NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The Eightieth Meeting

NATIONAL ADVISORY COUNCIL ON AGING

May 25, 2000

National Institutes of Health
Building 31, Conference Room 6
Bethesda, Maryland 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
May 25, 2000

The 80th meeting of the National Advisory Council on Aging (NACA) was convened on Thursday, May 25, 2000, at 1:00 p.m. in Building 31, Conference Room 6, 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, May 25, from 1:00 to 5:00 p.m. The meeting was closed to the public on Thursday, May 25, from 5:00 p.m. to adjournment 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. Elizabeth Barrett-Connor
Dr. John Cambier
Dr. Judith Campisi
Dr. Rose Dobrof
Dr. Patricia S. Goldman-Rakic
Dr. Richard Goldsby
Dr. Mary S. Harper
Senator Mark Hatfield
Dr. John Rowe
Dr. Ilene Siegler
Dr. James Vaupel
Dr. Jeanne Wei
Dr. Myron Weisfeldt
Dr. David A. Wise
Dr. Phyllis Wise

Ex-Officio Participants:

Dr. Saadia Greenberg

Absent:

Dr. Dennis Ausiello
Dr. Fred Gage
Dr. Dennis Selkoe
LTC Dr. George F. 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:
Shirley V. Brown, Gerontology News
Pat Kobor, American Psychological Association
Alan Kraut, American Psychological Society
Russell Morgan, SPRY Foundation
Susan J. Whittier, NIH Osteoporosis and Related Bone Diseases~National Resource Center

In addition to NIA Staff, other Federal employees attending were:
Kathleen Bond, HRSA Bureau of Health Professions
Suchira Pande, NIDDK/NIH

I. CALL TO ORDER

Dr. Hodes called the meeting to order at 1:05 p.m. and welcomed members.

Director's Status Report

To give Council a better insight into the impact of budget on the Institute's current activities, Dr. Hodes shared the following information.

The President's budget request for FY 2001 is $725,949,000 which is a 5.5 percent increase over the FY 2000 budget. Of that amount, 64.2 percent would support Research Project Grant (RPG) activities. A similar percentage of FY 2000 funds support RPG activities.

At this point, there is no certainty as to what the final FY 2001 budget will be (in contrast to the President's requested increase, the House would provide 14.8 percent, and the Senate, 15.6 percent) but the House and Senate marks give reason for optimism. If sustained, it would be the third year of an approximately 15 percent increase for NIA and NIH overall. In a longer term perspective, from FY 1991 through the present, NIA had an 18 percent increase in FY 1992 followed by years of increases ranging between 4 and 7 percent, until the FY 1999 16 percent increase, the FY 2000 15 percent increase, and the potential for a similar increase in FY 2001.

This growth over the past two years and a prospect for similar growth next year has facilitated NIA's ability to support research. One metric that has received attention is the success rate--the percentage of applications submitted which are funded. Change in success rates is somewhat surprising, when viewed in juxtaposition to what has happened to NIA's overall budget. From FY 1993 through FY 1998 when the percent increase in budgets ranged from 4 to 7 percent, the success rates for the Institute were in the range of 24 to 33 percent. There was, however, an unanticipated decrease in the success rate from approximately 28 percent in FY 1999, to an estimated 22 percent in FY 2000--and, if NIA's budget increase in FY 2001 were to be at a 15 or 16 percent level, the success rate is

projected to be at 22 percent--a projection that is a lower success rate than at any time in the past decade. Possible contributors to declining success rates are being examined.

Several new staff members were introduced: Dr. James Corrigan, the new Chief of the Office of Planning, Analysis, and Evaluation; Dr. Dan Berch, who has joined the Behavioral and Social Research Program as a Special Expert; and Ms. Karen Bashir who has joined the Office of Extramural Affairs as a Program Analyst.

Dr. Hodes introduced Dr. Ruth Kirschstein, Acting Director, NIH, who commented on the recent NIH testimony before the House and Senate Appropriations Committees.

Dr. Kirschstein explained to Council that as the NIH has received substantial budget increases for the past two years, and seems likely to again this coming year, there is a desire within the Congress and in the country to know that the money is spent wisely and for the purposes for which it was appropriated. Dr. Kirschstein and the Institute Directors were asked, in their testimony before the House and Senate Appropriations Committees, to address how and for what purposes FY 1999 funds were spent, what advances have been made in clinical, behavioral, and basic studies, and to outline specific plans for increases in fiscal years 2000 and 2001. The Congress asked why NIH was funding fewer new and competing investigator-initiated research grants than had been predicted and why, in some cases, the success rates were not going up. NIH representatives emphasized to Congress that the number of grant applications increased substantially. Secondly, that although the individual research project grants are important for scientific progress, infrastructure improvements are essential to obtain the results and do the work that NIH is funding. Average costs also increased as a result of an NIH decision to pay at the full recommended amount.

Another issue addressed by the Committees was health disparities, including NIH activities directed at health differences between minority, rural, and urban poor populations and the majority population. In addition, the disparity in disease among populations is widening, for example, in prostate cancer, hypertension and heart disease, and diabetes. To address this issue, Dr. Kirschstein, continuing an initiative started by Dr. Varmus, formed a trans-NIH working group, which includes all of the Institute Directors, to put together an NIH strategic plan on health disparities between minorities and the majority population. That plan is nearing its final stages of completion.

Dr. Kirschstein also discussed with Council new policies and requirements for education on protection of human subjects, for review of clinical studies by Institutional Review Boards (IRBs), and for safety and data monitoring of Phase 1 and 2 as well as for Phase 3 clinical trials. Training and education in bioethics and how clinical research should be done will be required for all investigators who conduct clinical research starting with the October 1, 2000 receipt date for research grant applications. Conflict of interest issues will also be examined at an upcoming Department of Health and Human Services (DHHS) meeting, not only for individual investigators but for institutions as well, because of the deeper involvement of institutions in commercial aspects of research. The integrity of clinical research and the entire research enterprise depend on the principle of patient protection, an important aspect of clinical research, being carried out properly.

In discussion, Council addressed the shortage of clinical research personnel and speculated that a debt forgiveness program would ameliorate the situation. The need was raised to coordinate activities among the several agencies and organizations involved in monitoring clinical research. Also, the recent proposal for imposition of monetary sanctions by the FDA will have major impact on liability insurance and on the willingness of investigators to do clinical studies. Council expressed concern that these new requirements might further raise the cost of doing research.

Council members also discussed the need to improve the informed consent process and IRB review of consent documents. Financial difficulty for young or new investigators due to inadequate stipends and the large debt burden carried after completion of medical school was pointed out. Dr. Hodes and Dr. Kirschstein commented that NIH for a number of years had the ability to use a debt forgiveness program as a means for recruiting investigators into the intramural research program, particularly into clinical research. However, to extend such a program to extramural investigators would require legislation and, in spite of various attempts on the part of NIH, legislative opportunities have not materialized. At the present time, physicians are being trained in research through career development awards. New award mechanisms have been developed for clinical research curricula and individual training. Dr. Hodes commented that the career development award program is one in which there has been a disproportionate increase in budget allocation within NIA.

Council members also asked questions and expressed concern about increases in average cost of grant awards.

Future Meeting Dates

September 27, 2000 (Wednesday)
February 6-7, 2001 (Tuesday-Wednesday)
May 22-23, 2001 (Tuesday-Wednesday)
September 24-25, 2001 (Monday-Tuesday)

Consideration of Minutes of Last Meeting

The minutes of the February 8, 2000, meeting were approved as submitted.

II. REVIEW OF THE NIA MINORITY RESEARCH PROGRAM

Dr. James Jackson, Chair of the Minority Aging Research Ad Hoc Review Committee, presented the report of the committee's year-long review. In addition to acknowledging members of the committee, Dr. Jackson noted the exceptional leadership and hard work of Dr. Taylor Harden.

The charge to the reviewers was to assess the status and progress of minority aging research at the NIA by reviewing research and training initiatives from 1993 to 1998, by evaluating the effectiveness of NIA in enhancing the competitiveness of minority research applicants, and by

reviewing NIA's initiatives and activities that address major health problems from which older minority people suffer disproportionately.

The following questions guided the review: What are important aging research questions in minority populations and to what extent is NIA addressing these questions? Is the topical balance of minority aging research within each program appropriate to the program's mission? What are areas of science relevant to minority aging that NIA needs to address more rigorously? Is the scientific planning process appropriate for developing programmatic activities relevant to minority-aging research? What training mechanisms are most effective in developing minority investigators? How do we better encourage minorities to use existing mechanisms?

The committee held assumptions that informed and directed its thinking and recommendations:

- "Races, in the sense of genetically homogenous populations, do not exist in the human species today." The biological concept of race is untenable and has no place in biological sciences. (Freeman, H.P. 1998. *Cancer* 82:219-225)
- For purposes of the report, race and ethnicity are defined as social, cultural, political, and legal constructions denoting relationships among groups that reflect a cultural framework of societal, institutional, and political values (Harding, S., *Cancer* 82:221, 1998).
- There exist important and substantive science questions on race and ethnicity--in fact, aging research on minority populations is a new frontier in aging.
- There is a need to denote racial differences in explicit or operationally definable terms that are more descriptive and representative. (There is confusion about definition regarding race and ethnicity. At one level, there is the issue with regard to either self definitions, or "biological" definitions, e.g., "the one drop rule," of race. Other definitions of race are the ways in which people respond to phenotypical differences [visible characteristics].)
- Particular care must be taken in the design and conduct of research involving minority groups to minimize misinterpretations or the potential inappropriate application of results.
- There is an important need for greater efforts in recruiting and retaining minority participants in research studies.
- The 1999 NIA Strategic Plan and the recommendations of this review committee, though developed separately, are usefully interrelated.
- Programs of the NIA collaborate on projects and initiatives that address questions and issues of mutual interests.
- The NIA has been and continues to be committed to outreach, training, and capacity-building programs for individuals from population groups that are under-represented among scientists in aging-related research.

In general, the reviewers were enthusiastic about the efforts and progress made by NIA's extramural and intramural research programs. Some observations on the work in the various programs included the following:

- In the Biology of Aging Program portfolio, little prior research has been done on ethnic differences and biological aspects of aging. However, new initiatives have been developed for the

future, particularly in training and educational outreach programs that try to bring in to the field more individuals from diverse backgrounds.

- Much research in the Behavioral and Social Research Program has been related to issues of race and ethnic background, i.e., cognitive functioning, demography and population epidemiology, mortality, risk and disability, life expectancies, years lived with chronic health problems and disability, self-reported health and health problems, wealth status effect on health, chronic conditions, and disability. Scientific opportunities in this field were identified, such as identifying factors contributing to race and ethnic differences in health and cognitive development, and their role as possible determinants of health over the life course.
- Areas of ongoing research in the Geriatrics Program portfolio on race and ethnic differences include menopause, osteoporosis, physical frailty, diabetes, cardiovascular disease, cancer, and functional assessment and disability.
- The Neuroscience and Neuropsychology of Aging Program has a significant amount of ongoing research with a view to race and ethnic factors, such as visual functioning, insomnia, epidemiology of dementia, neuropsychological test development and appropriateness of assessment, cognitive functioning, and recruitment of race and ethnic groups for clinical trials.
- The Intramural Research Program and the Epidemiology, Demography, and Biology Program have a number of active research programs in this area with emphasis on recruitment of minority samples into laboratories, study of race and ethnic influences on normal aging, prostate cancer, vascular stiffness, intracerebral and carotid artery velocity, respiratory factors, and blood pressure regulation.

The committee presented the following recommendations for action by the NIA:

- Eliminate health disparities--Disentangle socioeconomic status (SES), environmental exposure, and race and ethnicity status on health; improve knowledge regarding prevalence of, and risk factors for, Alzheimer's disease, dementia, and other neurological and psychological disorders; conduct a review of the Alzheimer's Disease Research Centers (ADRC) and Satellite programs to determine participation and research relevance for minority populations; conduct research on the impact of SES, environmental exposure, health behaviors, race and ethnicity on differences in disease prevalence (cancer and cardiovascular disease), incidence, morbidity, and mortality among older population groups.
- Define race, culture, ethnicity, and SES--Continue to work on clarifying the most appropriate definition of, and use for, the concept of race, culture, and ethnicity in aging research; improve the working definitions of race, ethnicity, culture, and SES and encourage standardization across studies; host a conference to initiate a discussion of measuring and explaining cross-racial/cross-cultural differences in health and disease outcomes among various subpopulations; examine the contribution of the Intramural Research Program's Baltimore Longitudinal Study of Aging (BLSA) as a means to improve understanding of race and socioeconomic effect on health and effect of health on SES.
- Implement longtiudinal and life course studies--Longitudinal, population-bases studies are encouraged.
- Integrate biology, genomics, and genetics of aging--Genetics research is encouraged but with caution and sensitivity; continue research on biological and genetic variations that address the

relationships among genetic variations and social and cultural conditions within and among ethnic and racial minority groups; support the BLSA in clarifying and extending genetics research to focus on health issues and successful aging across population groups.

- Refine methods and strategies--Support research to improve methods and strategies for conducting research with minority populations; improve instruments and methods, including standardization across populations to study cognitive disorders and mental health decline in minority populations; improve scales and instruments for use across older population groups.
- Improve recruitment and retention of minorities in research--Encourage NIA to support research to improve strategies for recruitment and retention of minority elders in research with goals of hypothesis testing; assist the NIH to clarify the process of monitoring the inclusion of minorities in clinical studies.
- Strengthen and clarify the NIH policy on inclusion of minorities in clinical research--Seek to improve the NIH implementation of the policy on inclusion of women and minorities in clinical research; encourage the NIH and Office of Research on Women's Health (ORWH) to design a system for tracking inclusion of women and minorities in clinical research that will allow program staff to review recruitment and retention data as well as data that tracks the performance of investigators in meeting the mandate and intent of public law.
- Build capacity and enhance training and information dissemination--Devote resources to facilitating networks of scholars focusing on minority issues and to conferences focusing on common issues in career development; encourage NIA to commit to long-term support of the Resource Centers on Minority Aging Research (RCMARs); continue to support, develop and expand existing mechanisms for developing scientists focused on topics relevant to the aging of minority subpopulations; support mentoring of new investigators; expand physician scientists opportunities; disseminate information.

The review documented that NIA is an innovator in minority research in terms of promoting minority research; that research in minority aging is of sound scientific value; that the lack of clear definitions and clarification of boundaries between groups is a major problem in accepting the notion of ethnic or racial group biologically-bounded health conditions or processes; that some of what is observed in differences among racial and ethnic groups is the product of histories of cultural values, institutional practices, and political decisions linked to phenotypical differences among groups; that there is general concern with understanding aging-related processes among and within racial and ethnic groups; that there is a need for broader programming and more resources to be devoted to the development of new cohorts of minority investigators in aging; that there is a necessity for improved integration of research and training directed to the health needs of our growing racial and ethnic populations with the development of general planning of research and training at NIA as a whole.

The report of the Minority Aging Research Ad Hoc Review Committee was approved and accepted by Council as submitted.

III. WORKING GROUP ON PROGRAM

Dr. Jeanne Wei chaired the Working Group on Program meeting and presented their report to Council on behalf of Dr. Fred Gage who was unable to attend.

The first topic of discussion in the meeting of the Working Group concerned advisory meetings, conferences, and workshops. One of Council's responsibilities is to review concepts for workshops and conferences that are to be advisory to the Institute. An example of a meeting that fits the advisory meeting criteria is one in which a group is brought together by NIA to advise the Institute on issues likely to have direct implications for allocation of resources. Because advisory meetings benefit from the broad vision and perspective of Council, Council members are invited to attend the meetings, and recommendations from them are presented to Council for advice and comment.

Initiatives addressed were: the NIA-NIAMS Osteoarthritis Initiative, the Primate Caloric Restriction Studies, the Aged Non-Human Primate Resources, and a multi-Institute initiative based on recommendations from a National Academy of Sciences (NAS) report entitled "The Aging Mind." Plans were presented for a meeting on "HIV/AIDS and Aging: Prevention and Care Interventions for Older Adults" and a series of conferences on which the Institute is collaborating with the Robert Wood Johnson Foundation that deal with physical activity, exercise, aging, and health. After discussion, Council approved and accepted the recommendations of the Working Group for support of the concepts for these initiatives, the advisory meetings planned, and the report on "The Aging Mind."

Then followed a discussion on coding grant awards for Alzheimer's disease relevance. The NIA is required to report on research funding relevant to a variety of areas. NIA staff are currently reviewing the coding system for grant awards for Alzheimer's disease relevance. The goal is to update, refine, and further standardize a coding system that will show the extent to which NIA-supported research is relevant to Alzheimer's disease. The refined coding system will then be reviewed by extramural scientists and experts in the field, as well as staff from other Institutes. It is anticipated that people within the field as well as people who are not actively in the field will find the improved system useful and reliable.

A discussion followed of changes in the statistical information prepared for Council members at each meeting. The statistical package contains information that pertains to applications and results of review of applications that will be discussed at the Council meeting. The revised report reflected clarification and adjustments for new mechanisms, NIH-wide and within NIA. A decision was made following the last Council meeting to give Council budget information and cumulative data on awards once a year so that it will be accurate and consistent with other information reported by NIA.

The next topic addressed was Council review of programs. A sub-group of Council members had evaluated the process by which Council periodically reviews the Institute's research and training programs. Recommendations from the sub-group include: (1) Frequency and scope of review: The review should take place once every three years, and an entire program should be reviewed, rather than a portion of it, at each review; (2) Each program review should be based 50 percent on past

accomplishments and 50 percent on future directions; (3) Size and composition of the review team: the review group should be small and comprised mainly of present Council members with expertise about the program, plus present or past Council members with expertise in other areas. The reviewers might seek advice from other experts in unusual circumstances; (4) Materials sent to reviewers: reviewers want enough to allow them to assess the quality, breadth, and depth of the program without unduly burdening themselves or staff. Outcome data would be sent to reviewers, including number of grants funded, range of science, major publications and selected publications in major journals, important research findings, and important awards to grantees. A statement of key issues facing the program, key innovations, and successes are examples of other information that would be shared. For a sense of future directions, reviewers would be sent planned initiatives and workshops.

The Working Group considered whether it might meet in executive session. After some discussion, members indicated that it is probably not advisable on a regular basis but that it would be considered should a particular need arise.

Next, the press release from DHHS on protections for human research subjects was distributed and discussed. Dr. Kirschstein commented on this topic earlier in this meeting (see page 3).

The final topic discussed was review of longitudinal studies. Longitudinal studies address questions important to aging. Since they often are judged as not innovative, and since innovation is a review criterion, longitudinal studies may be disadvantaged in review. Working Group members will consider the issue further.

IV. REPORT: BSR PROGRAM REVIEW

A preliminary report of the Behavioral and Social Research (BSR) Program review was given by Drs. Ilene Siegler and James Vaupel.

The committee had high enthusiasm for the scientific directions that were proposed. Extensive material was reviewed and the committee supported Dr. Richard Suzman's vision for BSR and his strategy for further strengthening the Program.

A number of recommendations agreed upon by the committee relate to:

- Increased interaction and discussion among BSR staff about substantive research opportunities that cut across disciplinary boundaries. Scientific staff should have broad interests that cut across disciplinary boundaries and should come from various disciplinary backgrounds. Knowledge of biology, especially genetics and physiology, is desirable. The role of staff is not to defend disciplinary entitlements, but to develop emerging research opportunities, including opportunities that cut across disciplines.
- Recruiting researchers on sabbaticals and leaves of absence to help develop research initiatives.
- The need for a flexible program structure to facilitate shifting emphases on new targets of cross-cutting substantive research opportunities.

- The need for a Deputy Associate Director, who will also serve as a Health Scientist Administrator (HSA), with strong managerial abilities and broad interests.
- Emphasis on cross-cutting research areas, e.g., economics and psychology, or demography and behavioral genetics, and on the interface of behavioral and social science research and biology, especially genetics and physiology. Most of these contributions will be from a disciplinary perspective but the goal is to bring these different perspectives together to focus on common substantive questions.
- Setting priorities for program development to focus limited staff resources on the most promising opportunities to develop a portfolio that furthers the goals of BSR and NIA.

Three targets of opportunity were highlighted as particularly important:
1. Design and evaluation of behavioral and economic interventions and experimental trials and how to translate research findings into public health.
2. Encouragement of cognitive research along the lines of the NAS report, "The Aging Mind."
3. Encouragement of research on reducing health disparities.

A written report on the review will be presented at the next Council meeting.

V. PROGRAM HIGHLIGHTS

A. Dr. Burton Singer, of Princeton University, was introduced by Dr. Richard Suzman, Associate Director, Behavioral and Social Research Program, to present results of his current BSR-sponsored research on allostasis, allostatic load, and pathways to health outcomes (Singer, B., & C. Ryff, *Ann. New York Acad. Sci.*, 896: 96-115, 1999).

Dr. Singer introduced the concept of *allostatic load*, a measure of strain on the body, produced by repeated ups and downs of physiological response, by demands placed on multiple physiological systems, and by elevated activity of physiological systems under challenge (Seeman, T., B. Singer, et al., *Arch. Intern. Med.* 157: 2259-2268, 1997).

He then discussed research on social relationships which have a long record of association with mortality outcomes and, when positive, with protective factors (Seeman, T.E., L.F. Berkman, et al., *Ann. Epidemiol.*3: 325-335, 1993). His research team found that cumulative adversity in social relationships over the life course is indicative of elevated levels of allostatic load, and a high degree of positive relationships is reflected, in later life, by lower levels of allostatic load (Seeman, T.E., L.F. Berkman, et al., *Ann. Epidemiol*. 3: 325-335, 1993). "Social relationship profiles" constructed from these data were based on "positive pathways" and "negative pathways," such as measures of interaction of individuals with their parents during childhood, and relationships with a spouse or a significant other in adulthood. Analysis showed that other aspects of life histories, particularly a persistent economic advantage, can be protective against physiological wear and tear, regardless of relationship history. Alternatively, having at least one episode of economic adversity combined with negative relational experience is conducive to high allostatic load. Such analyses have led

Drs. Singer and Ryff to hypothesize that cumulative positive social relationship pathways have a strong ameliorating effect on allostatic load for persons with any economic adversity. Conversely, being on a negative relationship pathway enhances the negative impact of any economic adversity. Also, having persistent economic advantage overrides the impact of the negative relationship pathway. Finally, there is a pattern of resilience that pertains to any period of economic adversity combined with positive relational experience and low allostatic load.

He concluded by pointing to this research as beginning the development of an early warning system, defined by a set of biomarkers, which is predictive of mortality and multiple chronic conditions in later life, and which also seems to represent a physiological signature of cumulative adversity, relative to advantage.

Discussion raised questions of whether sex-differences were addressed in analysis, whether the findings can be generalized cross-culturally, and the potential importance of finding physiological pathways through which psychosocial factors mediate physiological effects.

B. Dr. Bruce M. Psaty, a professor of Medicine, Epidemiology and Health Services, from the University of Washington, Seattle, was introduced by Dr. Evan Hadley, Associate Director, Geriatrics Program. He presented data from the Cardiovascular Health Study (CHS) in a talk entitled, "Medication Use in Older Adults: Recent Trends and Health Outcomes."

National guidelines for drug therapies generally rely on the results of clinical trials, i.e., evidence-based medicine. Observational studies such as the CHS provide an opportunity to assess how well evidence-based guidelines have been implemented and to identify areas that may need improvement in older populations. The CHS is an observational study of older adults. Because many trials have excluded older participants, little is known about drug use and outcome in this population. Therefore, it is possible to use the CHS to assess the association between drug use and selected outcomes in older adults to help fill in gaps in research knowledge, particularly with respect to drug safety (Psaty, B.M., et al., *JAMA* 282:786-790, 1999).

The CHS is an NHLBI-funded population-based cohort study of risk factors for coronary heart disease (CHD) and stroke in persons aged 65 years and older (Fried, L.P., et al., *Ann. Epidemiol.* 1:263-276, 1991). In 1989-1990, 5201 older adults were recruited from 4 U.S. sites, and in 1992-1993, an additional 687 African Americans were recruited using the same methods. All participants underwent an extensive exam at baseline, annual exams, and follow-up for cardiovascular events. Several CHS ancillary studies focusing on medications and drug-gene interactions were funded by the NIA (AG 09556 and AG 15366). At baseline, 76 percent of subjects were taking at least one prescription medication and the average number of prescription medications for all participants was 2.3 (Psaty, B.M., et al., *J. Clin. Epidemiol.* 45:683-692, 1992).

Dr. Psaty summarized published and unpublished data. The use of diuretics, a therapy that is proven to be safe and effective for the treatment of high blood pressure (NIA/NHLBI co-sponsored "Systolic Hypertension in the Elderly Program"), declined considerably between 1990 and 1997 in CHS participants (Psaty, B.M., et al., *JAMA* 270:1837-41, 1993; Psaty, B.M., et al., *JAMA*

273:1436-1438, 1995). Angiotensin converting enzyme (ACE) inhibitors are known to be effective in patients with heart failure, yet their use increased only modestly between 1990 and 1995 in CHS (Smith, N.L., et al., *Arch. Intern. Med.* 158:1074-1080, 1998). Anticoagulants such as warfarin are effective in preventing stroke in patients who have atrial fibrillation, and the use of warfarin did increase steadily in CHS participants (Smith, N.L., et al., *Arch. Intern. Med.* 159:1574-1578, 1999). Cholesterol-lowering with HMGCoA reductase inhibitors ("statins" drugs), is effective in preventing CHD; yet in CHS, the use of statins in older adults remained low (Lemaitre, R.N., et al., *Arch. Intern. Med.* 158:1761-1768, 1998).

These data can also be used to address questions of drug safety. In one analysis, the use of aspirin was associated unexpectedly with an increased risk of ischemic stroke in women (Kronmal, R.A., et al., *Stroke* 29:887-94, 1998). Preliminary data were also summarized on the angiotensin type 1 receptor polymorphism. The variant "C" allele was much less common in African Americans than in whites. In African Americans, the "C" allele appeared to modify the effect of type of drug therapy on blood-pressure control as an outcome.

A large number of questions remain unanswered. These include trends in the use of, and associations with, beta-adrenergic blockers, calcium channel blockers, ACE inhibitors, hormone replacement therapy, non-steroidal anti-inflammatory agents, alpha-adrenergic blockers, and other agents. Licit drug use is common in older adults. The assessment of drug use is an essential part of the study of the health of older adults. Analyses related to trends can document progress or identify gaps. Assessment of drug-disease associations can also complement information from clinical trials. Studies on drug-gene interactions may become important for helping clinicians to select proper and effective drug therapies in older adults.

Discussion emphasized the importance of doing clinical trials in older people to influence the care and health of older people.

C. Dr. Marcelle Morrison-Bogorad, Associate Director of the Neuroscience and Neuropsychology of Aging (NNA) Program, described how basic research on Alzheimer's disease (AD) has led to promising clinical trials.

Alzheimer's disease is characterized by the buildup of plaques and tangles in specific regions of brain, as well as inflammation, oxidative stress, and brain cell dysfunction and death. While each of these pathologies is being addressed through research aimed at stopping its development or progression, it is in the possibility of preventing buildup of plaque that major advances have recently taken place.

The background to the recent discoveries reaches back to the turn of the last century. In 1906, Alzheimer described dementia in a middle-aged patient and, when she died, described the characteristic plaques and tangles in her brain. Little new happened in research on this disease until the 1970s. With the establishment of the NIA in 1974, the expanded focus of research on aging led over time to substantial growth in funding in AD research. In 1984, George Glenner isolated the plaque from brain blood vessels, found it was composed of a protein fragment, and sequenced it.

From this peptide sequence, molecular biologists deduced the sequence of the messenger ribonucleic acid (RNA) that made it and, using it as a probe, identified the one gene that contained this messenger RNA sequence and therefore the instructions for making the plaque amyloid out of the 100,000 or so in the human genome. So, the gene was isolated and its sequence determined, then the structure of the protein which contains the amyloid fragment, the amyloid precursor protein (APP). Antibodies that specifically recognize the APP protein inside a cell were made and used to locate APP and amyloid in cells and to find out how amyloid is snipped out of APP and deposited in brain. In 1991, the importance of APP to AD research got a major boost from the discovery that a mutation in the APP gene can cause an early onset form of inherited AD in some families. Most scientists now believe that the deposition of amyloid causes all the clinical and brain pathology of AD (the amyloid hypothesis).

After years of work, scientists could identify different places in amyloid's "life cycle" where they could possibly stop its damage: They could try to stop amyloid from being produced; they could stop aggregation; they could prevent harmful effects of aggregation, or they could make soluble the amyloid that was formed. A major concentration of effort was focused on finding the enzymes that cut up APP to form amyloid and its derivatives, ß- and τ-secretases. And if these two enzymes work efficiently, amyloid gets clipped out and ß-amyloid plaques form in brain. Another enzyme, named α-secretase, cuts in the middle of amyloid, stopping plaque production. Scientists are hunting for drugs that can inhibit the activities of the secretases that cut out amyloid or that can increase the activity of the secretase that snips amyloid in two.

The race to identify ß-secretase was successfully completed last year when several drug companies announced in quick succession that they had found the secretase. Knowing the structure of this enzyme will allow development of drugs that efficiently block this enzyme's activity. Meanwhile, several companies have already initiated phase 1 clinical trials to test the safety of compounds that either inhibit τ-secretase or activate α-secretase in healthy people. Additionally, another company is testing its amyloid vaccine (talked about at last Council) in another phase 1 safety trial. (Potter, H., and Dressler, D., *Nature Biotechnol.* 18: 125-126, 2000; Lin, X. et al., *Proc. Natl. Acad. Sci. U.S.A.* 97: 1456-1460, 2000; Schenk et al., *Nature* 400: 173-177, 1999.)

It is quite unlikely that these enzymes only act to cleave amyloid precursor protein. It is very probable that they have additional functions. The major question is whether we can affect the activities of the enzymes in snipping APP and cause a decrease in amyloid levels in brain without affecting other essential brain activities.

The other thing we do not know is whether removing amyloid from the brain will actually slow, or stop, cognitive decline in a person with Alzheimer's disease. The amyloid hypothesis would say that is the case. If it is not, however, we might find we are very good at removing amyloid from the brain, but we will not have solved the fundamental problem of Alzheimer's disease--the relentlessly progressing dementia.

D. Dr. Debra Schwinn was introduced by Dr. Huber Warner, Associate Director of the Biology of Aging Program. Dr. Schwinn spoke on "α_1–Adrenergic receptor subtype: regulation by age and disease."

Dr. Schwinn's presentation addressed α_1-adrenergic receptors in smooth muscle tissue of the cardiovascular system, prostate and lower urinary tract. α_1-Adrenergic receptors signal to the cell nucleus via the G protein, Gαq, to stimulate the enzyme phospholipase-C-ß, releasing inositol trisphosphate (IP3) to the cytoplasm. IP3 then binds its own receptor on the endoplasmic reticulum which in turn releases calcium from intracellular stores to generate a wave of intracellular calcium increase. Another byproduct of the phospholipase metabolism is diacylglycerol, which activates protein kinase-C, in turn phosphorylating many proteins involved in longer term growth stimulation. This mechanism provides short (increasing intracellular calcium) and long-term (protein phosphorylation) responses from α_1-adrenergic signals.

There are several subtypes of adrenergic receptors. Dr. Schwinn's work focuses the α_1-adrenergic family, particularly α_{1a}, α_{1b}, and α_{1d}. Benign prostatic hyperplasia (BPH) originates in the prostate smooth muscle stromal tissue. Work conducted by the Lefkowitz laboratory, in which Dr. Schwinn participated, showed that human prostate stromal tissue expresses α_{1a} adrenergic receptor mRNA. With that knowledge, pharmaceutical companies began to develop highly selective α_{1a} antagonists to relax the prostate smooth muscle, with the expectation that relieving the prostatic obstruction would functionally enlarge the urinary tract and lead to reductions in obstructive (hesitancy, urgency) and irritative symptoms (frequency, irritability) associated with BPH.

In the lower urinary tract, α_{1d} predominates in human bladder, and also in spinal cord innervating the bladder (Malloy, B.J., et al., *J. Urol.* 160: 937-943, 1998). This information came from a small study (13 subjects), mostly men. A larger study is underway which should demonstrate any gender differences. In a study conducted by Dr. Schwinn of partial bladder obstruction in a rat model, after six weeks the predominant adrenergic receptor subtype changed from α_{1a} to α_{1d} in hypertrophic bladder. Thus, in LUTS (lower urinary tract syndrome) the obstructive component is α_{1a}, and the irritative component is α_{1d}.

Alpha adrenergic receptor subtypes were also explored in cardiovascular tissue (Rudner, S.L., et al., *Circulation* 100: 2336-2343, 1999). From a study of 500 vessels from 384 patients, in 20 different vessel beds, but mostly arteries, some veins, and a couple of arterioles, the major adrenergic receptor subtype expressed in splanchnic and coronary arteries at the mRNA and protein levels, and in functional studies, is $\alpha_{1a.}$ In mammary artery, both α_{1a} and α_{1b} are expressed, with 1a predominating in younger individuals (< 55 years old) and 1b predominating in older individuals (>65 years old).

α_{1a} antagonist compounds are promoted by drug companies to relieve prostatic obstruction of the urinary tract, but they do not relieve the irritative symptoms of BPH. To do that, an α_{1d} adrenergic receptor antagonist is required. Thus both types of adrenergic receptor antagonists should be utilized in men to relieve both types of symptoms. In women, only the α_{1d} antagonist would be required, particularly since treatment with the α_{1a} receptor antagonist is associated with increased

incontinence in women. Furthermore, in elderly patients the studies conducted in vascular tissue suggests that α_{1b} antagonists should not be used because of the increased α_{1b} content in arteries of older people (Schwinn, D.A., and G.A. Michelotti, *B.J.U. International* 85 [suppl. 2]: 6-11, 2000). Thus, any non-selective adrenergic receptor antagonist proposed for use to improve symptoms of LUTS in older people should be titrated to minimize α_{1b} antagonist effects that might cause untoward cardiovascular effects. This presentation by Dr. Schwinn provided a strong indication of the value of translational research in improving the health of older men and women.

Council members asked about implications of Dr. Schwinn's work for detrusor hyperactivity and about effects on brain function. More research is needed before the questions can be answered.

VI. 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 1191 applications requesting $1,007,465,146 for all years was reviewed. Council recommended 745 for a total of $627,816,271 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

VII. ADJOURNMENT

The 80th meeting of the National Advisory Council on Aging was adjourned at 6:30 p.m. on May 25, 2000. The next meeting is scheduled for September 27, 2000.

Attachments:

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

[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.

VIII. 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.

[3] These minutes will be approved formally by the Council at the next meeting on September 27, 2000, and corrections or notations will be stated in the minutes of that meeting.

Attachment A

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

Ausiello, Dennis A., M.D. (2003)
Chief, Medical Services
Massachusetts General Hospital
Boston, Massachusetts

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

Cambier, John D., Ph.D. (2003)
Ida and Cecil Green Professor and Chairman
Department of Immunology
University of Colorado Health Sciences Center
and National Jewish Medical & Research Center
Denver, Colorado

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
New York, New York

Gage, Fred H., Ph.D. (2001)
Professor
Laboratory of Genetics
The Salk Institute
La Jolla, California

Goldman-Rakic, Patricia S., Ph.D. (2000)
Professor of Neuroscience
Department of Neurobiology
Yale University School of Medicine
New Haven, Connecticut

Goldsby, Richard A., Ph.D. (2000)
Professor
Department of Biology
Amherst College
Amherst, Massachusetts

Harper, Mary S., Ph.D. (2001)
Geropsychiatric Research Consultant
and Distinguished Adjunct Professor
The University of Alabama
Tuscaloosa, Alabama

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

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

Siegler, Ilene C., Ph.D., MPH (2003)
Professor of Medical Psychology
Department of Psychiatry & Behavioral Sciences
Duke University
Durham, North Carolina

Selkoe, Dennis J., M.D. (2001)
Professor of Neurology and Neuroscience
Center for Neurologic Diseases
Brigham and Women's Hospital
Boston, Massachusetts

Vaupel, James W., Ph.D. (2001)
Director and Professor
Max Planck Institute
for Demographic Research
Rostock, Germany

Wei, Jeanne Y., M.D., Ph.D. (2001)
Senior Physician
Division of Gerontology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

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

Wise, Phyllis M. Wise, Ph.D. (2003)
Professor and Chair
Department of Physiology
College of Medicine
University of Kentucky
Lexington, Kentucky

Ex Officio Members

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

Ruth L. Kirschstein, M.D.
Acting irector
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.

Attachment B

The Director's Status Report of May 2000 (Attachment B) is posted as a separate document.