



National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

February 8, 2005

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL ARTHRITIS AND MUSCULOSKELETAL
AND SKIN DISEASES ADVISORY COUNCIL**

**MINUTES OF THE 55th MEETING
February 8, 2005
8:30 a.m. to 4:00 p.m.**

I. CALL TO ORDER

The 55th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on February 8, 2005, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting began at 8:30 a.m.

Attendance

Council members present

Dr. Graciela S. Alarcon
Dr. Gena R. Carter
Dr. Bevra H. Hahn (attended by teleconference)
Ms. Victoria B. Kalabokes
Dr. Brian L. Kotzin
Dr. Martin J. Kushmerick
Dr. Cato T. Laurencin
Dr. Robert J. Oglesby (Ex Officio)
Dr. Jack E. Parr
Dr. Francesco B. Ramirez
Ms. Mary Elizabeth Replogle
Dr. Randy N. Rosier
Dr. Raymond Scalettar
Dr. John R. Stanley
Dr. Lawrence G. Raisz (attended by teleconference)
Dr. Steven L. Teitelbaum
Ms. Sharon F. Terry
Dr. Jouni J. Uitto

Council members not present

Dr. Richard T. Moxley

Staff and Guests

The following National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) staff and guests attended:

Staff

Dr. Deborah Ader
Dr. Janet Austin
Mr. Steven Austin
Mr. Gahan Breithaupt
Dr. Eric Brown
Ms. Kelli Carrington
Mr. Frank Cromwell
Ms. Jennifer Curry
Ms. Teresa Do
Dr. Elizabeth Gretz
Mr. Dean Guidi
Dr. Steven Hausman
Ms. Lisa Hill
Ms. Jane Hymiller
Dr. Oluwasegun Ijiyemi
Dr. Stephen I. Katz
Dr. Cheryl A. Kitt
Dr. Gayle Lester
Dr. Richard Lymn
Mr. Robert Miranda-Acevedo
Dr. Alan Moshell
Ms. Melinda Nelson
Dr. Glen Nuckolls
Dr. James Panagis
Ms. Wilma Peterman
Ms. Karen Rudolph
Ms. Nicole Schuett
Dr. Susana Serrate-Sztejn
Dr. William Sharrock
Ms. Helen Simon
Ms. Robyn Strachan
Ms. Yen Thach
Dr. Madeleine Turkeltaub
Dr. Bernadette Tyree
Dr. Yan Wang
Ms. Eileen D. Webster-Cissel

Guests

Ms. Roberta Biegel
Dr. Harold Davidson
Mr. Dale P. Dirks
Dr. William Elwood
Ms. Christy Gilmour
Ms. Patricia Brandt Hansberger
Ms. Darlene Kerr
Ms. Erin Ransford
Ms. Eileen Resnick
Ms. Anne Scanley
Ms. Alison Strock
Dr. Bob Weller
Ms. Marilyn Weisberg
Ms. Susan Whittier

Other NIAMS staff members and guests also were present. Dr. Stephen Katz, Director of the NIAMS, chaired the meeting.

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 54th Council Meeting, held September 21, 2004.

III. FUTURE COUNCIL DATES

Future Council meetings are planned on the following dates:

June 14, 2005
September 13, 2005
January 19, 2006
May 25, 2006
September 28, 2006

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz informed Council members that Dr. Oretta Mae Todd, a former member of the Advisory Council, died on January 28, 2005. Dr. Todd was an advocate for patients with arthritis and other chronic diseases and was an active participant in the Health Partnership Program and Arthritis Foundation (Michigan Chapter). In 2004, Dr. Todd received an outstanding alumnus award from Skidmore College upon the 50th anniversary of her graduation from that institution.

NIAMShorttakes

The NIAMShorttakes, prepared by Mr. Ray Fleming, includes a letter from Dr. Katz focusing on recent concerns about drug therapies for arthritis and how to balance the risks and benefits of nonsteroidal anti-inflammatory drugs, particularly COX-2 inhibitors. The Shorttakes also provides a more complete version of the NIAMS' research advances and plans. This information is available on the Web site and also is distributed to volunteer and professional organizations that work with the NIAMS.

New Council Members

Dr. Katz welcomed four new members to the Council. Dr. Gena Carter works as a patient advocate and has training in diagnostic radiology. She also is a volunteer with the Alliance for Lupus Research and served as the chair of the inaugural New England Walk With Us to Cure Lupus Walk-a-thon. Dr. Martin Kushmerick, of the University of Washington, has expertise in numerous fields related to muscle research, including radiology, physiology, biophysics, and bioengineering. Dr. Lawrence Raisz, from the University of Connecticut Center for Osteoporosis, is an expert in the bone and mineral fields. He was a member of the committee that reviewed NIAMS' Specialized Centers of Research Program and served as Scientific Editor of the Surgeon General's Report on Osteoporosis and Bone Health. Dr. Bevra Hahn is a rheumatologist, Professor of Medicine, Chief of the Division of Rheumatology, and Vice Chair for Faculty Affairs in the Department of Medicine at the University of California–Los Angeles School of Medicine.

Personnel Changes at the NIH and the NIAMS

Mr. Tommy Thompson, Secretary of the Department of Health and Human Services (DHHS), has resigned. The new Secretary is Mr. Michael Leavitt, who previously served as Governor of Utah and Administrator of the Environmental Protection Agency. Dr. Elizabeth Nabel has been named director of the National Heart, Lung, and Blood Institute (NHLBI), and Dr. David Schwartz has been named as the Director of the National Institute of Environmental Health Sciences and the National Toxicology Program.

Dr. Peter Lipsky is no longer serving as Scientific Director of the NIAMS but will continue his duties as the Chief of the Autoimmunity Branch in the NIAMS Intramural Research Program (IRP). Dr. Paul Plotz currently serves as the Acting Scientific Director of the NIAMS, in addition to his position as Chief of the Arthritis and Rheumatism Branch. A search is underway for a permanent Scientific Director, led by Drs. Robert Balaban (NHLBI) and Peggy Crow (Hospital for Special Surgery) and Advisory Council members Drs. Brian Kotzin and Steven Teitlebaum.

Dr. Eric Brown has joined the NIAMS as a Scientific Review Administrator, and Ms. Helen Lin will serve as a Special Volunteer in the Scientific Review Branch. The Institute's Office of Communications and Public Liaison has three new members: Ms. Karen Rudolph (Project Officer for the NIAMS Information Clearinghouse), Ms. Elizabeth Lordan (Public Liaison Officer and Senior Editor), and Mr. Richard Clark (Information Specialist for Rheumatic and Bone Diseases).

Recent NIH Activities

The new NIH ethics regulations regarding conflict of interest were published in the Federal Register on February 3, 2005, and will be evaluated over 1 year. The NIH seeks input on these new regulations, and further details are available at the NIH Web site. The new regulations focus on prohibited outside activities, financial holdings, and awards. All NIH employees are prohibited from engaging in outside employment with "substantially affected organizations," such as biotechnology, pharmaceutical, and medical device companies, hospitals, clinics, health insurers, health science- or health research-related trade organizations, professional associations, consumer or advocacy groups, and educational institutions or nonprofit independent research institutes that are or recently were NIH-funding applicants, grantees, contractors, or Cooperative Research and Development Agreement (CRADA) partners. Certain exceptions may permit an employee to engage in clinical practice with a health care provider, such as at a hospital, in private practice, or to deliver a lecture as part of a continuing medical education program, such as Grand Rounds, at a grantee institution. All NIH employees who file public or confidential financial disclosure reports, their spouses, and their minor children, must sell stock owned in pharmaceutical, biotechnology, and other companies involved in the research, development, or manufacture of medical devices, equipment, preparations, treatments, or products. All other employees and their spouses and minor children will be allowed to own up to \$15,000 of such stock (value as of February 3, 2005). The goals of these regulations are to strengthen the programs of the NIH and to help the NIH regain the public's trust.

The current NIH policy on public access to research results gives authors discretion in posting their research papers for up to 12 months. The NIH is setting a precedent for a federal agency by establishing a publicly accessible venue in which scientists can publish research results. This policy is expected to take effect in spring 2005.

The NIH has halted the use of cox-2 inhibitors in a large cancer prevention trial and has suspended a study of the use of these drugs in a large Alzheimer's disease prevention trial, both funded by the NIH.

Update on Budget and Congressional Activities

For fiscal year 2004, the NIAMS funded 245 new and competing continuation applications for a success rate of 20.1 percent; detailed budget information is available at the NIAMS Web site. For fiscal year 2005, the President has signed an appropriations bill for the NIH providing \$28.7 billion; after reductions, the net amount for NIH is \$28.3 billion, with \$511 million for the NIAMS. The NIAMS anticipates maintaining last year's success rate of approximately 20 percent, although the percentile through which applications are paid will be reduced by 1 percent, to the 16th percentile. The complete NIAMS funding plan for 2005 is available at the NIAMS Web site. For fiscal year 2006, the NIH received an increase of \$145.7 million or 0.5 percent, largely due to enthusiasm for the NIH Roadmap Initiative. The NIAMS received an increase of 0.4 percent, for a total of \$513 million. Despite the essentially flat budget, the NIAMS is expected to maintain the success rate at the level of the past few years.

Muscular dystrophy continues to be an area of great interest and activity to many Institutes at the NIH, including the National Institute of Neurological Disorders and Stroke and the National Institute of Child Health and Human Development. In January 2005, a progress report on the status of the implementation of the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act) was submitted to Congress. The document was prepared with input from the Centers for Disease Control and Prevention's (CDC) section on birth defects. Dr. Katz serves as chair of the Muscular Dystrophy Coordinating Committee.

Highlights of Recent Scientific Advances

- Drs. Betty Diamond and Bruce Volpe, of Columbia University, have identified a subset of anti-DNA antibodies in the blood of lupus patients with cognitive problems that bind to N-methyl-D-aspartate (NMDA) receptors on nerve cells in the brain. A mouse model demonstrated that, if the blood brain barrier is broken, these antibodies bind to neurons, leading to cell death in an area of the brain that regulates emotions and memory. An NMDA receptor inhibitor appears to prevent nerve cell damage by these antibodies in the brain.
- Dr. Peter Gregersen and his colleagues have identified a single nucleotide polymorphism (SNP) associated with a twofold increase in rheumatoid arthritis risk. The SNP is located within a gene encoding the enzyme PTPN22, which is involved in activation of T cells. This same SNP has been linked to Type 1 diabetes, and subsequent work by Dr. Gregersen suggests it also may increase risk of other autoimmune diseases such as lupus and autoimmune thyroiditis. Autoimmune diseases have been observed to run in families, and this work identifies a possible genetic susceptibility.

- Dr. Tejvir S. Khurana and colleagues at the University of Pennsylvania have demonstrated that injection of a fragment of the protein heregulin improves the structure and function of muscles in mice that develop a disease similar to Duchenne muscular dystrophy. After injection of heregulin, mice showed improved muscle strength and decreased levels of inflammation compared to control animals.
- Mr. Robert McLean of the Hebrew Rehabilitation Center for the Aged, and colleagues determined that levels of homocysteine may be predictive of fracture risk in the elderly. Dr. Raisz has written an editorial in *Nature Medicine* discussing the importance of this finding.
- Dr. Jeffrey Katz, Boston University, analyzed and defined a positive relationship between surgeons and hospitals performing a high volume of total knee replacement surgeries and the outcomes for this intervention. The experience of the hospital as well as the surgeon affects surgical outcome.
- Studies performed by Dr. Brian Berman and colleagues at the University of Maryland, with support from the National Center for Complementary and Alternative Medicine, demonstrated that acupuncture relieves pain and improves function in knee osteoarthritis. This represents the first clinical trial of sufficient rigor, size, and duration that has shown that acupuncture helps reduce pain and functional impairment in osteoarthritis of the knee.
- Dr. John Sundberg of The Jackson Laboratory and his colleagues identified an inbred strain of mice that develops a condition similar to the adult onset form of alopecia areata. This mouse model has been used to identify genes involved in susceptibility for this condition; researchers hope to extrapolate these findings to humans.

Highlights of Recent and Upcoming Activities

Drs. Richard Moxley and Richard Lymn recently cochaired a workshop on the burden of muscle disease, which sought to identify existing data on the cost and scope of muscle diseases, focusing on the muscular dystrophies, and seeking strategies for developing new information sources. Outcomes from this workshop will be summarized and presented at the next Council meeting.

Dr. Gayle Lester is leading planning activities for a meeting entitled, “Bone Quality—What Is it and Can We Measure it?” The NIAMS is cosponsoring this meeting with the American Society for Bone and Mineral Research, INSERM (the French National Institute for Health and Medical Research), and other NIH institutes. The meeting will be held May 2-3, 2005, and will define measures of bone quality for predictive value for fractures.

The NIAMS issued two requests for proposals on January 14, 2005. These are broad agency announcements soliciting 1) innovative therapies for rheumatic and skin diseases, and 2) pilot and feasibility trials for osteoporosis.

The NIAMS currently is developing a long-range plan covering the years 2005 to 2009. Details will be discussed at the next Council meeting. On April 11 and 12, 2005, the NIAMS will hold its annual scientific retreat at which needs, gaps, and opportunities in research supported by the NIAMS extramural program will be identified.

Comments From the Council

Dr. Raisz asked how the 0.5 percent increase in the budget would affect next year's payline. Dr. Katz answered that this small budget increase is one issue the Council will discuss at this meeting, to obtain advice from the Council on how to work with the small budget increase for this year and for the foreseeable future.

V. REVIEW OF THE MEMORANDUM OF UNDERSTANDING

Dr. Steven Hausman led Council members through the review of the Memorandum of Understanding, the guidelines and rules under which the NIAMS operates with the Council. The Council is the determining body for grant applications; an award cannot be made unless the Council has approved the application at a Council meeting. During review of the applications, the Council is notified using the electronic council book of certain issues, such as animal welfare, animal subjects, ethical issues, applications from foreign institutions, and applications for greater than \$500,000. In reviewing applications, the Council can concur; nonconcur based on scientific grounds with a recommendation that the application be reviewed; or denote high program priority (directive to pay) or low program priority (directive not to pay). In addition, applications can be deferred by the Council for further information and for discussion at a subsequent meeting. NIAMS staff review the applications before they are reviewed by the Council. Staff can take administrative actions that do not require Council concurrence, such as approval of grants with budgets of \$50,000 or less, scientific review and evaluation awards (pay for study sections to meet and review applications), additional support for applications transferred to another institution, and various administrative actions such as change in the length or time of award. Additionally, applications can be awarded prior to a Council meeting, which may be done as the end of the fiscal year approaches. Dr. Cheryl Kitt or one of her staff will send an announcement to one or more Council members listing the applications for which the NIAMS seeks early en bloc concurrence; once at least one Council member responds, those applications can be funded before the Council meeting.

Dr. Hausman called for a vote on the Memorandum of Understanding. A motion was made to accept the Memorandum, and it was seconded and passed by the Council.

VI. SURGEON GENERAL'S REPORT ON OSTEOPOROSIS AND BONE HEALTH

Dr. Joan McGowan, Bone Diseases Program Director and Chief of the Musculoskeletal Diseases Branch, served as a Senior Scientific Editor for this recently published report along with Dr. Raisz. This was Surgeon General Richard Carmona's first report; he initially was reluctant to produce an extensive book of research findings and wanted instead to produce a document that was written for the general public. The purpose of these reports is to use the Surgeon General's position as chief public health spokesperson for the nation to present authoritative material on matters important to national public health policy. Dr. Carmona's efforts largely have been directed toward homeland security, but he also is very interested in health disparities and prevention. The editors of this report were Drs. McGowan, Raisz, Allan Noonan (Scientific Editors) and Ms. Ann Elderkin (Managing Editor).

The Bone Coalition (American Society for Bone and Mineral Research, National Osteoporosis Foundation, Paget's Foundation, Osteogenesis Imperfecta Foundation) approached both the Surgeon General and Congress to advocate for production of this report. For the first time, Congressional language called on the Office of the Surgeon General to produce a report, which is an unusual start for a report of this nature.

The report presents a summary of current evidence related to bone health in a public health context. The purpose of the report, from the point of view of the Office of the Surgeon General, is to make scientifically valid health and treatment information available to health providers and consumers, to serve as a guide for health services (many government agencies as well as private payers will use this as an authoritative document on which to base their treatment and preventive services options), and to illustrate the documented scientific consensus in areas where there is consensus. The report is based on the fact that there is information and some evidence that certain lifestyle practices or medical interventions known to promote bone health are not being adopted or implemented by the public or in clinical settings. Additionally, adopting these known beneficial practices will have a positive impact on public health.

Dr. McGowan presented data describing examples of trends in osteoporosis medicine use. Despite an upward trend in hip fracture patients receiving bone-active medications after their fractures, by 2000 only slightly more than 20 percent of patients received medication. This indicates that physicians do not recognize that treatment options are available for prevention of the next fracture. Additionally, few patients received bone active medications before hip fracture. True fragility fractures are not recognized as manifestations of weak bone, and there appears to be little knowledge of available interventions (e.g., bisphosphonates, calcitonin, hormone replacement therapy) that promote bone

health. A key point of this report is to have fracture recognized as a sentinel event in bone health.

Creation of the report involved advice from several committees, including an intergovernmental trans-HHS committee, several section leaders, and approximately 50 authors who wrote different sections of the report. A Congressional appropriation was received (it is unusual to receive funding for these reports), and the Surgeon General's Web site was used to solicit comments from the public, advocacy organizations, and scientists concerning material that should be included and emphasized. Public comments were collected and a workshop was held in December 2002, at which participants presented their five most important issues. The workshop covered a spectrum ranging from basic and clinical science through health services research and public health to determine the kinds of information the public needs and how they should receive it. Next came evidence reviews, writing, and editing, followed by peer review of each chapter by both scientists and lay people. After incorporating suggested changes, the document was sent for departmental clearance. These reports must be cleared by every agency and office in DHHS to ensure consistency with other information on this topic available through DHHS. Concurrent with production of this report, a document entitled *Dietary Guidelines for Americans* was released, and it was necessary to ensure that this document on general nutrition and the report on bone health did not contradict one another. The report was released on October 14, 2004, and currently is in the dissemination and action phases. Promotion of the report by the Office of the Surgeon General is finite, but it is hoped that the report still will be in use 40 years from now (as is the case for the smoking report) and will continue to be a stimulus to improve bone health.

Dissemination of the report is an integral part of the process, and the report is available at the Surgeon General's Web site. Dr. Carmona especially was interested in developing the "People's Piece" for the general public as a very accessible, illustrated document that conveyed the essence of the report to consumers in a useful manner. A summary of the report was given to Council members and also to public health officials. Specific material has been prepared for certain target audiences. For example, people over 45 or 50 years old who have had recent fractures should be informed that this could be a sign of underlying fragile bone. These people should bring the fractures to the attention of their health care professionals, and physicians should be aware of "red flags" for poor bone health, such as fractures and, for example, young girls with amenorrhea due to intense physical activity. Some health care systems have been targeted and proposals developed to assist physicians in taking appropriate actions and for promoting community health. These activities take place through the media, researchers, advocacy organizations and foundations, and policymakers—in particular the Centers for Medicare & Medicaid Services (CMS), which sets Medicare policies.

Updated information, electronic forms of the documents, and PowerPoint slides outlining key points from the report are available at the Surgeon General's Web site. The NIAMS is participating in distribution of these materials; eventually, the NIH Osteoporosis and Related Bone Diseases~National Resource Center will take over distribution. The NIAMS has provided funding for reproduction of this document, also available in Spanish, and for distribution to state public health coordinators who will develop public health campaigns at the state level. The "People's Piece" was included in the February issue of *Good Housekeeping*, and Merck has paid for and will distribute 500,000 copies of the "People's Piece." Dr. McGowan also informed Council members that an evaluation of the report is planned.

Dr. Raisz commented that he was very pleased with the outcome of the report. He added that "social marketing" of the report represents a significant challenge, particularly for arranging ways in which the different constituencies, such as foundations, industry, and local, state, and federal governments can work together to develop better dissemination plans. He was somewhat disappointed in the level of dissemination of the report and, while not wanting to discuss this formally at the meeting, asked Council members to contribute ideas for better dissemination of the report.

VII. BIENNIAL REPORT ON NIAMS PROGRESS IN MONITORING WOMEN AND MINORITY ISSUES IN GRANT APPLICATIONS

Dr. Madeline Turkeltaub, Clinical Coordinator, spoke about the NIAMS' progress in including women and minorities in clinical research. Initially, NIH policies urged, then encouraged, inclusion of women and minorities in clinical studies. In 1993, Public Law 10343 mandated inclusion, although there may be exemptions. Exemptions must be requested and justified by the principal investigator; for example, a NIAMS-funded study of osteoporosis and osteoporotic fractures in men was allowed to omit women. The underlying ethical principles of this mandate are justice and the importance of balancing research burden, and benefits. All Phase 3 clinical trials funded after October 1, 2000, are required to meet the following criteria:

- Women and minorities must be included in all clinical research studies.
- Women and minorities must be included in Phase 3 clinical trials.
- Trials must be designed to permit valid analysis.
- Cost is not allowed as an acceptable reason for exclusion.
- NIH is to support research that promotes outreach efforts to recruit and maintain women and minorities in clinical studies.

For accountability purposes, the NIH developed a tracking system to provide aggregated data to Congress. For further accountability, in 2001 the review process specifically incorporated considerations of compliance in grant

application priority scores. In addition, new standards for data on ethnicity and race were incorporated to correspond with the U.S. Census.

This information was presented to the Council in preparation for the report to Congress on compliance with Public Law 10343. Each Institute prepares a report based on aggregated data, and presentation of the NIAMS data at this meeting is part of the preparation process.

A summary of the information from fiscal year 2004 was presented. Information for fiscal years 2003 and 2004 was based on a subject population of approximately 37,000:

- 1409 research projects were funded
- 153 protocols were included in the tracking system at the close of 2004
- 5 of these were Phase 3 clinical trials

Comparison of data from 2003 to 2004 indicates a modest increase in total numbers of both male and female Hispanics or Latinos, and a modest increase in the overall percentage of Hispanic and Latino subjects, from approximately 2.7 percent in 2003 to nearly 4.0 percent in 2004. Enrollment of Asian males increased from 2 percent in 2003 to 18 percent in 2004, which was attributed to enrollment in a study arm based in Hong Kong. Total percentage of Black or African American subjects increased from 5.8 percent in 2003 to approximately 13 percent in 2004, with an increase observed for both males and females; this increase was attributed to a study of the epidemiology of bone loss in African American men and another on determinants of bone strength in Afro-Caribbean families. The NIAMS has had an excellent representation of females in funded clinical studies, although it continues to be difficult to recruit and retain subjects in proportion to their racial and ethnic distribution in the population in clinical studies in all areas. NIAMS professional staff continues to work with investigators to enhance efforts to recruit and retain minorities.

Dependent on Council approval, the report will be sent to Dr. Katz for certification and then to the Office of Research on Women's Health, which is charged with preparing the report of the aggregated NIH data for Congress.

A motion to accept the report was made, seconded, and passed.

VIII. PRIORITY SETTING—MEETING THE NEEDS OF THE COMMUNITIES

Due to budget constraints, the NIH as a whole is faced with difficult decisions. The NIH and the NIAMS must move science forward and serve many communities, including the scientific and the voluntary and advocacy communities. One change the NIAMS made, with Council approval, to help with budgeting for "big ticket" items was to accept grant applications for greater than \$500,000 only twice a year. Dr. Kitt will discuss the NIAMS' experience after 1

year of this new review schedule, focusing on vulnerabilities and attempting to set priorities concerning which applications the NIAMS should accept.

The second half of this Council meeting was devoted to discussion of the NIAMS budget and constraints in managing these resources. At the Institute Directors' retreat, priority-setting issues will be discussed further; for example, whether there are trans-NIH policies that would be useful to implement during challenging budgetary times. The major, underlying responsibility of the NIH as a whole is to continue to address new scientific needs and opportunities to fill gaps in research areas. The NIH has relied on input from the scientific community for soliciting and funding grant applications, but still needs flexibility to meet new areas of need. The goal of the following discussions was to obtain input from Council members concerning strategies the NIAMS might implement to maintain its ability to move science forward during years of small to nonexistent budget increases.

Overview of NIH and NIAMS Budgets

Dr. Katz presented an overview of the NIH and the NIAMS budgets. In fiscal year 2004, 86 percent of the total NIAMS budget funds the Extramural Program; the remaining 14 percent funds the IRP and Research Management and Support (RMS). Across Institutes, the NIH average is 84.2 percent for extramural projects and 15.8 percent for intramural programs and RMS, combined. The NIAMS designates 67.5 percent of its research dollars for Research Project Grants (RPGs), which is higher than the NIH average (54.1 percent). The NIAMS uses 7.5 percent of its budget to fund Centers programs, while the average across NIH is 9.1 percent. The NIAMS' IRP receives 9.8 percent of the Institute's budget, compared to an average of 9.5 percent across the NIH (although several Institutes do not have intramural programs). Training and career awards (T awards and K awards) represent 5.9 percent of the total NIAMS budget, compared to an average of 4.7 percent of other Institutes' budgets. The NIAMS' funding for Centers has decreased from 11 percent to 7.5 percent over the last approximately 10 years; during the same time, the budget for the IRP increased from approximately 8.5 percent to 9.8 percent. The decrease in funding for Centers resulted in a slight increase in funding for contracts that administer many of the Institute's clinical studies.

Priorities and Payline

Dr. William Sharrock presented information on the NIAMS priorities and payline. An Institute's payline is perhaps the single strongest indicator of budget constraints in a given fiscal year and, for extramural investigators, success in obtaining funding from the Institute.

Budget increases and corresponding paylines for 1995–2004 were detailed (information is available at the NIAMS Web site) to help identify variables that

contribute to variations in the payline from year to year and to provide information on devices the NIAMS has used to moderate the effects of budget increases or decreases on the payline. Paylines generally have paralleled overall budget growth, with large increases in the budget usually corresponding to a higher payline. To clarify, success rate and payline are not quite equivalent because the payline is based on percentile ranking and not all applications are percentile ranked. Applications for training and career awards, program project grants, and Centers are funded based on priority score alone and thus are not part of the percentile ranking. The percentile payline applies mainly to investigator-initiated R01s.

Data also were presented on the NIAMS' noncompeting base for the same 10-year span. For each fiscal year, most of the budget already is allocated to continuation of grants awarded in the preceding 3 to 4 years. Approximately 75 percent of the RPG dollars is committed to the continuation of previously awarded grants (25 percent of this budget is available for new competing grants). The noncompeting base has a significant impact on payline for a given year; if many grants were funded in preceding years, the following years' paylines may be lower because a larger proportion of the budget is committed to continuing grants. During the years of large budget increases (1999 to 2004), many new awards were made (paylines were approximately 20 to 24 percent). Since continuation costs for these awards must be funded from the current year's budget, funding available for competing awards is proportionately less.

Two ways to lessen the impact of the noncompeting base on future paylines would be to emphasize shorter term grants or to implement accelerated funding, whereby funding is increased during the initial years of a grant and decreased in subsequent years (with approval of the review group). Using data for 2004 and 2005, increasing the payline by 1 percent would require \$3.3 million. Another potential mechanism for moderating future noncompeting obligations is the R56 program, which provides interim funding. If an application seems worthwhile but ranks below the payline on the percentile scale, this program allows awarding of a 1- to 2-year grant to allow the investigator to collect more data and resubmit the application. Because this is only a 1- to 2-year award, the impact on the noncompeting base is not felt over several years.

Other factors that affect payline include administrative reductions and program set-asides. Set-asides refer to funds set aside at the beginning of the year for Requests for Applications (RFAs), including programs such as R03 grants and R21s, which have been targeted to new investigators and exploratory, high risk projects. Select pay, for funding of applications beyond the official payline, is also included in this category. Administrative reductions are reductions made in awards from budget levels recommended by study sections. These reductions have varied from 20 percent reductions in 1995 to between 0 and 9 percent during 1999 to 2003. Combining administrative reductions with decreases in funds put into set-asides and select pay could help increase the payline.

Shortening the average length of multiyear awards and limiting the amount of the budget used for set-asides have been proposed as actions for protecting the payline. Both approaches can have negative impacts. Shortening the length of multiyear grants hinders projects that require long-term investments and increases review burden because more applications would be received more frequently. Limiting set-asides limits the ability of the NIAMS to respond to new opportunities or specific initiatives that may arise. The traditional RFA tool possibly could be deemphasized without a significant impact on flexibility; RFAs can take a year to issue and generally have only a single submission date, which may or may not correspond to investigators' ability to submit applications. Select pay for discretionary awards for projects that break new ground or pioneer new techniques, however, should be protected. The R03 and R21 programs also have been useful for funding promising new investigators; more than 35 percent of investigators who received an R03 award eventually received either a K award or an R01, compared to 11 percent of investigators who did not receive an R03 award.

Maintaining select pay is important because grants often are tightly scored and there is little difference in merit between a grant that receives a score above the payline and one that falls just below it. Data comparing percentile rank to priority score were shown for two NIAMS study sections, Skeletal Biology, Development, and Disease, and Arthritis, Connective Tissue, and Skin. A difference in percentile of less than 10 percentile points may not reflect a study section consensus on the scientific merit of a grant. One point away from the payline, which may mean the difference between receiving funding or not, may not accurately reflect the comparative merit of a grant; percentile rankings become artificial when looking at the second or third decimal place of a priority score. Maintaining flexibility by using select pay helps to overcome this issue somewhat.

Because some Council members noted that doubling of appropriations dollars between 1997 and 2004 did not result in significant differences in the payline, Dr. Katz clarified that, during the years of budget doubling, the NIH Director, Dr. Harold Varmus, asked Institutes not to focus solely on increasing their paylines. Instead, the NIAMS made investments in clinical studies, including therapeutic interventions and observational studies, which were reflected in the contracts line of the budget. A significant amount of the money also was used for the increased costs of individual grants.

Council members discussed actions that could be taken to boost the payline and the impacts these actions might have on investigators and on the NIAMS' ability to achieve its scientific goals. Dr. Teitlebaum commented that maintaining the payline at an acceptable level is important for encouraging young investigators to pursue basic research as a career. Many potential investigators may opt instead for a career in industry or private practice because a low payline creates the

perception that they will not receive funding. Dr. Teitlebaum added that he thought the negative impact of shorter grants would be less than that of reduction in the payline or administrative cuts in grants budgets after grants have been awarded. If a grant is submitted with a certain budget, a 20 percent reduction in that budget could make it impossible for the investigator to carry out the work outlined in the grant proposal. It would be easier for an investigator to plan for a grant of shorter duration if this is known in advance. Several members expressed concern that reduction of grant duration from 4 years to 3 years would create a burden on the investigator to write a grant during Year 2 of a project. Dr. Francesco Ramirez mentioned that this might hinder projects that require a longer “start-up” period and also may tend to reward safe rather than creative science. Dr. Teitlebaum commented that not all grants would need to be reduced to 3 years; instead of an average duration of 4 years, the overall average duration could be reduced to 3.5 years. Dr. Raisz argued that cuts in the duration of grants would not have an impact for several years and would not help alleviate the current crisis of low paylines discouraging young investigators. The smallest possible administrative reductions would do more to increase the payline quickly.

Dr. Cato Laurencin asked why the emphasis needed to be on changes to RPGs. If RPGs, which represent investigator-initiated science, are important to the NIAMS, perhaps changes should be made in other areas of the budget to maintain the payline. Perhaps new programs, for example, in clinical research, will have to be secondary to maintaining the RPGs. Dr. John Stanley agreed and added that the NIAMS must define what is most important, particularly whether science and the goals of the Institute are best served by investigator-initiated projects or by science directed by the Institute. He commented that it also is important to ensure that the Institute’s public constituencies understand the decisions faced by the NIAMS. Many of these constituencies recommend that the NIH issue RFAs in their areas of interest, perhaps without complete knowledge of how this affects the budget for investigator-initiated research, which most groups agree is important for achieving scientific goals.

Ms. Sharon Terry commented that RPGs are important for maintaining a pipeline for young scientists, but the public gradually will become less interested in supporting the NIH if only basic research is emphasized. Thanks in part to the Roadmap Initiative, the public now is interested in how basic research can be translated into new treatments and technologies. RPGs should not be abandoned, but perhaps individual investigators could be encouraged to focus more on translational research. Dr. Ramirez commented that perhaps the importance of translational research could be emphasized during the review process, which might encourage more proposals focused on translational research without necessarily requiring programmatic changes. Dr. Kushmerick responded that perhaps the message of the Roadmap Initiative had been heard by most investigators, who do strive to incorporate into their applications a sense of potential clinical utility for their projects. Ms. Terry clarified that what she thought the public would like to see was research directed more toward cures and

treatments for particular conditions and more coordination with health outcomes. Individual investigators may not see this “bigger picture,” and it may be up to people such as Council members to try to move resources in this direction.

Big-Ticket Items

Dr. Kitt presented information on the NIAMS’ strategy for funding “big-ticket” research. Big-ticket research, grants with budgets greater than \$500,000, includes collaborative multidisciplinary research projects such as program projects (P01s) and large R01s. Until recently, the NIAMS has followed the NIH policy of reviewing these applications three times a year 6 weeks in advance of a receipt date. Because of the increasing numbers and cost of these applications, the NIAMS has decided to review these large applications together and only twice a year.

The numbers of requests for these applications and numbers of applications received have risen significantly. Before 2005, the NIAMS accepted for review all applications brought to the Council’s attention (NIAMS program staff does a superb job communicating to the community what grants will or will not be considered for review). Recently, the NIAMS received approximately 33 applications for grants with a budget greater than \$500,000, and 23 were accepted for review.

The numbers of applications for P01s alone have increased over time, with the exception of 2005, in which the same number of applications was received as in 2004. Only nine of these grants will be reviewed; if all are approved, the NIAMS will commit a maximum of \$9 million to fund these grants. Receipt of large R01 grant applications also has increased, in part because of competing renewals coming in this year and the increasing costs of the grants. It is hoped that the new review policy will help the Institute balance scientific needs with fiscal constraints. Committing to fund these large projects also will have an impact on the available budget and, thus, on the payroll.

Dr. Ramirez opened discussion, commenting that he is the recipient of a P01 grant, which was instrumental in launching his career. The P01 provides a good system for allowing a new investigator to interact with a broader program and can provide mentors to help promote a new investigator’s research. P01s also can help promote multidisciplinary and translational science because a sole investigator cannot do these sorts of projects alone. Problems with P01s include a perceived lack of accountability and rigor in review; in the past, once an investigator received a P01, he or she generally did not lose it. Another problem is the difficulty in using P01s to coordinate activities among researchers from different institutions. P01s would seem to provide an ideal opportunity for this sort of collaboration but are hindered by administrative impediments. Eliminating P01s probably is not desirable, but P01s could be changed to have the same scope, rigor, and accountability as R01s. Another option is to ask recipients of R01

awards if they would like to combine themselves into a P01 group and, by so doing, receive additional funding to make the research more cohesive.

Dr. Katz commented that some Institutes, such as the National Eye Institute, do not have Centers; instead, they identify critical masses of investigators and provide funds for core groups of individuals. Recently, NIAMS program directors have outlined on the Web site a higher level of expectation for program projects, which should help increase rigor and accountability. There also are other funding opportunities for projects with budgets greater than \$500,000 besides the P01 grants. These large-scale projects provide opportunities for research that can make a difference in the clinical practice of medicine that most likely would not be sponsored by industry or other entities besides the NIH.

Intramural Research Program

Dr. Paul Plotz presented details on the NIAMS IRP. Among IRP activities are research programs focused on autoimmunity, led by Drs. Peter Lipsky and Richard Siegel, which receive 8.5 percent of the IRP budget. The Arthritis and Rheumatism program, which includes studies of inflammatory and genetic muscle diseases, is run by Dr. Plotz and receives 2 percent of the IRP budget. Researchers in Inflammatory Biology and Genomics, led by Dr. Daniel Kastner, conduct basic research on new inflammatory pathways discovered during the study of febrile illnesses and also are part of a larger consortium looking for genes that contribute to rheumatoid arthritis and related diseases. This program receives 5 percent of the IRP budget. The Lymphocyte Cell Biology program, led by Drs. John O'Shea, John Rivera, and Raphael Casellas, studies pathways in inflammatory signaling and the genes involved in these pathways. Research on cartilage structure, developmental biology, and molecular genetics underlying connective tissue diseases is led by Dr. Rocky Tuan and other scientists in the Cartilage Biology and Orthopaedics Branch and receives 8.5 percent of the IRP budget. Drs. Kuan Wang, Vittorio Sartorelli, and Li Po Yu are in the program on basic muscle biology, studying topics such as muscle biophysics and development, structure and force generation, and general muscle biology. This program receives 7.5 percent of the IRP budget. A small skin biology unit run by Dr. Maria Moraso receives 3 percent of the budget, and a structural biology program that includes studies of the high-resolution structure of viruses, prions, and other molecules important to a range of diseases receives 4 percent of the IRP budget.

Clinical research accounts for approximately 25 percent of IRP program expenses. This program incorporates many investigators and includes training and community outreach programs. The program also encompasses clinical studies performed by Drs. Plotz's, Lipsky's, and Kastner's groups, and includes therapeutic studies such as autologous stem cell treatment of lupus and treatment with other new and experimental biological reagents. The Orthopaedics and Clinical Investigative Program currently is theoretical, but is expected to be active

in the near future. Twelve percent of the IRP budget pays for support activities, such as light imaging, crystallography, biodata mining, flow cytometry, and animal experimentation, which are used by many IRP groups.

Dr. Katz discussed new areas of research he would like to develop within the IRP. In the 1990s, the NIAMS planned to develop a program in orthopaedics and musculoskeletal medicine, with the goal of providing a site for the training of investigators in this field. Recruitment of Dr. Tuan was part of the effort to bring orthopaedic surgery to the Clinical Center, but recent attempts at expanding the program have been unsuccessful.

Dr. Kushmerick asked whether the IRP could provide resources for the investigation of new scientific issues as they come to the NIAMS' attention, which may be more efficient than using an RFA. He suggested that known experts in the extramural program could be included in this effort and perhaps invited to work at the NIH to take advantage of the facilities. Dr. Plotz answered that a committee is examining the possibility of allowing extramural investigators to use campus facilities. He is unsure of current progress on these discussions but commented that there are difficulties in allocating space and funds for outside investigators to work at the NIH; nonetheless, these efforts could facilitate collaborations and interactions among investigators.

Dr. Teitlebaum commented that the mission of the IRP should be clarified. It may be difficult to ask researchers to abandon their fields of investigation to undertake NIAMS-directed research but, given current budget constraints, it may be time to direct research within the IRP, particularly toward emphasizing translational research. Dr. Katz agreed that the mission of the IRP should be distinguished from the extramural program. He added that the IRP is capable of performing research that the extramural program cannot undertake; for example, longitudinal studies encompassing large subject cohorts. Dr. Stanley added that the IRP also provides training for future investigators.

Training Issues

Dr. Stanley presented information concerning training opportunities sponsored by the NIAMS. Training and career awards include the career development awards (K awards), individual fellowships, and group training grant awards. Students pursuing PhDs receive predoctoral fellowships (F31s) or institutional training grants (T32s) to support them during graduate school. Postdoctoral fellows receive F32 fellowships and are eligible for K awards and senior fellowships when they become independent investigators. For researchers with professional degrees (MD, DDS, DDO), institutional training grants provide support during residency, postdoctoral fellowships are available for specialty and subspecialty training, and K awards are available for independent investigators.

Dr. Stanley commented that as the Principal Investigator on a National Research Service Award (NRSA) training grant, he thinks that the training grants may be too successful. The relative ease of receiving training grants allows many young people to be trained but, after training, they find that it is difficult to obtain funding with which to start their careers. A recent study in the *Journal of the American Medical Association* showed that 40 percent of investigators who receive one NIH grant never receive another. He suggested that the NIAMS consider cutting back on training grant awards, training fewer people, and using the savings to provide more access to research grants early in trainees' careers. Dr. Katz agreed that the NIAMS has too many trainees, but is hesitant to cut that number without having a better way to determine who would be a successful investigator in the future. Cutting back on the amount of money set aside for training grants would allow those dollars to be used elsewhere (perhaps for early career awards) but also would result in fewer trainees entering the field.

Dr. Randy Rosier commented that it may not be accurate to define a successful scientific career only in terms of success in obtaining NIH grants. Many people may go through the training process and then work in industry or other areas of the economy that affect public health; these contributions would be missed if success is measured only as success in obtaining grants. Dr. Graciela Alarcon agreed that training goes beyond training academicians, and although it is desirable to decrease the drop between the number of trainees and number of academic investigators, former trainees working in other fields still make important contributions. Dr. Gena Carter added that training grants serve to reward people for their abilities and what they currently produce, not for what they may do in the future. She related the experience of another organization, which awards grants to postdoctoral fellows and trainees at various stages of training and ultimately has funded 39 Nobel Laureates; limiting the number of trainees at any particular point in the training process may increase the risk of losing someone with excellent potential.

Another issue discussed was that of training foreign trainees. Non-U.S. citizens are not eligible for training grants, despite providing a substantial amount of labor to research laboratories. Several Council members expressed concern that perhaps too much money was allocated for training grants for which a substantial minority of trainees (non-U.S. citizens) were not eligible. This could result in fewer investigators, particularly clinical investigators, in the pipeline because of the lack of training funds. Council members also asked whether the success of foreign-born trainees could be compared to that of U.S.-born trainees. Foreign trainees generally are funded through their mentors' R01 grants; this could be used as a way to track their subsequent performance and to compare it to recipients of NRSA's (only U.S. citizens are eligible for this award). The success of foreign trainees might indicate whether it would be wise to allocate more funding for their training. Dr. Stanley commented that during these times of tighter budgets, perhaps the NIH should not be funding the training of investigators who are not U.S. citizens. Needing foreign trainees to perform the

work in laboratories is a different issue than providing funds for their training. The NIH may need to make decisions concerning whether it will continue to fund foreign trainees or foreign research in general. Dr. Ramirez argued that many foreign trainees remain in the United States and contribute to U.S. research. Ms. Terry added that, if the goal of NIH-funded research is to improve health, who is trained is less important than whether they contribute to the improved health of U.S. citizens. Particularly for rare diseases, it may be important to strengthen the global research enterprise.

Health Services and Outcomes Research

Dr. James Panagis discussed the NIH's role in supporting health services and outcomes research. This research is defined as a field of inquiry that examines the impact of the organization, financing, and management of health care services on the access to, delivery, cost, outcomes, and quality of such services. Outcomes research also analyzes the impact of health care interventions from a patient's perspective, assessing how these interventions impact healing and quality of life.

Using this definition, for fiscal year 2004, NIAMS supported 22 projects at a cost of \$5.86 million, distributed among R01s, P01s, two T32 awards, and several career development awards. These studies can be expensive, and it is not realistic to assume that the NIAMS alone can fund all health services research in the fields of skin and musculoskeletal diseases. Collaborative funding is important to the success of this field of research.

Research needs for health services and outcomes research include standardized definitions and outcome assessment tools along with training support for future health services researchers. More or better analytical methodologies also are needed to address health outcomes research questions. The questions facing Council members concerning this research include defining the contribution of the NIAMS to health services research and whether the Institute should support more of this research.

Dr. Alarcon commented that a priority in this area is training new investigators. The current pool of investigators in this field is small and aging quickly, but competition for resources may discourage young applicants from entering the field. Basic science research may seem more appealing to many researchers, so efforts should be made to spur interest in health outcomes research and to encourage and support those interested in it. Dr. Katz suggested that there are many training opportunities beyond NIH-funded training, such as at the CDC; efforts need to be made to coordinate NIAMS efforts with outside training resources. The NIH is coordinating with several outside agencies, including the CMS, to better coordinate training and research efforts. Agencies such as the CMS could be useful at the outset of a study because they have large databases that could provide helpful information, ultimately improving the quality of a study.

Ms. Mary Elizabeth Replogle agreed that encouraging collaboration was important. Many of these studies, however, result in a very large return on investment; the amount of health-care dollars that can be saved by performing more effective procedures and interventions far outweighs the amount spent on the research, which should make this research easily justifiable to the taxpayer. Dr. Katz agreed that many of these studies result in significant savings in the health-care arena, but there still is the question of who should be responsible for performing the research. Many of these studies, when performed properly, ultimately result in savings, but the studies themselves can be extremely expensive to perform. Ms. Terry commented that the Health Resources and Services Administration performs a great deal of health outcomes research and may be another important collaborator, especially during tight budgetary times. Health outcomes research may need to be less of a priority for some NIH Institutes, particularly the organ- or disease-specific Institutes.

IX. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 535 applications in closed session requesting \$120,185,537 and recommended for \$119,728,419.

X. ADJOURNMENT

The 55th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 4:00 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

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

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