NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The Seventy-Ninth Meeting

NATIONAL ADVISORY COUNCIL ON AGING

February 9, 2000

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

CONTENTS

Click on the third (bookmarks and pages) icon on the Adobe toolbar for hyperlinks

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

NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
February 9, 2000

The 79th meeting of the National Advisory Council on Aging (NACA) was convened on Wednesday, February 9, at 8:00 a.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 Wednesday, February 9, from 8:00 to 11:00 a.m. and again from 12:45 to 2:45 p.m. The meeting was closed to the public on Wednesday, February 9, from 11:00 to 11:45 a.m. for the discussion of the Intramural Research Program and from 3:00 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. Dennis Ausiello
Dr. Elizabeth Barrett-Connor
Dr. John Cambier
Dr. Judith Campisi
Dr. Rose Dobrof
Dr. Fred H. Gage
Dr. Patricia S. Goldman-Rakic
Dr. Richard Goldsby
Dr. Mary S. Harper
Senator Mark Hatfield
Dr. Ilene Siegler
Dr. Dennis Selkoe
Dr. James Vaupel
Dr. Jeanne Wei
Dr. Myron Weisfeldt
Dr. David A. Wise
Dr. Phyllis Wise

Ex-Officio Participants:

LTC Dr. George F. Fuller
Dr. Saadia Greenburg
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.

Absent:
Dr. John Rowe

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

Members of the Public Present:
Nancy Aldrich, Aging Research & Training News
Shirley V. Brown, Gerontology News
Tom Hogan, The Blue Sheet
Sharon Moss, American Speech, Language, and Hearing Association

In addition to NIA Staff, other Federal employees attending were:
Jill Einstein, CSR/RRB/NIH
Elliott Postow, CSR/RRB/NIH

I. CALL TO ORDER

Dr. Hodes called the meeting to order at 8:00 a.m. and welcomed members and introduced new members. Other announcements included the appointments, within NIA, of Dr. Huber Warner as the Associate Director of the Biology of Aging Program, and Dr. Mark Mattson as the new laboratory chief of the Laboratory of Neurosciences. He also commented on the current status of the NIA strategic plan--that it has now been submitted for review by NIH, may be further modified to reflect comments that result from that review, and will ultimately be released to the public.

Director's Status Report

After introductions, Dr. Hodes began the meeting with a tribute to the late Ms. Gail Jacoby, formerly NIA's Director of the Office of Planning, Analysis, and Evaluation. Ms. Jacoby, her husband, and younger daughter died in a private plane crash. She is sorely missed by the NIA and NIH community.

Dr. Hodes reported that Dr. Harold Varmus, NIH Director, had resigned, effective December 31, 1999. Dr. Ruth Kirschstein is Acting Director while the search for a new director is ongoing. Other staff changes are described in the Director's Status Report which is attached to these minutes as Attachment B.

Dr. Hodes noted that for FY 2000, 64.3 percent of the NIA budget is in the Research Project Grant category (RPG), which is above the NIH average and reflects the NIA commitment to investigator-initiated research. The Research Management and Support (RMS) category, at 3.4 percent, represents a relative decrease in resources to carry out scientific management activities and program development. The Intramural Research Program constitutes about 9.9 percent of the Institute budget, approximately the NIH average level. Contracts and training components received increases of 4.3 and 6.0 percent respectively.

In pointing out budget trends, Dr. Hodes noted that from 1993 through 1998 increases to the NIA budget ranged between three and seven percent; from 1999 through 2000 increases ranged from 15 to 16 percent--two years of substantial growth. Although the success rate increased with modest increases in appropriation, paradoxically the greater increase in appropriations in 1999 was accompanied by a drop in success rates. A major factor contributing to this paradox was that average grant costs increased substantially as the budget increased substantially. Another contributing factor was that the number of applications increased as the budget was expected to grow. A final factor is that years in which there is a large increase in appropriation, in turn, create pressure on the out-year commitment base. Strategies are being examined that may reduce the extent of the out-year commitment that is occasioned by a single year in which a large increase is received. These include (1) supporting shorter-term research projects, (2) supporting infrastructure projects which are much needed and which usually have high first year costs and low out-year costs, and (3) forward funding outstanding projects from the following year.

Council members asked what level of increase would be needed to sustain current success rates and about methods of tracking performance that include the number of funded projects from new as well as established investigators. Dr. Hodes acknowledged that there are other measures of success than success rate but pointed out that all such measures are poor surrogates for the scientific advances that are enabled by the kind of funding increase that NIA has received. He commented that it was through the determined efforts of Senator Hatfield and a few colleagues that these increases have been possible. Dr. Hodes also pointed out that it is impossible to predict reliably what grant costs will be; therefore, it is difficult to provide an accurate estimate of what will be needed to sustain or improve upon current success rates.

Future Meeting Dates

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 24-25, 2001 (Monday-Tuesday)

A change in the meeting date in September 2001 was pointed out.

Consideration of Minutes of Last Meeting

The minutes of the September 23-24, 1999 meeting were approved as submitted.

II. REVIEW OF THE NIA MINORITY RESEARCH PROGRAM

Dr. Taylor Harden, Assistant to the Director for Special Populations, NIA, presented an update on the NACA review of the minority aging research programs at NIA. The review panel, headed by Dr. James Jackson, was charged to review NIA's programs on minority aging. At the same time, the

committee was asked to assess NIA's programs to recruit and train researchers from diverse ethnic and racial backgrounds. The panel plans to have a final draft of their recommendations ready for Council's perusal and adoption at the May 2000 Council meeting. In Council discussion, it was suggested that a copy of the data put together for the review panel which covered all four NIA Extramural Programs should be given to new Council members.

III. WORKING GROUP ON PROGRAM

The first topic at the Working Group on Program (WGOP) was discussion of a recommendation for Council review of programs. Discussion focused on ways to standardize the review process to facilitate extramural program comparisons and to reduce staff burden in preparation of materials for reviewers. NIA staff recommended using sourcebooks as basic material (data) for review. WGOP members noted that sourcebooks do not include quantitative indices of outcome measures such as lists of publications in prominent journals (by grantees), grantee awards, or other objective measures of success. In addition, sourcebooks do not focus on where a field is going and how much of the program's success is attributable to NIA grantees versus what is attributable to efforts outside of NIA-supported research.

A subgroup--Drs. Vaupel and Siegler in conjunction with Dr. Gage--was asked to work with staff to modify this proposal to supplement the sourcebook with outcome measures and other comparison data. Drs. Vaupel and Siegler reported on a short meeting about improving efficiency and efficacy of review by using Council and staff time more efficiently, and by balancing outcome measures of past performance with consideration of future opportunities for research and resource allocations. They will continue to work, communicate with staff, and then meet and report at the May meeting.

Council discussion revealed expressions in favor both of more direct interaction between Council and staff and of benchmarking as an approach to evaluating NIA-supported research in the context of the broader fields of science.

The next topic was the May review of the Behavioral and Social Research (BSR) Program. The BSR program has functioned with its current organization for 25 years. A different program structure might be more appropriate as a consequence of scientific progress and a greater focus on interdisciplinary research. Reviewers will be encouraged to examine gaps in the program areas such as behavioral and social aspects of genetics and an interface between psychology and physiology.

The next topic was Advisory meetings. One of Council's responsibilities is to review concepts for workshops and conferences that are to be advisory to the Institute. The NIA is required to have all advisory input from groups, organizations, or processes that come to the Institute channeled through appropriate means and mechanisms as set forth in the provisions of the Federal Advisory Committee Act. These generally involve action by a chartered advisory group. 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 in a manner 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. There were reports of two meetings held--"Testing Biological Intervention to Promote Healthy Aging," and "Genetics of Alzheimer's Disease." Council accepted these reports. There were actions on meetings planned including "Social Personality in Adulthood and Aging Research Opportunities," "Health Care Organization Research," "Behavioral Intervention Research," "Behavioral Medicine and Biopsychology," "Testosterone Replacement in Men," and an advisory panel on "Exceptional Longevity." After discussion and recommendations by Council, Council approved these and recommended to Dr. Hodes that they be supported.

The fourth item on the agenda, the progress report on the review of minority aging programs, was spoken of earlier in the Council meeting.

Dr. Gage summarized the WGOP's discussion of microarray resources for extramural use. As information emerges about the genome, there is interest in how multiple genes are expressed within a particular setting at a given time. The NIA Intramural Program has expertise in the production of microarrays that allows multiple genes to be screened simultaneously.

Given strong interest in such arrays among the extramural community, Dr. Kevin Becker is leading an intramural effort to tie a service of providing arrays to the community to the goal of collecting from the community data obtained via the arrays. The Intramural Research Program (IRP) thus intends to develop a central data bank on genetic expression. The proposed intramural facility is meant to complement rather than compete with existing commercial facilities.

In discussion, staff commented that a parallel effort has been going on among the NIA's extramural staff to make administrative supplements available for extramural investigators to purchase or use equipment to facilitate this kind of genome research. Council members commended the NIA leadership for this activity and asked how NIA's effort relates to similar efforts in other Institutes. Dr. Hodes responded that other intramural efforts are ongoing and coordination is developing.

Although the WGOP had discussed review issues concerning the Center for Scientific Review (CSR), discussion at Council was held until after the presentation from Dr. Ehrenfeld, the Director of CSR.

The seventh topic on the WGOP agenda was: Coding Grant Awards for Alzheimer's Disease relevance. Coding of grants was said to be helpful to document to Congress and the public the levels of expenditures for various types of research. Discussion followed on the NIA staff efforts to develop a more accurate and useful coding system and evaluate the extent to which NIA-supported research is investigating Alzheimer's disease. The procedures will be shown to outside scientists and representatives of the Alzheimer's Association to obtain their input and comments.

The final topic was the Statement of Understanding which is the agreement on operating procedures between the Council and the Institute staff that defines which applications and actions come to the Council and which the Council allows the staff to act on without consulting Council. The Working Group recommended approval.

The Council voted to approve the Statement of Understanding.

Council then reviewed and discussed the data presented both in the Annual Data Report and in the Statistical package for the current Council round. Dr. Hodes explained that the data provide a snapshot of NIA activities and provide a first-cut on some outcome measures of NIA initiatives and programs.

Council discussion centered on the sharp increase in success rate for program project applications. These large grants may be seen as limiting opportunities for new investigators seeking support for regular research grants, although members acknowledged that the large projects themselves may support new investigators. Dr. Hodes indicated that the topic of large (PO1-like) grants and smaller grants will be placed on the agenda of a future meeting of the WGOP.

IV. REVIEW OF THE INTRAMURAL PROGRAM LABORATORY OF NEUROSCIENCE

Dr. Dan Longo, Scientific Director, explained that review of each intramural laboratory takes place on a four-year cycle, a timeline that allows for review of all components of the intramural program. Presentations of intramural laboratory reviews made to Council are based upon reviews that have taken place one calendar year before, providing time for response to the review to have occurred.

In the past year, many changes have been made in the Intramural Program prompted by the peer review from the Board of Scientific Counselors in May 1998. The work of the Laboratory of Neurosciences (LNS) has been strengthened. Dr. Stanley Rapoport, former Chief of the LNS based in Bethesda, now heads the Laboratory's Section on Brain Physiology and Metabolism. Dr. Mark Mattson was recruited as the new Chief of the LNS based in Baltimore at the Gerontology Research Center (GRC). A new Clinical Director, Dr. Darryl Abernethy, joined the Intramural Program in April 1999. Several other areas of active growth are the Baltimore Longitudinal Study of Aging and the Laboratories of Endocrinology and Cardiology and recruitments in those areas are underway.

The first speaker of the session, Dr. Stanley Rapoport, reported on his research on phospholipid action and brain signal transduction. Phospholipids participate in brain signal transduction and neuroplasticity. Furthermore, abnormal phospholipid metabolism contributes to numerous human brain diseases, including neuropsychiatric disorders, Alzheimer's disease, stroke, and Parkinson's disease. Yet, compared with recent advances in imaging and understanding *in vivo* brain glucose metabolism and blood flow, progress on brain phospholipid metabolism *in vivo* has been limited. Dr. Rapoport's goal has been to develop and apply a new "fatty acid" method to quantify and image the *in vivo* kinetics of brain phospholipid metabolism in health and disease.

With regard to signal transduction, it is known that neurotransmitters, after binding to receptors at nerve synapses, can activate certain signaling enzymes, including phospholipase A_2, phospholipase C, and adenylate cyclase. Activation releases "second messenger" molecules that engender biochemical reactions to change behavior. One of these molecules, arachidonic acid, is released by activation of phospholipase A_2.

Over the last 10 years, Dr. Rapoport reported that his laboratory has developed a method to image and quantify arachidonate release in the brain *in vivo*. The method involves injecting intravenously a radiotracer of arachidonic acid, then measuring its incorporation into brain phospholipids by quantitative autoradiography or direct chemical analysis in animals, or positron emission tomography (PET) in humans (Robinson, P. J., et al., *Brain Res. Rev.*, 17: 187-214, 1992; Rapoport, S. I., *Neurochem. Res.*, 24: 1403-1415, 1999).

With this method, his group has shown in rats that the rate of arachidonate release from brain phospholipids is very dynamic, some 100-fold more rapid than previously thought, consistent with the roles of this second messenger in signaling. Release of arachidonic acid in rat brain is suppressed 80 percent by chronic treatment with lithium (Chang, M. C. J., et al., *Neurosci. Lett.*, 220: 171-174, 1996)**,** a drug that has been used to treat bipolar (manic-depressive) disorder for 50 years without its mechanism of action being agreed on. The suppression is due to reduced molecular activity (reduced mRNA and protein levels) of a phospholipase A_2 that selectively releases arachidonate from brain phospholipids (Rintala, J., et al., *Neuroreport* 10(18): 3887-3990, 1999). Thus, Dr. Rapoport proposes that the mechanism of action of lithium in bipolar disorder is to reduce the turnover of arachidonic acid in brain.

In animal models of Alzheimer's and Parkinson's disease, his laboratory has also shown that disturbed arachidonate-related signaling occurs in response to stimulation by the neuroreceptors, acetylcholine and dopamine, respectively. With Dr. William Eckelman at the Department of Nuclear Medicine at the NIH Clinical Center in Bethesda, Dr. Rapoport's group then showed that arachidonate-related brain signaling can be imaged in humans using positron emission (PET) (Rapoport, S. I., *J. Neurochemistry, Suppl.*, 74: S21, 2000). On the basis of these studies, they propose that it is possible to extend the method with PET to examine and understand altered cholinergic and dopaminergic signaling in patients with Alzheimer's or Parkinson's disease, respectively. Such altered signaling likely underlies characteristic memory and motor disabilities in these patients.

Questions from Council members focused on whether the time course of lithium induction was of the same order as the rate of arachidonate release observed in the reported research (The research team is currently exploring time-course effects.); whether the specificity of the effect (which is specific to one of thirteen phospholipids identified in humans) would hamper attempts to use it to image lithium activity in humans (Dr. Rapoport's proposed approach is to use a provocative test of a drug to stimulate arichidonate activity and thus increase sensitivity.); the many effects that lithium has in the central nervous system (Dr. Rapoport is proposing the phospholipid-arichodonate route as a final common pathway of action.); whether the research team has used *in vitro* techniques to investigate mechanisms of action (Dr. Rapoport indicated that the long-term effects of lithium require an intact brain in which to be demonstrated. However, follow up studies on hypothesized mechanisms would be appropriate for *in vitro* techniques.); whether, in neurodegeneration, the effects of disturbed arachidonate-related signaling lead to cell loss, or to change of receptor activity (The studies have not yet revealed evidence one way or another.); the potential of the imaging method to be sensitive to changes in receptor action prior to cell loss (Dr. Rapaport believes that the technique is very promising in this regard and could lead to presymptomatic identification of Alzheimer's or Parkinson's disease.). Members also commented that given data on the down-regulation of neurotransmitter receptors in normal aging, the method offers potential to link this action to the

responsible signaling pathways and sought whether other investigators were able to image signaling *in vivo*. (Though one Japanese researcher is making some progress, no other investigators have developed a successful method.)

Dr. Longo introduced the second speaker, Dr. Mark Mattson, NIA's new Chief of the Laboratory of Neurosciences. Dr. Mattson recently joined the NIA, coming from the University of Kentucky. He has already published over 250 papers on a variety of aspects of neurodegenerative diseases.

Dr. Mattson's goals are to understand why neurons degenerate by using genetic models, cell culture, and *in vivo* models where nerve cells are subjected to conditions that are thought to be occurring in the brain during aging and during major degenerative disorders. His move to NIA lets him link his ongoing research with resources that allow research findings from related areas to be linked to research on neurodegeneration. To illustrate the approach, he described work completed while at the University of Kentucky and ongoing work at NIA's Gerontology Research Center (GRC).

The studies completed at Kentucky included:

- Work on a proposed free radical-calcium pathway that may be causally involved in the toxic effects of amyloid beta peptide. (The amyloid beta peptide [Aβ] is widely thought to play an important role in the cascade of events that lead to Alzheimer's disease.)

- Research using both cultured neurons and a mouse model found that presenilin mutations cause alterations in calcium regulation in the endoplasmic reticulum (an organelle within nerve cells) that render the cells vulnerable to increased oxidative stress, impaired energy availability, and impaired glucose availability. Mutations in presenilin have been causally linked to early onset Alzheimer's disease. (Guo, Q., et al., *Nature Med.* 5: 101-107, 1999.)

- Work focused on properties of synaptic terminals and dendrites. Dr. Mattson's work has contributed to the accumulating evidence that the factors initiating cell death can all occur in synaptic terminals and dendrites. His research team has also found that neurotrophic factor receptors are located in synaptic terminals. These can stabilize mitochondrial function at the synapse independently of transcription-mediated effects.

Among the ongoing work that Dr. Mattson reviewed:

- Dr. Kruman working in Dr. Mattson's laboratory has been exploring the effects of homocysteine on neurons. Homocysteine, a compound whose levels are elevated in plasma and which appears to be a prominent risk factor for cardiovascular disease, also shows elevated levels in Alzheimer's patients. Dr. Kruman has found using *in vitro* hippocampal preparations that homocysteine does induce neuronal cell death and that it induces DNA damage in cells. However, that damage can be prevented by treating neurons with the compound, 3-amino-benzamide.

- Working with Dr. Nigel Greig at GRC, Dr. Mattson is taking advantage of work on the P53 protein. Much evidence indicates that the P53 protein plays a role in tumor suppression by initiating cell death in cells that appear to be precancerous. Additional work had found that pifithrin-alpha, PFT-Alpha, is itself a selective inhibitor of P53. Dr. Mattson reported that P53 levels are elevated in degenerating neurons and raised the possibility that, although P53 is protective against cancer formation, the same action on neurons may lead to neuronal degeneration. He and Dr. Greig found that at moderate concentrations in *in vitro* preparations, PFT-Alpha is protective against Aβ and staurosporine, a drug that induces cell death.

- Working with Dr. Hodes, Dr. Mattson is exploring telomerase as a way to protect neurons in the adult brain from insult. The telomerase enzyme protects loss of DNA from chromosome ends during cell division. Dr. Mattson has found that agents that suppress TERT (telomerase reverse transcriptase, the catalytic subunit of telomerase) activity in developing neurons also make the neurons more vulnerable to various insults. TERT is not normally present in the adult brain. Therefore, with Dr. Hodes, he is trying to express TERT in transgenic mice such that neurons in the adult brain will have telomerase in order to investigate whether its presence protects against neuronal insults associated with neurodegenerative disorders. (Fu, W., et al., *J. Mol. Neurosci.* 14: 3-15, 2000.)

- Dr. Mattson is also taking advantage of expertise on dietary restriction at GRC to further his work on dietary restriction and neurodegeneration. He is focusing both on identifying the full range of effects of dietary restriction on the brain and exploring whether a model that considers dietary restriction a mild stressor accounts for its effects on the brain. In prior work, his group has found both that dietary-restricted rats are more resistant to several neuronal insults than control rats and that dietary-restricted rats show elevated levels of heat-shock protein and neurotrophic factors in parts of the brain--suggesting that dietary restriction is acting as a mild stressor. In addition:

- Recent work by Zhihong Guo, a postdoctoral researcher in Dr. Mattson's group, has shown a possible link between dietary restriction and Alzheimer's disease. It is known that Aβ impairs the ability of cells to take up glucose and maintain ion homeostasis. It also impairs mitochondrial function. Using a preparation from isolated synaptic terminals, Dr. Guo has found that the terminals of dietary-restricted animals appear to be more resistant to neuronal insult and to show elevated levels of heat-shock proteins. Similarly the effects of neuronal insult on mitochondrial function are reduced in dietary restricted animals.

- In related work at GRC, Drs. Lane, Roth, and Ingram had found that dietary supplementation with 2-deoxy-D-glucose, which restricts energy availability to cells, also mimics some of the effects of dietary restriction. Dr. Mattson's group found that when the same compound is administered to rats who are later exposed to neuronal insults that mimic Alzheimer's, Parkinson's and Huntington's diseases, and stroke, neurons in the brains of the rats administered the compound are more resistant to the insults than control animals. The team also reported evidence that the compound appears to act as a mild stressor. (Duan, W. and M. P. Mattson, *J. Neurosci. Res.* 57: 185-206, 1999.)

Questions from Council members included: (1) whether episodic feeding with maintained calories has the same effect as dietary restriction (Episodic feeding in rats leads to reduced calorie consumption which has the same effect as continuous feeding at the same reduced calorie level.); (2) why telomerase is favored as an approach with post-mitotic cells (The neurons on which the reported effects of telomerase were observed were not dividing. Dr. Mattson's group is exploring another effect of telomerase beyond adding DNA onto chromosomes during meiosis.); (3) whether drug-discovery targets are suggested by the amyloid-free radical-calcium pathway (Antioxidants and agents that stabilize calcium homeostasis are logical candidates. Inhibitors of beta-secretase are also suggested. However, the approach depends on whether the target is a final common pathway that may be associated with several diseases, or an earlier part of the cascade that may be associated with a single disease.); (4) whether fluid intake was controlled in the dietary restricted animals (It was not.); (5) whether the endoplasmic reticulum might be a common site for the aberrant processing that leads to Alzheimer's disease (Dr. Mattson concurred and acknowledged that the work from several laboratories is implying a common abnormality in the endoplasmic reticulum.); and (6) whether the manipulations reported had been investigated on P53 knockout mice (No.).

V. DISCUSSION OF THE INTRAMURAL RESEARCH PROGRAM

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]

VI. PEER REVIEW ISSUES

Dr. Ellie Ehrenfeld, Director, Center for Scientific Review, reviewed her efforts to manage review in a way that would serve the scientific community well. Therefore, when she came to NIH, she reached out to the community and learned that most concerns about review focused on the organization and composition of study sections. Specifically, there was concern that emerging areas of science do not fit into existing review groups and that existing review groups lack the breadth to conduct quality reviews of the increasing multi- and interdisciplinary research projects. On the other hand, some expressed concern that areas of science that are relatively unproductive are garnering more resources than they should. In short, she pointed out that review groups have evolved over time and that it is appropriate to do a comprehensive assessment to see if NIH has the right spectrum of study sections to adequately review current and future science.

A panel was convened in 1998 with members selected for vision, breadth, and past contributions to development and directions of various scientific fields. The panel was asked to examine the organization of integrated review groups. These are clusters of study sections organized to review applications in a broad field with flexibility to move applications easily within the cluster to the study

[2] For the record, it is noted that members absented themselves from the meeting when the Council discussed items which may have resulted in a conflict of interest for the member.

section that can offer a particular application the best review. Phase I of the assessment considered the structure, scope, and organization of the clusters and how they function. The Phase I Boundaries Report proposed a set of integrated review groups, cultural norms that affect reviewer behavior, and principles for establishment of study sections. The report was posted for comment, and more than 800 comments from individuals and groups were received and considered.

A Phase II implementation plan is being completed with the goal of choosing individual science-driven study sections to populate the integrated review groups. The scientific community will be involved in study section design and in the evaluation that will take place once the new organization is operational. Challenges to be dealt with in Phase II include the need for a critical mass of applications to review, a balance between depth and breadth, and the decision that study sections should serve more than a single Institute. Changes already have been made in response to comments received, including the addition of an aging research review group. Phase II is expected to include interaction with several advisory groups. While the system is being designed, plans for its evaluation are being developed. These include clearance to survey reviewers, applicants, and Institute staff before the new study sections are in place (baseline data collection) and afterwards. Lastly, external advisory groups are being formed for each integrated review group. About once every five years, each integrated review group will be site visited and assessed by its advisory/oversight committee on, e.g., scope of the science being considered by the study section, study section composition, and expertise. The Scientific Review Administrators (SRAs) and study section chair will be evaluated as well.

Dr. Ehrenfeld emphasized that the task is exciting and challenging but the result should be a more flexible review system that attends to scientific status, future directions, and quality review.

A Council member asked whether Councils will be involved in the process, particularly in the evaluation. Dr. Ehrenfeld noted that Council members might help suggest external scientists to help with design issues as well as with the evaluation that will occur about 18 months after the changes are in place. Another Council member suggested that the definition of a reviewer's term be made more flexible in order to make recruitment of qualified reviewers more likely. Dr. Ehrenfeld indicated awareness of this issue and said that some accommodations already are being made, but the options need to be systematized and advertised. The difficulty of recruiting adequate numbers of outstanding reviewers in a small field like aging was addressed. Dr. Ehrenfeld also noted that changes in academic health centers also impact on availability of reviewers in clinical areas.

In response to an inquiry about the kinds of pilot studies underway, Dr. Ehrenfeld said that they include shared slots (two or three people fill a single area of expertise but only one attends any given meeting). When asked about senior observers or participants who assume different roles in review from the other members, Dr. Ehrenfeld said that that experiment yielded mixed response. There was resentment from some reviewers that the senior members spoke but did not study and prepare reviews on the applications. Having two classes of study section members may bring more problems than desirable--much depends on the individual. Training study section chairs and members is particularly important to maintain balance and high quality review. A well-trained chair who is

sensitive to the group dynamics may be a better solution than bringing in an overseer or senior scientist whose role is different from that of the other members.

The option was brought up of a continuous off-line (in contrast to traditional in-person meetings of NIH review groups) review process that might expedite review and enable more reviews to occur simultaneously, or for pre-meeting electronic communication among reviewers to better focus the discussion that takes place at meetings. Another issue raised was conflict of interest and its impact on review, particularly in small fields of science. Dr. Ehrenfeld mentioned that Dr. Varmus appointed a trans-NIH committee to look at conflict of interest rules and NIH's interpretation of them. NIH is grappling with how to find a better balance between regulations that will allow expertise for high quality review yet maintain aspects of conflict of interest rules that protect their intent. The need for reviewers representing cultural, ethnic, race, income, and gender diversity was raised. Dr. Ehrenfeld responded that there are many constraints placed on nomination slates. Databases are searched to develop them. Scientific societies are especially useful when they provide staff with pre-vetted lists of potential reviewers whom they know are qualified, having good judgment and a good sense of fairness. In the end, the quality and success of the peer review system rests with the reviewers. Therefore, it is important that they be active scientists who are familiar with writing grant applications and who are grant recipients.

Dr. Ehrenfeld was thanked for an informative, open, and stimulating discussion.

VII. PROGRAM HIGHLIGHTS

Dr. Warner, Associate Director of the Biology of Aging Program, introduced Dr. Carol Greider who spoke on: The Role of Telomeres in Cellular Senescence and Aging.

Telomeres are highly repetitive sequences of DNA located at the ends of chromosomes. Telomeres protect the ends of chromosomes from both shortening and from participating in deleterious rearrangements. Experiments conducted over the last 15 years have shown that telomeres are maintained by the enzyme telomerase, which is a DNA polymerase with an essential RNA component that provides the template for the addition of telomeric DNA repeats to chromosome ends. The enzyme telomerase has been implicated in both cancer and cellular senescence.

If one looks at the length of telomeres in primary human cells that are dividing in culture, telomerase activity is off and the telomeres shorten progressively each time the cell replicates its DNA and divides. However, in mammalian germline cells, including humans, telomerase activity is on and telomere length is maintained because telomerase is able to add lost sequences to the chromosome ends. Normal human cells have a limited division potential (50-60 divisions per individual cell). After a predetermined number of cell divisions, normal cells undergo a process of replicative senescence and cease dividing. However, immortalized cell lines and cancer cells are able to reactivate the silent telomerase enzyme and maintain telomere length after several hundred cell divisions, thus promoting unlimited cell divisions without cellular senescence.

To further study the role of telomeres and the telomerase enzyme in normal biology, Drs. Carol Greider and Ron DePinho created a knockout (KO) mouse that completely lacked the telomerase enzyme. This was accomplished by deleting the mTR gene that encodes the essential RNA template of the telomerase enzyme resulting in a total lack of telomerase activity in the mTR KO mice. Extended breeding of the telomerase KO mice to generation 7 revealed a progressive shortening of the telomeres and increasing chromosome fusions with each generation accompanied by a progressive decline in fertility. Therefore, the inability to maintain the length of telomeres when the function of telomerase is compromised actually leads to chromosome fusion events that can lead to genetic instability and trigger the apoptosis program and cell death.

Further analysis of the telomerase KO mice suggested that telomerase activity is actually required for the growth of tumor cells *in vivo*. This was studied by cross breeding the telomerase KO mice with INK4a mice, mice that lack two tumor suppressor genes, p16 and p19, and normally develop tumors at a very high rate compared to normal mice. Comparison of INK4a mice with and without telomerase activity revealed a 50 percent reduction in tumor incidence in the telomerase deficient mice after the fifth generation. In mice of earlier generations no difference in tumor incidence was noted indicating that it is not the absence of the telomerase enzyme per se but rather the short telomeres generated after five generations that leads to the inability of spontaneous tumors to grow. However, unexpected results were found when the telomerase KO and p53 KO tumor prone mice were crossbred. The p53 tumor suppressor gene is involved in the maintenance of genome stability. In the absence of p53 and telomerase activity, an increased tumor incidence was noted. Thus, loss of both genes acts cooperatively to increase genetic instability that ultimately results in an increased tumor incidence in mice with non-functional p53 and telomerase genes. (Blasco et al., *Cell* 91: 25-34, 1997; Lee et al., *Nature* 392: 569-574, 1998; Chin et al., *Cell* 97: 527-538, 1999)

Dr. Elizabeth Barrett-Connor, Council member, was introduced by Dr. Evan Hadley, Associate Director of the Geriatrics Program. She presented data from the Rancho Bernardo study that has been ongoing for 28 years. Participants were enrolled between 1972 and 1974 and attended a follow-up visit between 1984 and1987 when blood was drawn for the evaluation of sex hormone levels. The objective was to determine the role of sex hormones as predictors of chronic diseases of aging, such as diabetes, heart disease and osteoporosis. It was observed that while total testosterone changes little in men until very old age, bioavailable testosterone decreases markedly with age. Thus at ages 50-59 only 2.5 percent of men are hypogonadal, while 35 percent are hypogonadal in the ninth decade.

In women with intact ovaries, total testosterone increases with age so that premenopausal levels of testosterone are maintained or even increase, and bioavailable testosterone remains constant postmenopause. Women who had a hysterectomy with bilateral oophorectomy have significantly lower levels of both total and bioavailable testosterone than women who had a natural menopause. Interestingly, hysterectomized women whose ovaries were conserved have intermediate testosterone levels.

Because men have 20 times as much testosterone, but also 4 times the amount of estrogen as postmenopausal women, attributing gender differences between postmenopausal women and men on the basis of estradiol may be unwarranted.

Dr. Barrett-Connor's group had hypothesized that testosterone would correlate positively with bone density, and indeed there is a significant association at radius, spine, and hip in men. However, only a weak association between testosterone and bone density is observed in women. In contrast, in both sexes, estrogen is significantly associated with bone density at all sites measured. (Ferrini and Barrett-Connor, *Am. J. Epidemiol.* 147, 1998)

Although testosterone is reputed to be a health hazard for men, when relationships between testosterone and common risk factors for cardiovascular disease and depression were examined, no significant associations were found between testosterone and blood pressure, cholesterol, triglycerides, glucose, or BMI (body mass index). Total testosterone did not appear to be associated with cardiovascular death. Similarly, neither testosterone nor estradiol were related to heart disease in women. In men (but not in women) higher testosterone levels were associated with less depression as measured by Beck's Depression Index. (Barrett-Connor et al., *J. Clin. Endocrinol. and Metab.* 84, 1999)

Twelve cognitive measures were evaluated to examine the relationship between estradiol and testosterone and cognitive performance. In men, low estradiol and high testosterone levels predicted better performance on cognitive function tests. Women who had higher testosterone levels scored better on the MiniMental Status test, but higher estrogen levels were not associated with better cognitive function scores. (Barrett-Connor and Goodman-Gruen, *J. Am. Geriatric Soc.* 47, 1999; *J. Clin. Endocrinol. and Metab.* 84, 1999)

Intervention studies using improved methods to deliver physiologic doses of testosterone by dermal patch are being contemplated to clarify the clinical relevance of observed interesting relationships with sex hormones. A better understanding of testosterone and estrogen metabolism may provide useful insights into differential susceptibilities to some of the chronic diseases of aging.

Council members asked Dr. Barrett-Connor to clarify the nature of the sample. Dr. Barrett-Connor explained that women on hormone replacement therapies were excluded and, because of limited funding, the study sample was largely Caucasian. They asked whether a ratio measure of testosterone to estradiol levels would provide a clearer picture. Dr. Barrett-Connor responded that when her group had employed ratio measures, testosterone levels alone continued to drive the effects. Finally, a Council member asked Dr. Barrett-Connor's opinions on why her data show no relation between estrogen and cognitive function. Dr. Barrett-Connor expressed the view that prior reports of relationships were confounded by inadequately controlled selection effects.

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).[3]

A total of 802 applications requesting $206,572,432 for all years was reviewed. Council recommended 549 for a total of $157,605,782 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 79th meeting of the National Advisory Council on Aging was adjourned at 5:00 p.m. on February 9, 2000. The next meeting is scheduled for May 25-26, 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.[4]

_____

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

Prepared by Miriam F. Kelty, Ph.D.

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

[4] These minutes will be approved formally by the Council at the next meeting on May 25-26, 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)
Distinguished Adjunct Professor of
Nursing and Social Work
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 February 2000 (Attachment B) is posted as a separate document.