NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The Seventy-sixth Meeting

NATIONAL ADVISORY COUNCIL ON AGING

February 3-4, 1999

National Institutes of Health
Building 31, Conference Room 6
Bethesda, Maryland 20892

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NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
February 3-4, 1999

The 76th meeting of the National Advisory Council on Aging (NACA) was convened on Wednesday, February 3, at 10:30 a.m. at 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 3, from 10:30 a.m. to 2:00 p.m. and again on Thursday, February 4, from 8:00 a.m. to 1:00 p.m. The meeting was closed to the public on Wednesday, February 3, from 2:00 to 6:00 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code, and Section 10(d) of Public Law 92-463.[1]

Council Participants:

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

Absent:

Dr. Elizabeth Barrett-Connor
Dr. Judith Campisi
Dr. Richard Goldsby
Senator Mark Hatfield
Dr. John Rowe
Dr. George Fuller
Dr. Judith Salerno
Dr. Jeanette Takamura

[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 Supplement A.

Members of the Public Present:
Nancy Aldrich, Aging Research and Training News
Shirley Brown, Gerontology News
Andrea Castrogiovanni, American Speech-Language-Hearing Association
Tom Hogan, The Blue Sheet
Pat Kobor, American Psychological Association
Roni Neff, Center for the Advancement of Health

In addition to NIA Staff, other Federal employees attending were:
Ms. Diana Jaeger, OPERA
Dr. Michael Micklin, Center for Scientific Review

I. CALL TO ORDER

Dr. Hodes introduced Dr. Myron Weisfeldt and Dr. Rose Dobrof, new members of the National Advisory Council on Aging (NACA). Dr. Weisfeldt is Chairman, Department of Medicine, and Professor at Columbia University, New York and a cardiologist. Dr. Dobrof is a Brookdale Professor of Gerontology, Brookdale Center on Aging, Hunter College, New York.

Dr. Hodes announced that Ms. June McCann, NIA Committee Management Officer and Executive Secretary of the Council, is retiring after 22 years with NIA. He and the entire Council expressed their appreciation and good wishes.

Future Meeting Dates

September 23-24, 1999 (Thursday-Friday)
February 8-9, 2000 (Tuesday-Wednesday)
May 25-26, 2000 (Thursday-Friday)
September 27-28, 2000 (Wednesday-Thursday)
February 6-7, 2001 (Tuesday-Wednesday)
May 22-23, 2001 (Tuesday-Wednesday)
September 25-26, 2001 (Tuesday-Wednesday)

Consideration of Minutes of Last Meeting

The minutes of the September 23-24, 1998 meeting were approved as submitted.

Director's Status Report

Dr. Hodes reviewed NIA's FY99 budget and the FY 2000 budget requested by the President. Specific budget information is appended to these Minutes. He noted the instability of budget increases, so that a year with a higher budget allocation often is followed by a year with a much smaller increase. This instability makes budgetary planning difficult. In FY 1999, the NIA budget for Research Centers increased by 10%, the first increase in many years. Since the projected budget for FY 2000 is for no increase in Research Centers, NIA will make an effort to assure an equivalent funding level will become available for Centers that compete in FY 2000.

Although the success rate for grant applications fluctuates, it is more stable from year to year than are budget increments. A substantial increase is allocated to the intramural research program for opening a clinical research unit at the Bayview campus in Baltimore in collaboration with Johns Hopkins University. Overall, Dr. Hodes expressed confidence that the research community is submitting high quality applications that have the potential to make excellent use of budgetary increases.

In discussion, Council pointed out that it was anticipated that NIH budget increases would continue for several years. Now, with the FY 2000 budget increase projected to be approximately 2%, the research community is faced with little prospect of support for the increased number of applications that it was encouraged to submit. It was also observed that even with a likely budget increase of 17% over 2 years, the research community has generated so many applications or applications that are so costly that the success rate has not changed. In discussion of whether NIA and NIH are able to manage a major single year budget increase appropriately, the sense of Council was that there are sufficient meritorious applications awaiting funding and that there is an opportunity to respond to equipment and other infrastructure needs.

II. APPLICABILITY OF THE FREEDOM OF INFORMATION ACT TO GRANT RECIPIENTS

Ms. Diana Jaeger, Acting Director, Office of Policy for Extramural Research Administration (OPERA) briefed the Council on implications of an extension of the Freedom of Information Act (FOIA) to grantees' research data. The 1999 Omnibus Appropriations bill included a provision that directed the Office of Management and Budget to amend OMB Circular A-110 (Uniform Administrative Requirements for Grants and Other Agreements with Institutions of Higher Education, Hospitals and Other Non-Profit Organizations) to extend the FOIA to require that Federal awarding agencies assure that all data produced under an award will be made available to the public. Further, if the agency obtaining the data does so at the request of a private party, a reasonable user fee may be charged. Ms. Jaeger noted that NIH supports the sharing of research data but feels it is essential that concepts be clarified to assure data integrity, confidentiality for research participants, the intellectual and the financial investments of the researchers, and the continuation of research.

Ms. Jaeger told Council that an NIH Working Group is developing a response to the proposed legislation, and that when a Notice of Proposed Rule Making (NPRM) is issued, NIH will comment through DHHS and to OMB directly. She emphasized that NIH perceives this amendment as a major science policy issue. Therefore, NIH is informing the research community of the change and is encouraging organizations and individuals to keep informed and to comment to OMB.

In discussion, Council members could foresee many implications of the legislative change. For example, the Health Care Financing Administration and other organizations might be reluctant to share data with researchers. If those doing secondary analyses of existing data sets were required to pay fees, where would the funds come from? Other members wondered about whether biological materials constitute data, and the value of data as intellectual property. Drs. Hazzard and Blau agreed to draft a statement for Council to forward to OMB and to the Deputy Director for Extramural Research, NIH.

III. INTRAMURAL PROGRAM REVIEW

Dr. Dan Longo, Scientific Director, reminded Council that the Intramural Research Program is reviewed by the Board of Scientific Counselors. Each review encompasses two laboratories, so that each program is reviewed about every four years. Individual NACA members serve as ad hoc reviewers for the Board. He reported that the program overall was reviewed favorably by a Blue Ribbon Panel appointed by the Director, NIH, and that the report of that review was sent to Council members.

Two laboratories reported to Council, the Laboratory of Molecular Genetics and the Laboratory of Personality and Cognition.

The Laboratory of Molecular Genetics (LMG) is investigating the molecular basis for aging and age-dependent diseases. Studies are focused on DNA-related mechanisms such as DNA repair, replication and transcription, and genomic instability. The increased occurrence of DNA damage that has been observed with increasing age in many biological systems may be due to changes in DNA repair. LMG has a special interest in the fine structure of DNA repair which includes the study of the DNA repair processes in individual genes.

Dr. Vilhelm Bohr, the Chief of LMG, noted that premature aging syndromes such as Werner's and Cockayne's are excellent biological model systems for the molecular study of aging. Researchers in the laboratory have found defects in DNA repair and in basal transcription in cells from patients with Cockayne syndrome. They have purified the Werner protein and biochemically characterized its activity, which involves the unwinding of DNA (helicase). Dr. Bohr also discussed work on DNA damage in Alzheimer's disease; on the role of the P21 protein; on possible changes in ribosomal DNA in humans; and on the process of somatic hypermutation. He described clinical longitudinal research in the Baltimore Longitudinal Study on Aging exploring whether the genome becomes less stable with increasing age. Finally, he indicated that Dr. Seidman has joined the lab and has started a program studying triplex oligonucleotide structures. These can be used to target specific genes in DNA and to provide

a mechanism for targeted knockout of particular genes that are implicated in aging, thus allowing their role in the aging process to be addressed.

The Laboratory of Personality and Cognition conducts basic and clinical research on individual differences in cognitive and personality processes and traits. The laboratory investigates the influence of age on these variables and their reciprocal influence on health, well-being, and adaptation. It employs longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

Dr. Paul Costa, Chief of the Laboratory of Personality and Cognition, reported that the Personality, Stress and Coping Section has conducted systematic basic research in personality guided by the Five Factor Model (FFM) which asserts that personality traits can be understood as aspects of 5 factors: Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness. He reported that the model is now the prevailing conception of personality in psychological research. He described work using the model that indicates that some changes in personality may be early indicators of Alzheimer's disease. He also described a large cross-cultural study showing consistency of factor structure in the model across cultures. However, the study did show some consistent changes in personality in adulthood in some cultures other than the U.S. In the cognition section, performance of Baltimore Longitudinal Study on Aging (BLSA) participants on the Benton Visual Retention Test has led to the test's identification as a potential early marker for Alzheimer's disease. That finding is being followed up using neuroimaging techniques. Finally, he described ongoing work investigating whether estrogen provides a protective effect on memory.

IV. NIH DIRECTOR'S AFTERNOON LECTURE

James P. Smith, Ph.D., Senior Economist at RAND and an NIA MERIT Awardee, delivered a lecture on the results from the pilot study for the New Immigrant Survey (NIS-P) on February 3, 1999 as part of the NIH Director's Wednesday Afternoon Lecture series.

The NIS-P is the first step in a plan to carry out a comprehensive, multi-cohort longitudinal survey of new legal immigrants to the U.S. and their children. Dr. Smith, the Principal Investigator of this project which is funded by three Federal agencies including NIH, presented the goal of the study: to advance understanding of the socioeconomic status of immigrants from a wide range of countries and their effects on the U.S., including on public health and on a number of health conditions of interest to the NIH. The longitudinal data collected will permit tracking the mobility and adaptation of the immigrants and their children to the U.S. Dr. Smith presented some results from the NIS-P on the health, schooling, language skills, and earnings of legal immigrants, and discussed challenges in conducting a survey of this kind.

V. 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 793 applications requesting $646,138,782 for all years was reviewed. Council recommended 586 for a total of $489,797,485 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

VI. TASK FORCE ON TRAINING

Dr. Blau introduced the recommendations of the Task Force on Training by describing the reasons for the formation of the Task Force and its membership. She presented the recommendations for approval by Council. After discussion of the appropriate benchmark with which to compare National Research Service Award (NRSA) stipends; of the best means to support junior scientists who are beyond the immediate postdoctoral years; of salary restrictions on career awards; and of the relative merits of training on training grants and training on research grants, Council approved the following recommendations:

1. The Task Force (NACA) recognizes that the recent substantial increase in NRSA stipends for predoctoral and postdoctoral students has significantly addressed the need for adequate stipends for research trainees. At the same time, the Task Force (NACA) recommends continuing diligence in ensuring that stipends remain adequate in future years. At the postdoctoral level, parity with NIH intramural stipends is recommended as an appropriate standard.

2. The NIA should broaden the definition of appropriate training for aging research to include training in the late-life diseases and conditions that affect older people, and biological, psychosocial, neuroscientific, and behavioral perspectives on these diseases.

3. The NIA should issue program announcement(s) clarifying the issue of what is appropriate training in aging research, and seeking applications for training in focused areas that recognize the important interdependence of aging research and basic research in biological, clinical, neuroscientific, and psychosocial fields.

4. The NIA should issue guidelines to review committees that encompass an expanded definition of aging research in the context of review of training applications. Where necessary, membership should be expanded to provide appropriate review.

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5. NIA is urged to develop additional materials (such as a web page) highlighting key information that will make Training Directors aware of existing flexibility in the NIA and NIH administration of these programs.

6. NIA should adapt and expand the existing mentored career award mechanism (K01) to allow a track for research scientists and staff scientists as well as faculty.

7. The Task Force (NACA) strongly supports the current broad availability of opportunities for research experience available to predoctoral and postdoctoral students on NIA and NIH research grants.

VII. GERIATRICS PROGRAM REVIEW

Dr. Hazzard reported on the review of the Geriatrics Program. He complimented the staff, particularly for the degree to which they have formed collaborations both within the extramural programs at NIA and across the NIH. Geriatrics is a broad and multidisciplinary subject area and without these collaborations, he noted, the program would risk becoming superficial, isolated, or redundant. He then reported on the four sections of the program that had been reviewed.

Cancer. Reviewers recommended that the program develop a formal arrangement with NCI in which NCI commits resources to the study of cancer and aging. Also panel members suggested that NIA resume collaboration with the Veterans' Administration to focus on tumors that have a high incidence in older men. Regarding initiative development, reviewers recommended both a broad announcement focused on treatment in the elderly across a wide variety of tumor types, and more focused announcements on use of adjuvant therapies; on the biology associated with cancer in the elderly (with the Biology of Aging Program), and on the uses of radiation therapy. Reviewers also recommended additional funding for the program area.

Osteoporosis. Reviewers commented on the breadth of the portfolio in osteoporosis and endocrinology. They said that the portfolio is too broad for a single individual to lead and urged that the osteoporosis and endocrinology portfolios each be assigned a program administrator. They identified research challenges in the field, including better definition of the roles of calcium, Vitamin D, and estrogen, and of the mechanisms of accelerated bone loss in old age. They identified needs for further study of the role of nutrition in osteoporosis; of the nature of gender differences in bone biology, pathogenesis, and treatment of osteoporosis; of improved methods of diagnosis and screening; and of new methods to measure the expression of local factors that regulate bone turnover and strength. They recommended small-scale studies and analyses of existing data sets to address these opportunities. They also suggested a cost-benefit analysis of interventions in elderly post-fracture patients.

They recommended that a small advisory group be formed to provide multidisciplinary input on future directions including basic science developments that are ready for clinical investigation, and urged that the links between basic biology and the geriatric osteoporosis program be strengthened. They suggested expanding the workshop on Selective Estrogen

Receptor Modulators (SERMs) to include SARMs (androgen) and the use of these drugs in both sexes.

Musculoskeletal. Given the prevalence of frailty and weakness as contributors to health care needs in the elderly, the program area's focus on sarcopenia is well-founded. However, reviewers suggested a more focused portfolio of research than was offered at the program review meeting. Among areas needing development, reviewers identified exploration of the basic mechanisms, including neural changes, that generate sarcopenia; development of anabolic agents that counteract sarcopenia and minimize harmful effects of testosterone; and analysis of the integrative mechanisms that give rise to the substantial gains achieved by short term training programs on strength and performance. It was pointed out that the Geriatric Program's focus should be chosen in relation to, and in collaboration with, the efforts of the Neuroscience and Biology of Aging programs at NIA and related programs at NIAMS. Reviewers praised the concept and operation of the musculoskeletal working group. They praised the recent workshop on muscle blood flow and saw opportunities for further research in the area, perhaps in collaboration with NHLBI. Reviewers supported the NIA publication: Handbook on Exercise Advice for the Elderly (produced by the NIA Public Information Office with the technical assistance of GP staff).

Pepper Centers. The Pepper Center (Older American Independence Centers) program was acknowledged to have created a national focus on Geriatric Medicine and to have contributed substantively to the growth of the field through the success of the Centers' emphasis on career development of promising clinical investigators. Their clinical trial portfolio has focused on important issues related to independence in the elderly, helped by the core resources which have guided research along thematic lines. Reviewers urged that consideration be given to the future development of new directions, with investigators encouraged to propose novel cores, resources and research. Further, reviewers urged that the centers be broadened from their predominantly clinical base to include basic as well as behavioral and social science. The flat budget was considered detrimental to the Program. Reviewers recommended a rate of growth of about one center every three years.

Dr. Hazzard concluded his review by noting that the reviewers consider that the program on geriatrics has provided the Institute with an excellent return on investment and should be continued with modest growth and no major change in strategy.

In discussion, Council members raised several topics including pharmacokinetics, excessive disability, obesity, the role of poverty, and the provision of home care. Dr. Hazzard indicated that the wealth of possible topics underlines the need for the program to focus its agenda.

VIII. NACA TASK FORCE ON MINORITY AGING RESEARCH

Dr. Jackson reported that the NACA Task Force on Minority Aging Research had discussed three topics: Monitoring the inclusion of women and minorities in clinical research; the Resource Centers for Minority Aging Research; and the forthcoming review of minority aging research planned for the Council meeting in September 1999. NIA staff provided updates on NIA outreach activities.

Monitoring the inclusion of women and minorities in clinical research. Council members were provided figures showing by ethnicity and gender the numbers of participants in clinical research supported by NIA. Dr. Jackson reported concerns with the data that limit its usefulness. For example, the system tracks cumulative data from the point of recruitment although there is no indication whether subjects who were initially recruited completed the study; the data are skewed by very large population based studies; and data entry as well as decisions about which studies to include are made by many different people, probably resulting in inconsistent data. Discussion focused on what response is appropriate. One proposal was to share the concerns with the NIH Office of Research on Women's Health (ORWH) who designed the system for entering and monitoring the data. Dr. Jackson proposed working with a small group of NIA staff who would coordinate with ORWH to suggest specific improvements to the system.

Resource Centers for Minority Aging Research (RCMARs). In a progress report on these Centers, Dr. Jackson described their goals as fostering the development of minority investigators trained in aging research; fostering the growth of research on minority aging; and increasing the participation of minority individuals as participants in clinical research on aging. He described early success in supporting a substantially larger than expected number of promising minority researchers in their early careers; in a large number of publications, including several in leading journals, on minority aging topics; in collaboration with the Pepper Centers that may help to increase participation in clinical research; and in planning conferences on measurement issues relevant to working with ethnically diverse groups. He also mentioned a related initiative on networks to increase the cultural diversity of the research workforce on aging. The funded grants are collaborating closely with the RCMARs to identify promising students and faculty from a broad array of colleges and universities. The efforts of both Dr. Harden and Dr. Stahl in fostering these initiatives were acknowledged.

Planned review of minority aging research. Dr. Jackson reported on the results of a conference call with the group charged to review the minority aging research portfolio at NIA. The review will be conducted at the September Council meeting. Reviewers expressed an interest in gathering data on initiatives conducted prior to 1993 – the proposed starting date for data collection. However, planning has focused primarily on the intellectual basis for the upcoming review. Reviewers shared the perception that the review seeks to enhance NIA's efforts in going beyond describing differences by ethnic groups to probing what it is about minority status that is scientifically important. Nevertheless, reviewers differed sharply on the extent to which they considered ethnic and minority status to be explanatory concepts, intermediate variables, or marker variables that reflect underlying differences in socioeconomic status and similar variables. Dr. Jackson identified a need to develop a working paper on this subject prior to the review. He noted that NIA and NACA are addressing what is likely to be an important issue across NIH.

NIA outreach activities. Dr. Harden described a recent Technical Assistance Workshop held in conjunction with the 1998 meeting of the Gerontological Society of America and cosponsored by the NIH Office of Research on Minority Health. She also described the forthcoming Summer Institute on Aging Research, cosponsored by the Brookdale Foundation, and to be

held in July 1999, and a regional meeting to be held at the University of Arizona in Tucson. In planning the latter meeting, NIA worked with Dr. Carol Barnes at the University of Arizona, a former Council member, to increase outreach to local Native American communities.

IX. WORKING GROUP ON PROGRAM

Dr. Gage reported on the meeting of the Working Group on Program. Eight topics were discussed.

The first issue addressed was the purpose of Council review of programs, how the review is used, and whether the review should be of past performance or focus on prospective change. The nature and amount of information that is needed by Council reviewers in advance of the review was addressed, as was the need for commonality across different program reviews, and whether reviewers should make recommendations to the Institute.

In discussion it was pointed out that Council reviews of programs have moved from being presentations to becoming more interactive and evaluative, in which reviewers assess entire programs or selected areas and make recommendations to the Institute. Recommendations that emerge in conjunction with one review become incorporated into the review process. For example, all programs have been asked to include reviewers who are independent of the program and/or Institute, to include at least one representative of another program so that interaction within the NIA can be addressed, and to apply a panel of objective outcome measures along with more subjective ones. Discussion followed about composition of review groups, timing of reviews, and nature and depth of discussion that the review format afforded. The sizable cost to staff of collecting data for program reviews was noted. It was pointed out that changes in the programs over time reflect both responsiveness to reviews and changes in science. Council was asked to consider whether a common guideline for program reviews would be useful or whether Council members should develop its own preferred format for each program review. The sense of Council was that indices would be helpful, particularly since Council membership changes. Since a round of program reviews will be completed at the May Council meeting, it would be useful to consider assessment criteria at the September meeting. One suggestion was that NIA consider that each program's subsequent review might address their response to the previous review's recommendations. It was recognized that when Council review of program takes place in conjunction with the Council meeting and related activities, there is time pressure that limits the extent of time to consider and prepare a thoughtful report. An effort will be made to schedule the next program review well in advance of the Council meeting so that the report on the review can be further developed. Other members pointed out that such scheduling would increase the number of meetings they would attend, and that the benefits of the increased time commitment would need to be balanced against the benefits of the separate program review and Council discussion. Dr. Hodes emphasized that how Council conducts review of programs has been an evolving process during the past 5 years, and that Institute staff would continue to work to make both the process and product informative.

Dr. Gage reported that the Working Group addressed issues to be brought up in the Geriatrics Program review and in the planned review of NIA's minority programs. Both items were discussed earlier in the Council meeting.

Council review of special actions was discussed. This discussion ensued from the previous meeting when applications submitted on behalf of Council members were the subject of Special Actions. Concern was expressed by some members about real or apparent conflict-of-interest. Staff were asked to examine options about how other Councils handle similar circumstances. After considering several options, the Working Group recommended a change to the Statement of Understanding that is described below.

Dr. Gage reported that the Working Group was informed that each Institute is required to prepare and submit a strategic plan by December 1999. The Working Group considered how best to get public input to/comment on the plan. Suggestions included public hearings in conjunction with scientific meetings, posting a draft on a website, holding special meetings at NIH, and contacting defined groups with a known commitment to aging and requesting feedback. The WGoP believed that it would be most fruitful to present a draft and solicit comment. Council members suggested that e-mail notification of interested persons, including grantees, might elicit useful comments.

The Working Group discussed the fact that comment from the scientific community on science policy issues that impact on investigators often is solicited, but generally response is meagre. There have been a number of such issues lately, including support for training of investigators, proposed amendments to OMB Circular A-110 already referred to, and draft reports issued by the National Bioethics Advisory Commission. Institute staff disseminate information to Council members and ask that they enlist the expertise and assistance of their colleagues and of the societies to which they belong. Council members acknowledged the importance of participation in such matters and were encouraged to respond to such invitations as individuals.

Dr. Gage summarized the WGoP's discussion about whether NIA should reconsider its decision not to participate financially in support of the Center for Inherited Disease Research (CIDR). CIDR is an infrastructure resource for high throughput genotyping that was developed to serve organizations that do not themselves have such capability. The basis for a prior recommendation of Council that NIA not participate was doubt of the need for such a facility for aging research. During discussion, Council members raised questions about the cost-benefit ratio of participating and about whether such analyses would be more cost effective to NIA grantees if NIA participated, particularly since experience has shown that Alzheimer's disease analyses are the ones most frequently conducted. Council believed additional information about relative cost would be helpful in making a recommendation.

Also discussed was the extent to which CIDR is able to provide the scope of services anticipated. Council requested that Dr. Nussbaum, the NIH representative to CIDR, be invited to the May 1999 meeting of Council to make a presentation and answer questions to help guide an NIA decision. In the meantime, the CIDR Board of Governors has been asked to estimate the financial investment requested of NIA should the Institute decide to enter an

agreement. Dr. Hodes asked that members of Council submit questions and issues for Dr. Nussbaum to address.

The WGoP approved and recommended that Council adopt the proposed amendments to the Statement of Understanding: 1. “NIA staff may expedite award of applications within the 20th percentile that request up to $250,000 direct costs per year, provided that they raise no policy or scientific concerns. The second level of review will be either electronically or by fax before the council meets.” 2. "If an application involving a Council member as principal investigator is identified for an individual action, in order to avoid the appearance of conflict of interest, a group which may include former members of NACA will be appointed by the Director to provide advice or act on the application, as appropriate." Both changes were approved.

New Business: Council members voted to reopen discussion of FOIA and OMB Circular A-110 to act on a comment to be forwarded to OMB. After discussion, the following statement was unanimously approved.

> The National Advisory Council on Aging expresses concern over the potential implications of the extension of the Freedom of Information Act under the 1999 Omnibus Appropriations bill in its direction to OMB to amend Circular A-110 as related to its agreement with Institutions of Higher Education, Hospitals and Other Non-Profit Organizations. As currently drafted and undergoing review and comment from the public, the proposed revision may negatively impact the conduct of research by such institutions for a broad array of reasons.
>
> These range from concerns over privacy of individuals who voluntarily participate in clinical and other research studies, to inappropriate access to and potential misuse of all details of research at every stage of its conception, execution, and timely dissemination of results, all of which may diminish the productivity and, perversely, even serve to discourage the spirit of openness in communication and collaboration that has been a hallmark of the remarkable American biomedical and social science research enterprise.

Council accepted the draft and asked that it be forwarded in their behalf.

X. RESEARCH HIGHLIGHTS

Dr. Hadley, Associate Director of the Geriatrics Program, described recent advances in the assessment of bone structure. He indicated that the risk of fracture associated with osteoporosis is a function of both bone density and bone quality. Recent improvements in high resolution imaging combined with techniques of fractal geometry now allow bone quality to be assessed noninvasively. Much bone consists of trabeculae with space between them. A characteristic of osteoporosis is that these trabeculae become fragmented. Fractal analysis divides an area into a series of grids and counts how often a segment from one grid extends into another grid. Applied to images of bone, it is a measure of how fragmented the trabeculae are – a measure of bone quality.

Dr. Hadley described the work of an NIA grantee, Dr. S. Majumdar, who has applied these techniques in a case-control study of patients with hip-fractures and matched controls. Majumdar (Link et al., *J Bone Miner.Res.* 1998;13:1175-1182) found that the structural deficits assessed by fractal analysis of high resolution images were more highly correlated with fractures than were bone density measures. Though the study is small scale and needs to be confirmed, it offers promise of identifying individuals who are at high risk for fracture and the possibility of providing an intermediate end point (as opposed to fracture) for assessment of treatments for osteoporosis.

Dr. Bellino, Acting Associate Director of the Biology of Aging Program, introduced Dr. Lee Sweeney from the University of Pennsylvania who described work conducted in collaboration with Dr. Nadia Rosenthal on loss of muscle mass and strength with increasing age (Barton-Davis et al. 1998, *Proceedings of the National Academy of Sciences*, 95, 15603-15607). Dr. Sweeney noted that in all mammals, including humans, muscle loses mass and strength, slows down, and loses its most powerful fiber types with increasing age. His research team believes that the problem is a decline in the ability of muscle to repair itself. Muscle is continuously injured during use. It maintains satellite cells within the basal lamina of muscle fibers. Upon injury, muscle signals the proliferation of these satellite cells by releasing a variety of growth factors. The cells proliferate and repair the muscle. Dr. Sweeney further specified the source of the age-related loss as a deficit in muscle's ability to signal the satellite cells to proliferate.

Using mice, Dr. Sweeney's group tested this hypothesis by using an adeno-associated virus to insert a synthetic gene into skeletal muscle. The gene allows only skeletal muscle to produce insulin-like growth factor –1 (IGF-1), one of the growth factors secreted by muscle during repair processes. The approach also allowed the group to limit the intervention to skeletal muscle in one rear leg of mice. The other leg was used as a control. If the investigators are correct, inserting the gene should stop the muscle loss associated with increasing age. When aging mice who had had the gene inserted into skeletal muscle were examined at a very old age, the injected muscle showed mass, force, and fast muscle fibers similar to a young mouse. The non-injected leg showed characteristic age-associated losses.

Before considering an intervention in humans, the research team is attempting to reproduce the result in larger animals. However, the result does offer promise of an intervention to combat loss of muscle function in the elderly.

Questions concerned whether there are similar effects in young animals (there are smaller effects); clarification that the effects did not change distribution of fiber types but prevented loss of fibers; whether very old animals with apparent muscle loss have been treated (a small number, only partial recovery); whether there were changes in systemic levels of IGF-1 (no); whether there were consequent changes in vascularity in the injected animals (not scored in that way); and whether endurance tests had been given to explore the vascularity hypothesis (only in vitro testing).

Dr. Morrison-Bogorad, Associate Director of the Neuroscience and Neuropsychology of Aging Program, introduced Dr. Selkoe, a Council member, who spoke of new work related to the amyloid-beta (Aβ) peptide (Wolfe et al. 1999, *Nature*, 398, 513-517). Dr. Selkoe

described the characteristic plaques and tangles in the brains of patients with Alzheimer's disease and indicated that the plaques are composed of aggregates of 40-42 residue Aβ peptides. Dr. Selkoe indicated that these peptides are cut out from the amyloid precursor protein (APP) following the stepwise action of a series of protease enzymes and result in a small fragment of APP, the Aβ peptide, being released. As the accumulation of the Aβ peptide is believed to be important in the cascade of events leading to Alzheimer's disease, much work has been conducted to characterize the events leading to its release. Work to date indicates that the release is the result of a two-step process. First, a protease enzyme, known operationally as beta-secretase, cleaves APP leaving a 99 amino acid fragment that is still embedded in the membrane. Second, another enzyme, the so-called gamma-secretase, cleaves within this transmembrane segment of APP and releases the Aβ peptide fragment. Neither of these enzymes has been identified.

Dr. Selkoe then described the Presenilin-1 and –2 genes. Mutations in these genes are the most common autosomal dominant cause of early onset Alzheimer's. Although rare, the autosomal dominant form of early onset Alzheimer's is instructive regarding possible mechanisms in the much more prevalent late onset form. The presenilin genes have been well-studied but to date their precise functions are not known. Normally the presenilin protein, a transmembrane protein, is cleaved into two fragments. In examining the amino acid chain of this protein as it winds its way through the membrane, Dr. Selkoe's group identified two aspartic acid residues in the middle of two transmembrane domains. Several lines of evidence suggested that these aspartates might be crucial for the cleavage of the presenilin protein as well as for the gamma secretase cutting of APP which releases the Aβ peptide.

To test that hypothesis, his team mutated the aspartates to alanine residues making them nonreactive. His team found that mutating either aspartate was sufficient to stop the presenilin from being cut. More importantly, the same mutation resulted in a dramatic decrease in the production of the Aβ peptide. The group established a quantitative relationship such that as the amount of the nonreactive mutant presenilin increased, the amount of Aβ declined. Given the hypothesized role of Aβ in Alzheimer's disease, the result, if confirmed, is highly encouraging for identifying new ways to decrease Aβ production.

Dr. Selkoe concluded by describing his group's model of the mechanism. They believe that the two aspartates within the membrane portion of the presenilin constitute the active site of the gamma-secretase enzyme involved in the final stage of production of the Aβ peptide. He believes that the presenilin 1 protein is the elusive gamma-secretase, or at least is essential for its function. They are now examining predictions of the model that would support their conclusions.

Questions concerned what would be the strongest experimental confirmation of the model; whether naturally occurring mutations can be identified that are protective against production of Aβ by gamma secretase; and the role of inflammation in the cascade towards Alzheimer's disease. Dr. Selkoe indicated that being able to take purified presenilin and purified APP and put them together in an environment where they can fold into the membrane should result in Aβ production and would be the strongest test of the model. He indicated that mutations

protecting against production of gamma secretase might be found in populations that never develop Alzheimer's disease. He also indicated that inflammation is widely believed to result from the formation of plaques, a downstream event from the production of the Aβ peptide.

Dr. Richard Suzman, Associate Director of the Behavioral and Social Research Program, introduced Dr. David Wise, a Council member, who described cross-national research on the association between the structure of social security plans and the retirement age (Gruber and Wise, 1998; *American Economic Review*, 88(2), 158-163).

Dr. Wise pointed out that older adults are now participating in far fewer numbers than previously in the workforce both in the U.S. and internationally. This change has occurred despite improvements in health, gains in longevity, and declines in disability. He pointed out that many national plans are structured so that the gains of income (wage earnings) in continuing to work after a certain age are offset by losses to retirement benefits. His research team calculated the replacement rate for Social Security Benefits at ages over 60 in different countries. The replacement rate is defined as the size of the retirement benefit in proportion to earnings in the last year. The replacement rate is 80 to 90 percent of wage earnings in many countries. They also calculated the change in Social Security Benefits as a proportion of wage earnings as a result of an additional year's work. They found that, in many countries, the change is negative after age 60. Social Security benefits are reduced as a result of working an extra year. Plotting the size of this "tax" on benefits as a function of the proportion of men aged 55 to 65 who are not working in different nations' labor forces, the group found a strong linear relationship between the probability of not working at these ages and the size of the tax on retirement benefits generated by an additional year of work.

Council members, while noting the strong association and likely causality of the relationship, questioned how it is possible to determine causality when randomized trials cannot be run. Dr. Wise discussed several approaches to addressing the question. These include detailed analysis of particular patterns of retirement behavior before and after changes in retirement incentives were introduced, and a historical analysis of the reasons why the changes were introduced.

Dr. Hodes thanked the presenters and called for any items of new business prior to adjournment. Dr. Harper, speaking for Council members, indicated their strong appreciation for Ms. McCann's services to Council. Dr. Hodes echoed that sentiment.

XI. ADJOURNMENT

The 76th meeting of the National Advisory Council on Aging was adjourned at 1:00 p.m. on February 4, 1999. The next meeting is scheduled for May 27-28, 1999.

Attachments:

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

XII. CERTIFICATION

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

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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 May 27-28, 1999 and corrections or notations will be stated in the minutes of that meeting.