Surgeons, member of the Institute of Medicine of the National Academy of Sciences, and former President of the American Cancer Society and Chair of the President's Cancer Panel. The respondent, Dr. Raynard Kington, is Director of the Division of Health Examinations Statistics at the National Center for Health Statistics for the Centers for Disease Control and Prevention. He also serves as Director of the National Health and Nutrition Examination Survey. Dr. Kington's research has focused on the relationship between race, socioeconomic position, and health status, especially as it relates to older populations.

Dr. Freeman noted his longstanding interest in cancer and in health disparities. He cited his paper with McCord on "Excess Mortality in Harlem" (McCord, C., and Freeman, H. *New England Journal of Medicine* 322:173-177, 1990) showing that a Black male in Harlem has less chance of surviving to age 65 than a male in Bangladesh. He pointed out that poverty, because of its many effects on

resources, environment, behavior and attitude, is a major determinant of excess mortality. Cultural variation moderates the effect of poverty. Race is a poor marker by comparison.

He maintained that race as a biological category is untenable. Inconsistencies in how "Black" has been defined, the fact that a diminishingly small percentage of the genome codes for racial characteristics, and the evidence that the American Association of Physical Anthropology now holds that biological racial categories are untenable, were all adduced to make the point. Yet Dr. Freeman acknowledged that race as a concept is alive through racism. He invoked Harding's definition of race as a social construct determined by how one group sees and behaves towards another.

He sees the task for science as avoiding inappropriate use of racial categories--and thereby perpetuating racism--while, at the same time, allowing meaningful study of the effects of racism. Thus, for example, cancer researchers need to address the unequal distribution of cancer burden through developing meaningful groups organized by geography or genetic variation and should not rely on politically defined racial categories. However, race is meaningful in social science as a concept in the study of how groups of people have been treated and of how that treatment has consequences for health.

Dr. Kington expressed his respect and admiration for Dr. Freeman and endorsed his message that race as a variable is given force through the existence of racism. He went on to separate race considered as a variable in a search for the underlying explanations for health disparities, and race as an organizing variable for targeting interventions. He believed that much of the criticism of race by Dr. Freeman and others is directed at the first of these conceptions. In that context, the concept of race is criticized because it is a social or political construct rather than a biological indicator. Dr. Kington pointed out that other social constructs such as poverty and education have clear consequences for health and biology. Race is criticized because it is imprecise. He noted that, imprecise though it is, race remains a powerful variable in explaining differences in measures of health status. Race is criticized because racial groups are genetically, socially, and economically heterogeneous. Dr. Kington acknowledged that much research can be faulted for a simple descriptive use of racial categories that fails to recognize that heterogeneity. However, he argued that heterogeneity is advantageous for examining why there are profound differences in health status between groups because it allows sub-groups to be contrasted within a race. Other concepts than race have been offered to account for the differences. Dr. Kington pointed out that so far these concepts fail to provide the leverage or insight offered by race.

Dr. Kington argued that race as a categorizing concept used for surveillance research and for planning interventions remains noncontroversial because it is a powerful variable in determining home, work, and social experiences.

He also offered some thoughts on ways to improve research on racial differences. He concurred with Dr. Freeman in stating that descriptive categories (such as the categories of the Office of Management and Budget) should be replaced by more meaningful groupings in research. He urged an emphasis on research methodology to generate standardized instruments that work for different racial groups. He urged careful choice of objective measures of racism. He argued for the need for

interdisciplinary scientists who can move easily between the social variables that are important in racial research and the underlying biology of health. He appealed to scientists to recognize the importance of race in health and disease rather than confine such research to the lesser status of socially and politically sanctioned but scientifically dull.

In response to a question from Dr. Hodes on the relevance of race as a biological distinction, Dr. Freeman explained that he expects race to be an important dimension of variation but that the roots of racial distinctions are in culture, and heterogeneity of cultures rather than in genetic differences. Using the sickle cell disease example offered by Dr. Hodes, Dr. Freeman pointed out that prior to the 1950s sickle cell disease was assumed to be genetically linked to being Black. However, epidemiological research at that time showed that because sickle cell carriers are genetically protected against malaria, a Darwinian survival pattern emerged from malaria-prone regions of the world, including Africa. Subsequent within-cultural-group marriage maintained the unequal distribution of the sickle cell gene when groups emigrated to the United States. Thus environment and culture led to the racial association. Dr. Kington, while agreeing with Dr. Freeman that the roots of racial variation are in culture, pointed out that the substantial socioeconomic and cultural pressures introduced by racism likely interact with genetic variation. Thus he expects genetic markers to play a part in understanding racial differences in health through their interaction with social and environmental factors.

Responding to Dr. Hodes's comment that some have questioned the value of pursuing genetic differences between racial groups in the incidence of Alzheimer's disease, both Dr. Freeman and Dr. Kington urged considerable caution in interpreting such results because genetic and cultural heterogeneity within African Americans makes generalizations suspect. Dr. Kington added that expertise in racial and cultural variation is critical in research on health disparities.

Other comments from Council members included that families are an important social and health construct within many minority communities, that values in society and in science often work against advancement of minority research and minority health, and that an overlooked aspect of racism is about how racial groups see each other and themselves.

## III. REVIEW OF NIA MINORITY RESEARCH PROGRAM

Dr. Jackson stressed that throughout the review of the minority programs at NIA a strong theme had been the scientific importance of research on health disparities and on racial differences. He referred to the presentations by Drs. Freeman and Kington as providing much of the rationale why the profound differences in health status between racial groups are an important source of scientific information about social, economic, cultural, and biological factors contributing to health and disease. He faulted a prevailing scientific view that racial differences are nuisance variation that must be controlled. Like Drs. Freeman and Kington, he argued that race cannot be used as the sole basis for generalization. Instead, race differences provide evidence of significant variation that must be interpreted through other (social, cultural, biological) factors.

The committee's charge was to review NIA's programs on minority aging in light of the view that racial differences are scientifically important. At the same time, the committee was asked to assess NIA's programs to recruit and train researchers from diverse ethnic and racial backgrounds.

Questions addressed by the panel were: (1) What are the important aging research questions in the minority population, and is NIA addressing them? (2) Is the topical balance of minority aging research within each program appropriate to the program's mission? (3) What are the areas of science relevant to minority aging that NIA needs to address more rigorously? (4) Is the scientific planning process appropriate for developing programmatic activities relevant to minority aging research? (5) What training (or capacity-building) mechanisms are most effective in developing minority investigators, and how do we better encourage minorities to use existing mechanisms?

Dr. Jackson chose to highlight the following crosscutting areas from the overall recommendations:

1. Noting the paucity of information on patterns of adult development and aging in many minority groups, the panel called both for national surveys of these groups and for longitudinal studies of cognitive, behavioral, and social functioning within these groups. Emphasis was placed on the need to disentangle effects of socioeconomic status from other sources of variation--including the effects of racism. At the same time, while the panel welcomed research on biological and genetic variation, they urged that an approach be taken that addresses the relation between genetic variation and social and cultural conditions.

2. The panel urged that NIA devote resources to facilitating networks of scholars focusing on minority issues and on conferences focusing on common issues of importance, such as cross-cultural assessment.

3. Noting how panel members had heard and read similar concerns from staff in different NIA programs, the panel urged greater cross-program collaboration on scientific issues of importance in this area. Recruitment and retention of minority participants in research studies was particularly highlighted. Similarly they recognized a need for cross-institute collaboration on these issues across NIH.

4. Panel members voiced concern that NIH is implementing the policy on recruitment of minority participants inappropriately. The standard in use is one in which applications are assessed based on their intent to recruit minority participants. The standard needed is whether minority participation is addressing scientifically important questions. The panel urged NIA to take the lead in seeking change in the implementation of this policy.

In discussion, Council members referred the report on the review of NIA's minority programs back to the remarks made by Drs. Freeman and Kington. The question came up again about the validity of race and ethnicity constructs in science. Dr. Jackson responded that we do biological research but use a socially defined variable for race without knowing what the term means. Several questions addressed plans to link race to genetics and genomics, to cognition and personality, and to health outcomes.

The review panel plans to have a final draft of their recommendations ready for Council's perusal and adoption at the February 2000 Council meeting.

## IV. PROGRAM HIGHLIGHTS

Dr. Marcelle Morrison-Bogorad, Associate Director of the Neuroscience and Neuropsychology of Aging Program, described recent developments in research on the significance of neurofibrillary tangles in the pathogenesis of Alzheimer's disease and related dementias. She explained that the characteristic neuroanatomical hallmarks of Alzheimer's disease are senile plaques of insoluble material (composed largely of the β -amyloid peptide) and neurofibrillary tangles (composed of the protein, tau). Prior work had identified a mutation in the gene for the amyloid precursor protein that is associated with Alzheimer's disease, and had traced much of the mechanism through which the amyloid precursor protein is cut in several ways to produce β -amyloid which then aggregates into the senile plaques characteristic of the disease.

The weight of prior evidence, then, gave a substantial role to senile plaques in the development of Alzheimer's disease and many speculated that these plaques provoke neurofibrillary tangles by an as-yet-unspecified mechanism. However, Dr. Morrison-Bogorad reported recent findings on neurofibrillary tangles that offer the possibility that these tangles might contribute independently to the development of the disease.

Frontotemporal dementia with Parkinsonism, chromosome-17 type (FTDP-17) is an autosomal dominant disease. It has a late onset and the dominant pathology is the accumulation of neurofibrillary tangles, particularly in frontal cortex. β -amyloid rich plaques are not characteristic of this disease. Patients show behavioral and memory changes somewhat different from patterns found in Alzheimer's disease. Recent work has shown that FTDP-17 is associated with mutations in the tau gene. Most recently Hasegawa et al., (*FEBS Lett.*, 437: 207-10, 1998) and Hong et al., (*Science*, 282: 1914-17, 1998) have been able to describe how mutations in the tau gene affect the stability and assembly of microtubules and give rise to tangles. Some of the mutations in the gene increase the ratio of 4-repeat to 3-repeat forms of the tau protein. Individuals with the increased ratio of 4-repeat proteins go on to develop FTDP-17. Other recent papers further specify the mechanism of action of these and other mutations in the tau gene that cause FTDP-17 (D'Souza et al., *Proc. Natl. Acad. Sci.: U.S.A.*, 96: 5598-5603, 1999; Varani et al., *Proc. Natl. Acad. Sci.: U.S.A.*, 96: 8229-34, 1999).

It is clear then that neurofibrillary tangles in FTDP-17 can be caused by a cascade of events independent of plaque formation. At the same time, the above papers provided no evidence that these tangles can go on to provoke senile plaques. Although D'Souza et al. (1999) did report on one FTDP-17 individual whose brain did show an accumulation of β -amyloid plaques, the absence of other evidence of plaque formation in FTDP-17 patients prevents any conclusion about the relative order of tangles and plaques in the cascade that produces Alzheimer's disease.

Dr. Morrison-Bogorad concluded by observing that the tau protein has now taken on a significance to FTDP-17 dementia research that is parallel to the significance of the β -amyloid protein in Alzheimer's disease. The most striking feature of the recent work is how a small variation in the ratio of which kinds of molecule are synthesized can lead to a dementia as profound as FTDP-17.

Questions from Council concerned whether there are behavioral and or affective differences between FTDP-17 dementia and Alzheimer's disease--there are substantial differences--and the significance of the recent finding that a "vaccine" appeared to retard the build-up of plaques in PDAPP transgenic mice. (The lead investigator in the project has been invited to NIH to describe the work. NNA is working with the NIA program administrator for the immunology portfolio, Dr. Barbara Mittleman.)

Dr. Richard Suzman, Associate Director for the Behavioral and Social Research Program, described a study on aging, fitness, and neurocognitive function conducted by Arthur Kramer, Ph.D., in collaboration with Edward McAuley, Ph.D., (Principal Investigator R01AG12113) at the University of Illinois Urbana-Champaign (Kramer, A., et al., *Nature* 400:418-419, 1999).

Dr. Kramer's prior research had suggested that the effect of exercise on cognitive function in old age is specific to particularly age-sensitive aspects of cognitive performance. Also in searching for the underlying mechanism to explain this effect of exercise, Dr. Kramer had noted both that cerebrovascular sufficiency declines with advancing age and that some forms of exercise enhance cerebrovascular sufficiency. Therefore, in the present study, Kramer et al. sought support for the view that increased cerebrovascular sufficiency is responsible for the gains in cognitive performance resulting from exercise. He contrasted an aerobic exercise intervention--which was expected to improve cerebrovascular sufficiency with an anaerobic intervention. He also contrasted executive control measures (which are sensitive to age-related changes in cognitive function) with measures of tasks that do not require executive control. In the study, 124 sedentary adults, aged 60 to 75, were randomly assigned to six months of either aerobic walking or anaerobic stretching and toning exercise, and pre- and post-tested for cardiovascular fitness and cognitive measures.

Participants in the aerobic exercise program showed improvements in reaction times for executive control tasks but not for tasks that did not require executive control. The stretching/toning group showed no significant changes. The conclusions were that aerobic exercise increased cardiovascular fitness and improved cognitive functioning in sedentary older adults, even though the increase in fitness was quite modest. The exercises selected seemed to affect those processes that were the most highly age-sensitive and associated with executive control.

The results offer indirect support to the view that increased cerebrovascular sufficiency contributes to the gains observed. In later research Dr. Kramer intends to test that hypothesis directly by using neuro-imaging techniques. The results also imply an explanation for why some prior studies have found effects on cognitive functioning and others have not. The effects of exercise appear to be specific both to the kind of exercise taken and the kind of cognitive function assessed.

Council members discussed alternative interventions and endpoints and the possible role of motivation in mediating effects of exercise on cognitive function.

Dr. Evan Hadley, Associate Director for the Geriatrics Program, described research on: Genetic Mechanisms Involved in the Age-Related Increase of a Blood Clotting Factor (Kurachi, S., et al., *Science* 285: 739-43, 1999).

The tendency to form blood clots increases with age and contributes to heart disease and stroke. Researchers have found a genetic mechanism through which production of a protein involved in blood clotting increases with age. Finding the genetic regulatory mechanism provides opportunities to design drugs or other interventions to prevent the increased likelihood of clotting and its associated diseases in older persons.

As people age, many develop an increased propensity for their blood to clot within their blood vessels. This may be an important factor responsible for the rise with age in the rates of heart attacks and strokes. Clotting is regulated by a group of blood proteins, coagulation factors. The concentration in the blood of one of these, coagulation factor IX (FIX), tends to rise with age, suggesting that it may play a role in increasing clot formation.

Recently, scientists at the University of Michigan, supported by an NIA Older Americans Independence Center and an NIA Nathan Shock Center for Basic Biology of Aging, investigated genetic factors which regulate an increase with age in FIX. They used genetic engineering techniques to insert different forms of the human FIX gene into young mice, and measured how blood levels of the human FIX protein changed over the life span of the mice.

The different forms of the inserted gene varied in the size of the "flanking regions" of the FIX gene they contained. (Flanking regions are stretches of DNA that extend on either side of the DNA that codes for the FIX protein itself. They contain regulatory elements that control how much of the protein is produced.) By analyzing which parts of the flanking regions made a difference in how FIX levels changed with age, the investigators found two distinct elements regulating age-related changes. One is necessary to prevent a *decline* with age in FIX; the other, to cause its rise with age.

This study is significant in at least two ways. It is one of the first to examine genetic factors that influence how a physiologic function changes with age, rather than simply influence its level at one time, or its response to a short-term stimulus. Second, though the genetic regulatory elements identified do not in themselves "cause" the age-related changes in FIX, they provide the molecular mechanism through which these changes are mediated. Learning the specific elements of a gene which mediate aging changes permits a much more focused approach to finding the cellular or hormonal signals that interact with them. This opens opportunities for further basic studies on the causes of the change with age in FIX levels, as well as the potential to design drugs that could bind these regulatory elements to counter the rise with age in risk of adverse clotting-related conditions such as cardiovascular diseases and stroke.

Dr. Bellino, Acting Associate Director of the Biology of Aging Program, introduced Dr. Stavros Manolagas, the 1999 recipient of the Allied-Signal Research in Aging Award. Dr. Manolagas described recent work by his group on the mechanisms of bone remodeling and formation in

osteoporosis (Manolagas, et al., 1999; Manolagas, et al., 1999; both papers were presented at the American Society of Bone and Mineral Research Annual Meeting).

Osteoporosis, a progressive and increasingly debilitating loss of bone mass leading to increased risk of fracture, is highly associated with increasing age. With one very recent exception, current treatments can only retard the rate of further bone loss. The goal in treatment is to rebuild bone mass that is lost in osteoporosis.

One well-known precursor of osteoporosis is the loss of estrogen in women that occurs after menopause. Estrogen has a role in regulating the rate of bone remodeling. In prior work by his group, estrogen was identified as acting to suppress cytokines in the bone marrow. When estrogen is removed, these cytokines increase the rate of production of bone remodeling cells (osteoblasts and osteoclasts). This increased remodeling generates expanded remodeling space in the bone and less complete secondary mineralization. Thus it accounts for a rapid and early decrease in bone mineral density following loss of estrogen.

However, bone loss is progressive in osteoporosis. Not only is there an increase in the rate of production of bone remodeling cells but also a striking imbalance emerges with osteoclasts (bone-resorbing cells) showing prolonged lifespan relative to osteoblasts (bone-forming cells). Dr. Manolagas and his colleagues showed that estrogen deficiency increases osteoblast and osteocyte (bone-embedded osteoblast cells) cell death and that hormone replacement acts to reduce the rate of osteoblast and osteocyte cell death. Thus the presence of estrogen has opposite actions on the lifespan of osteoclasts and osteoblasts. Importantly they observed that unlike the effect of estrogen on the rate of bone remodeling--which depends on interaction with the transcriptional apparatus, the genome, of the cell--this latter effect appears to involve the outer cell membrane effect. In support of this observation, using *in vitro* and mouse *in vivo* studies, they were also able to show that a conjugate of estradiol that is impermeable to the cell membrane reduced cell death in osteoblasts and osteocytes.

Dr. Manolagas and his colleagues then were able to select a compound that differs from estradiol in that it mimics the nongenomic effect of estrogen on the cell surface but lacks the genomic effects of that hormone. His group administered that compound to estrogen deficient and to estrogen replete mice for a month. They reported increases in bone mass density and substantial increases in mechanical strength (a functional measure of bone strength).

Dr. Manolagas stressed that because this class of drugs has a highly specific effect on cell death in osteoblasts and osteocytes it is likely to generate few harmful side effects and is likely to be generalizable to other kinds of tissue in the body.

Discussion centered on the cell membrane estrogen receptor that appears to be responsible for this second mechanism of action in osteoporosis. Dr. Manolagas observed that it appears to be a receptor common to many types of cell. Questions also concerned whether interventions that decrease cell death may promote carcinogenic effects. Dr. Manolagas expressed the hope that the

small molecule, non-genome interactive drugs offer a likely tool to control cell death without promoting carcinogenesis.

## V. WORKING GROUP ON PROGRAM

Dr. Gage reminded Council members that one of their responsibilities is to review concepts for workshops and conferences that are to be advisory to the Institute. He reported on the Working Group's discussion of three planned advisory meetings: (1) the proposed Behavioral and Social Sciences Research advisory group for inter-agency agreements, (2) an advisory group on long-term care and national needs, and (3) a non-human-primate resources planning group. The Working Group supported plans for these meetings. After brief discussion, Council endorsed the Working Group's recommendation.

The Working Group addressed the program review process and whether or not the optimum amount of information is being achieved by the effort put forth by both staff and Council members. The Working Group considered the extent to which a program should be reviewed independently of other NIA programs, in the context of its component disciplines or in comparison to other NIA programs. It was acknowledged that moving from review of a single program to an approach that is more complex, means that the kinds of objective measures now being employed, e.g., publications in specific highly-regarded journals in a field, may be difficult to translate. In Council discussion, it was suggested that in every fourth cycle the Council should review the overall NIA program. More extensive discussion about reorganization of program reviews is planned for the February meeting after staff has time to formulate ideas for proposals.

Comments on the Working Group's third topic, strategic planning, were held for discussion later in the Council meeting.

The next item was resource development--a topic that grew out of discussion at last Council regarding the importance of genomics and the possibility that NIA could facilitate applications of micro-array technology. A sub-committee subsequently considered the possibility that NIA would contract to produce arrays that would be accessible to extramural grantees at a very reasonable cost. Council discussion focused on what will be provided (mouse filters or human filters), how the informatics and bioinformatics would work, the coordination of a database, user training, whether the proposed resource would have adequate flexibility, and whether this idea warrants the Institute's investment. More extensive discussion is planned for the February Council meeting.

Follow-up information was given by Dr. Kelty and Mary Jo Hoeksema on the revision to the Office of Management and Budget (OMB) Circular A-110, a rule proposed under the provisions of the Freedom of Information Act that would provide public access to research data generated under a Federally-funded research grant that are used by the Federal government in developing an agency action that has the force and effect of law. Council was provided a copy of Senator Richard Shelby's letter which is highly critical of the proposed changes in Circular A-110. The rule will become final on September 30 or October 1, after which further legislation may be introduced. Council was asked to keep aware of this issue--to track and respond to it, if desired.

The final item discussed was the statistical package that summarizes the number of grants that were applied for, the percentages that were supported, and the dollars associated with them relative to all of NIH funding. The report demonstrated that overall NIA's numbers correspond closely to representation across the other Institutes. In conclusion, Dr. Gage indicated that NIA is faring reasonably well within the review sections. Council discussion focused on success rates by program, what success rates mean, and how they are influenced by various mechanisms we use.

## VI. NIA STRATEGIC PLAN

Dr. Terrie Wetle, Deputy Director, NIA, gave an update on the NIA strategic planning process and solicited advice from Council in preparation for its October 15 launch on the web site for public comment.

At the last round of Council and in discussions with the Working Group on Program, major improvements were made in format and content of the plan outline. Meetings were held with several organizations--Gerontological Society of America, American Geriatrics Society, Gerontological Health Section of the American Public Health Association, Alliance for Aging Research, Hartford Foundation, and the Leadership Council on Aging--in which their input on the content of the plan was sought.

Dr. Wetle emphasized that the process of developing this plan has been a very effective device in opening up lines of communication to outside organizations and generating positive reactions and that it will have continuing positive effects in terms of viewing NIA as relevant.

The plan has three overall goals to be achieved through several subgoals and objectives. They are improvement of health and quality of life, understanding healthy aging processes, including understanding the basic biology of aging, understanding genetic properties, and other factors as well as looking in particular at brain function and cognition, and, finally, reducing health disparities among older persons and populations of older persons.

Dr. Wetle thanked the members of the Working Group on Program for their help in thinking through the plan and acknowledged Gail Jacoby, in particular, and the staff of the Office of Planning and Evaluation for having done most of the work on the plan.

An effort will be made to incorporate comments received from the public and from presentations at professional meetings before submission to Dr. Varmus on December 31.

Council discussion focused on how the plan would be executed, whether the plan had been sent to groups such as Hispanic Aging and Asian Pacific and other Institutes and aging groups within the HHS, whether further changes would be required after submission to Dr. Varmus, the positive effect of communicating with outside organizations, whether comments about strengthening and improving the peer-review process should be incorporated into the plan as part of the objective of enhancing

resources to support high-quality research, and how the plan meshes with activities associated with the government Performance and Results Act.

In relation to research infrastructure, a Council member suggested that the strategic plan include a statement that working to improve the peer review process is high priority for NIA. An example of an improvement already undertaken is the change in review criteria, especially the addition of "innovation" as a criterion. Another is the ongoing restructuring of review groups. However, an area in need of improvement is recruiting appropriately expert reviewers. It was acknowledged that most review is conducted by the Center for Scientific Review (CSR) but the point could be made relative to peer review conducted by NIA. Other members expressed skepticism about any changes in willingness to serve on the part of qualified reviewers.

Council was reminded that CSR is examining options to increase flexibility in relation to service on peer review groups and has made dozens of changes to retain a high quality, appropriately focused review system. Council suggested that Dr. Elvira Ehrenfeld be invited to a future meeting to discuss changes, her experiences, and her plans for the peer review process, including the report of the Panel on Scientific Boundaries for Review. When informed of the Peer Review Oversight Group (PROG), members indicated that a report from that group would be of interest.

Conflict of interest was brought up as a problem, particularly when many scientists in a given field network with each other. It was pointed out that the way research is conducted has been changing. With large consortia doing clinical trials, networks of investigators collaborating, and increasing frequency of academic-industry partnerships, definitions of what constitutes conflict-of-interest may need to be reconsidered in terms of institutional and individual involvements.

## VII. COMMENTS FROM RETIRING COUNCIL MEMBERS

Dr. Hodes recognized Council members who will be rotating off the Council at the end of 1999 and invited the three who were present to make comments.

Dr. James Jackson observed that serving on the Council had been a very enjoyable experience and also a surprise both in a positive and negative way. He said he had expected it to be an honorific function and found instead that it entailed a lot of work and involvement and was very productive. He went on to say that he leaves here as a richer person in scientific knowledge and experiences and he appreciated the opportunity to participate and perhaps have some impact.

Dr. Helen Blau said that she, also, did not expect this Council to be such a proactive group and felt very excited that they could have an impact. She complimented Dr. Hodes on having fostered that environment by encouraging Council members to implement change and to challenge the existing way things are done. She said she had enjoyed meeting the exceptional group of people on the Council and getting to know the people in the Institute and that she takes away very good feelings and a lot of new knowledge from her experience as a Council member.

Dr. Jeffrey Bluestone commented that it had been a very pleasant surprise to be welcomed to the Council so warmly when in fact he was an outsider to the process. He also said that this Council has had an impact on the whole NIH, on the whole perception of what a Council could be and do.

## VIII. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[2]

A total of 574 applications requesting $554,652,374 for all years was reviewed. Council recommended 382 for a total of $391,143,883 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

## IX. ADJOURNMENT

The 78th meeting of the National Advisory Council on Aging was adjourned at 12:30 p.m. on September 24, 1999. The next meeting is scheduled for February 8-9, 2000.

Attachments:

A. Roster of Council Members
B. Director's Status Report to the NACA

## X. 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 Miriam F. Kelty, Ph.D.

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[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 only applied to applications that were discussed individually, not to "en bloc" actions.

3 These minutes will be approved formally by the Council at the next meeting on February 8-9, 2000 and corrections or notations will be stated in the minutes of that meeting.

**MEMBERSHIP ROSTER**
**NATIONAL ADVISORY COUNCIL ON AGING**
NATIONAL INSTITUTE ON AGING
(All terms end December 31)

Chairperson
**Richard J. Hodes, M.D.**
Director
National Institute on Aging
National Institutes of Health
Bethesda, Maryland 20892

Barrett-Connor, Elizabeth L., M.D. (2000)
Professor
Department Family and Preventive Medicine
School of Medicine
University of California - San Diego
La Jolla, California

Blau, Helen M., Ph.D. (1999)
Professor and Chair
Department of Molecular Pharmacology
Director of Gene Therapy Technology
Stanford University School of Medicine
Stanford, California

Bluestone, Jeffrey A., Ph.D. (1999)
Professor and Director
Ben May Institute for Cancer Research
University of Chicago, MC 1089
Chicago, Illinois

Campisi, Judith, Ph.D. (2002)
Senior Scientist
Division of Cell and Molecular biology
Lawrence Berkeley Laboratory
University of California
Berkeley, California

Dobrof, Rose, DSW (2002)
Brookdale Professor of Gerontology
Brookdale Center on Aging
Hunter College of the City of New York
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Gage, Fred H., Ph.D. (2001)
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Laboratory of Genetics
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Goldman-Rakic, Patricia S., Ph.D. (2000)
Professor of Neuroscience
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Yale University School of Medicine
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Goldsby, Richard A., Ph.D. (2000)
Professor
Department of Biology
Amherst College
Amherst, Massachusetts

Harper, Mary S., Ph.D. (2001)
Distinguished Adjunct Professor of
Nursing and Social Work
Tuscaloosa, Alabama

Hatfield, Mark O. (2001)
Retired U.S. Senator
Portland, Oregon

Hazzard, William R., M.D. (1999)[1]
Professor and Chairman
Department of Internal Medicine
Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, North Carolina

[1]Effective 10/15/99, Dr. Hazzard's address changed to:
Professor of Medicine, University of Washington
Manager, Geriatrics & Extended Care
VA Puget Sound Health Care System, Seattle, Washington.

Jackson, James S., Ph.D. (1999)
Professor
Institute for Social Research
The University of Michigan
Ann Arbor, Michigan

Rowe, John W., M.D. (2000)
President and CEO
Mount Sinai – NYU Medical Center & Health System
Mount Sinai Medical School
New York, New York

Selkoe, Dennis J., M.D. (2001)
Professor of Neurology and Neuroscience
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Vaupel, James W., Ph.D. (2001)
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Max Planck Institute
for Demographic Research
Rostock, Germany

Wei, Jeanne Y., M.D., Ph.D. (2001)
Director
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Weisfeldt, Myron L., M.D. (2002)
Chairman Department and Professor
Department of Medicine
Medical School
Columbia University
New York, New York

Wise, David A., Ph.D. (2002)
Professor
National Bureau of Economic Research
Cambridge, Massachusetts

**Ex Officio Members**

Donna E. Shalala, Ph.D.
Secretary
Department of Health and Human Services
Washington, D.C.

Harold Varmus, M.D.
Director
National Institutes of Health
Public Health Service
Bethesda, Maryland

LTC George F. Fuller, M.D.
White House Physician
Washington, D.C.

Judith A. Salerno, M.D., M.S.
Chief Consultant, Geriatrics and Extended
Care Strategic Healthcare Group (114)
Department of Veterans Affairs
Washington, D.C.

Jeanette Takamura, Ph.D.
Assistant Secretary
Administration on Aging, DHHS
Washington, D.C.