Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Diabetes and Digestive and Kidney Diseases Advisory Council
May 23, 2008

I. CALL TO ORDER

Dr. Griffin P. Rodgers, Director

Dr. Griffin P. Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called to order the 177th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Friday, May 23, 2008, in Conference Room E1/E2, Natcher Building (45), NIH, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Nancy Andrews
Dr. Janice Arnold
Ms. Janet Brown
Dr. Charles Elson
Dr. James Freston
Dr. Mark Magnuson
Dr. Juanita Merchant
Dr. William Mitch
Dr. Brian Monahan
Dr. Jerry Palmer
Dr. David Perlmutter
Ms. Margery Perry
Ms. Lisa Richardson
Dr. Anthony Schaeffer
Mr. James Schlicht
Dr. Patrick Tso

Also present:

Dr. Griffin P. Rodgers, Director, NIDDK, and Chairperson, NIDDK Advisory Council

Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

In addition to Council members, others in attendance included NIDDK staff members, Center for Scientific Review (CSR) Scientific Review Officers, and other NIH staff members. Guests were present during the open sessions of the meeting. Attendees included the following:

Abraham, Kristin- NIDDK
Agodoa, Lawrence - NIDDK
Akolkar, Beena - NIDDK
Appel, Michael - NIDDK
Arreaza-Rubin, Guillermo - NIDDK
Amir, Syed - CSR
Badger-Faupel, Jessica - NIDDK
Barnard, Michele - NIDDK
Bishop, Terry -NIDDK
Blondel, Oliver - NIDDK
Bethum, Najma - CSR

Beverly, Kevin - Social Scientific Systems
Brown, Clarice - Social Scientific Systems
Calvo, Francisco - NIDDK
Carrington, Jill - NIDDK
Castle, Arthur - NIDDK
Chang, Debuene - NIDDK
Christiansen, Dane - Digestive Diseases National Coalition
Clay, Shawna - NIDDK
Cowie, Catherine - NIDDK
Curtis, Leslie - NIDDK
Davila-Bloom, Maria - NIDDK
Densmore, Christine - NIDDK
Doo, Edward - NIDDK
Doherty, Dee - NIDDK
Donohue, Patrick - NIDDK
Edwards, Michael - NIDDK
Eggerman, Thomas - NIDDK
Eggers, Paul - NIDDK
Everhart, James - NIDDK
Farishian, Richard - NIDDK
Faupel-Badger, Jessica - NIDDK
Ferguson. Frances - NIDDK
Feld, Carol - Hill Group
Fisher, Rachel - NIDDK
Fonville, Olaf - NIDDK
Gansheroff, Lisa - NIDDK
Garfield, Sanford - NIDDK
Giambarresi, Leo - American Urological Foundation
Goter-Robinson, Carol - NIDDK
Greene, Elizabeth - NIDDK
Gutierrez-Lugo, Elizabeth - NIDDK
Guo, Xiaodu - NIDDK
Haft, Carol - NIDDK
Hanlon, Mary - NIDDK
Hilliard, Trude - NIDDK
Harris, Mary - NIDDK
Hoff, Eleanor - NIDDK
Hoofnagle, Jay - NIDDK
Horlick, Mary - NIDDK
Hoshiazi, Deborah - NIDDK
Howard, Stuart - NIDDK
Hubbard, Van - NIDDK
Hyde, James - NIDDK
James, Stephen - NIDDK
Jerkins, Ann - CSR
Johnson, Michelle - NIDDK
Jones-Perry, Aretina - NIDDK
Jones, Teresa - NIDDK
Jordan, Craig - NIDCD
Karp, Robert - NIDDK
Ketchum, Christian - NIDDK
Kim, Sooja - CSR
Kimmel, Paul - NIDDK
Kusek, John - NIDDK
Laughlin, Maren - NIDDK
Lee-Chon, Angie - NIDDK
Leschek, Ellen - NIDDK
Linder, Barbara - NIDDK
Malik, Karl - NIDDK
Manouelian, Denise - NIDDK
May, Michael (Ken) - NIDDK
McGowan, Melissa - NIDDK
McKeon, Catherine - NIDDK
Miles, Carolyn - NIDDK
Miller, David - NIDDK
Miller, Megan - NIDDK
Moen, Laura - NIDDK
Mims-Moxey, Marva - NIDDK
Mullins, Christopher - NIDDK
Narva, Andrew -NIDDK
Nicholson, Krystle- NIDDK
Newman, Eileen -NIDDK
Nyberg, Leroy - NIDDK
Patel, D.G. - NIDDK
Payne, Phyllis - NIDDK
Pike, Robert - NIDDK
Podskalny, Judith - NIDDK
Pope, Sharon - NIDDK
Rasooly, Rebekah - NIDDK
Robinson, Terra -NIDDK
Rosenberg, Mary Kay- NIDDK
Ross, Catherine – Bio Search Team Placement
Rushing, Paul - NIDDK
Sahai, Atul - NIDDK
Salomon, Karen - NIDDK
Sankaran, Lakshmanan - NIDDK
Sato, Sheryl - NIDDK

Savage, Peter - NIDDK
Sechi, Salvatore - NIDDK
Seef, Leonard - NIDDK
Sharpe, Angie – Consortium of Social Science Associations
Sheard, Nancy - CSR
Singer, Elizabeth - NIDDK
Shoneck, Ted – Tunnell Government Services Group
Smith, Philip - NIDDK
Star, Robert - NIDDK
Stone, Arthur - NIDDK
Tatham, Thomas - NIDDK
Torrance, Rebecca - NIDDK
Wade, Kristen - NIDDK
Wallace, Julie - NIDDK
Wellner, Robert - NIDDK
Weisman, Jennifer - NIDDK
Wilder, Betsy - NIDDK
Wilson, Teresa - NIDDK
Williams, Garman - NIDDK
Wright, Elizabeth -NIDDK
Wright, Daniel - NIDDK
Woynarowska, Barbara - NIDDK
Xie, Yining -NIDDK
Yanovski, Susan - NIDDK
Zeller, Charles - NIDDK

C. ANNOUNCEMENTS

Dr. Griffin P. Rodgers, Director, NIDDK

Dr. Rodgers thanked all the Council members for their participation and made the following announcements.

Council Members

Dr. David Altshuler: Attending his first meeting as a new Council member, Dr. Altshuler is Professor of Genetics and Medicine at Harvard Medical School and Director of the Program in Medical and Population Genetics at the Broad Institute of Harvard and the Massachusetts Institute of Technology. His research focuses on two intertwined goals: (1) to characterize and catalogue patterns of human genetic variation, and (2) to apply this information to dissect the genetic contribution to common human diseases, in particular type 2 diabetes and cardiovascular disease risk factors. For example, Dr. Altshuler is pursuing an exciting new project in premature coronary artery disease. His research interests also include prostate cancer, systemic lupus erythematosus, rheumatoid arthritis, and age-related macular degeneration. Throughout his career, Dr. Altshuler has contributed to knowledge of the patterns of genetic variation in the human genome; led in the creation of publicly available, genome-wide single nucleotide polymorphism (SNP) and haplotype maps; developed methods for genetic analysis; and contributed to the discovery of genes for type 2 diabetes, systemic lupus erythematosus, and prostate cancer. Dr. Altshuler earned both his M.D. and Ph.D. degrees from Harvard in 1994. His research has been funded by the NIDDK and other NIH institutes since 2002. He is presently Principal Investigator on three NIH supported research projects and is also Co-Investigator of a Center for High Throughput SNP Genotyping and Analysis funded by the National Center for Research Resources (NCRR).

NIDDK Grantees

Dr. Sum P. Lee: A long-standing NIDDK grantee and former member of the NIDDK Advisory Council, Dr. Lee has accepted the position of Dean of the Faculty of Medicine at the University of Hong Kong. Dr. Lee is a distinguished gastroenterologist and Professor of Medicine in the Department of Medicine at the University of Washington. Part of Dr. Lee's recent research focus has been on the relationship between obesity, insulin resistance, and the metabolic syndrome in pregnancy. This research also includes study of intrauterine programming of the developing fetus, and subsequent evolution of growth, development, diabetes, and obesity. Dr. Lee has been supported in his research by grants from NIDDK since 1992. He presently holds three grants from the NIDDK and one from the National Cancer Institute. Dr. Lee served as a member of the NIDDK Advisory Council from 2002 to 2005. The NIDDK wishes him well in his new position.

NIDDK Staff Members

Division of Kidney, Urologic and Hematologic Diseases--Dr. Paul Kimmel: In March, Dr. Kimmel rejoined the Division as Director of the Translational Kidney Genetics Program and a full-time Program Officer for the Clinical Acute Kidney Injury Program. Dr. Kimmel will also be spending some time at The George Washington University as a Professor of Medicine and will continue to be involved in clinical and research activities. Previously, Dr. Kimmel was the Director of the Division of Renal Diseases and Hypertension at George Washington University, and the Director of Education of the American Society of Nephrology. His clinical interests include diabetic nephropathy, cytokine biology in chronic kidney disease, psychological adaptation to chronic kidney disease, and HIV-associated renal diseases. A graduate of Yale University, Dr. Kimmel received his M.D. from New York University, and trained at Bellevue Hospital and the Hospital of the University of Pennsylvania. From 1998 to 2001, he served as a Program Director at the NIDDK with responsibility for overseeing the Diabetic Nephropathy Program and HIV Kidney Disease Program, as well as serving as the Project Scientist for the Family Investigation of Nephropathy and Diabetes (FIND).

Division of Diabetes, Endocrinology and Metabolism—Dr. Peter Savage: The Division is pleased to have Dr. Savage join their efforts as a Special Advisor on Clinical Research on detail from the National Heart, Lung, and Blood Institute (NHLBI). Dr. Savage received his M.D. from Tufts Medical School and completed post-doctoral training in internal medicine and a fellowship at Yale University prior to joining the NIDDK Intramural Program in Phoenix, AZ. He has served as an Assistant Professor of Medicine and as Deputy Director of the Adult Care Unit at the Diabetes Research and Training Center, University of Michigan; as Chief of the Endocrinology/Hypertension Section of the Detroit VA Hospital; and as an Associate Professor of Medicine at Wayne State University. At the NHLBI, he served as Chief, and later Director, of the Clinical and Genetic Epidemiology Branch within the Division of Epidemiology and Clinical Applications. Dr. Savage has had a leadership role for a large number of epidemiology studies, clinical trials, and biostatistical programs. While at the NHLBI, he played a major role in expanding clinical research on the cardiovascular complications of diabetes

and was a key person involved in the planning and development of the ACCORD clinical trial. He also served for ten years as the NHLBI's representative on the statutory Diabetes Interagency Coordinating Committee.

Review Branch--Dr. Thomas Tatham: In March, the NIDDK's Review Branch welcomed Dr. Tatham as a new Scientific Review Officer. Dr. Tatham earned a Ph.D. in Experimental Psychology from Temple University in animal learning. He subsequently received post-doctoral training in psychopharmacology. He is also a graduate of the Commerce Department's Science and Technology Fellowship Program. His academic career includes serving on the faculties of Mount Union College and the Uniformed Services University of the Health Sciences. Dr. Tatham came to the NIH in 1999 and has served as a Scientific Review Officer at the NIH Center for Scientific Review (CSR). In addition to his regular duties, Dr. Tatham served for several years as the CSR's Information Technology Liaison and, more recently, as Associate Director for Knowledge Management. In these capacities, he streamlined procedures for shipping materials to reviewers; produced a series of programs that automate many of the administrative aspects of summary statement production; and led an effort to use text-mining technology to automate the referral of grant applications. His accomplishments have been recognized by a DHHS Secretary's Award, Directors' Awards from both the NIH and the CSR, and the CSR Explorer Award.

Grants Management Branch: Three new Grants Management Specialists have joined the Branch: Ms. Krystle Nicholson, Ms. Marilyn Rosendorf, and Ms. Leslie Whipp.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 176th COUNCIL MEETING

Following a motion, the Council approved the Summary Minutes of the 176th Council meeting by voice vote.

III. FUTURE COUNCIL DATES

Dr. Rodgers called the attention of the Council to future meeting dates:

2008
September 24 (Wednesday)

2009
February 18-19 (Wednesday and Thursday)
May 13-14 (Wednesday and Thursday)
September 9-10 (Wednesday and Thursday)

Most of these meetings in 2009 are expected to be on a single day—Wednesday. However, the NIDDK requests that Council members hold both Wednesday and Thursday to ensure flexibility should a situation arise where a longer meeting is required.

IV. ANNOUNCEMENTS

Dr. Brent Stanfield
Director of Extramural Research, NIDDK

Confidentiality

Council members were reminded that material furnished for review purposes and discussion during the closed portion of the meeting is considered privileged information. The outcome of such discussion during the closed session may be disclosed only by the staff and only under appropriate circumstances. All communication from investigators to Council members regarding actions on applications must be referred to the Institute. Any attempts by Council members to handle questions from applicants could create difficult or embarrassing situations for the members, the Institute, and/or the investigators.

Conflict of Interest

Advisors and consultants serving as members of public advisory committees may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall ensure that a committee member does not participate in, and is not present, during review of applications or projects in which, to the member's knowledge, any of the following has a financial interest: the member, or his or her spouse, minor child, partner (including close professional associates), or organization with which the member is connected. To ensure that a member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the member, and this statement becomes a part of the meeting file. Dr Stanfield asked each Council member to read the statement provided regarding conflict of interest, and to sign and return it to him.

At Council meetings when applications are reviewed in groups without discussion, i.e., "en bloc" action, all Council members may be present and may participate. The vote of an individual member in such instances does not apply to applications for which the member might be in conflict. With respect to multi-campus institutions of higher education, Dr. Stanfield noted that an employee may participate in any particular matter affecting one campus of a State multi-campus institution of higher education, if the employee's disqualifying financial interest is employment in a position with no multi-campus responsibilities at a separate campus of the same multi-campus institution.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Griffin P. Rodgers

Fiscal Year 2009 Appropriations Bill

Dr. Rodgers noted that the President's budget request for the NIDDK for Fiscal Year 2009 is approximately $1.708 billion, which represents about a 0.1 percent increase over the Fiscal Year 2008 appropriation. Most of the Institutes and Centers at the NIH have a

similar percentage increase. With this budgetary landscape NIDDK will need to manage its resources with great care, and to shepherd the funds that become available when ongoing projects are terminated so that support can be provided to the most scientifically promising new research. This task is made more difficult because of a biomedical inflation rate of about 3.5 percent, which has led to a decline in the purchasing power of investigators over the last several years.

Congressional Interactions

The NIH Director, Dr. Elias Zerhouni, testified on the Fiscal Year 2009 President's budget request for NIH at a single House hearing, along with witnesses from the Centers for Disease Control and Prevention (CDC), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Agency for Healthcare Research and Quality (AHRQ). Given the Department-wide scope of this hearing, NIH Institute and Center Directors did not participate. Although a Senate hearing for the NIH was planned, it was later cancelled.

The Fiscal Year 2009 appropriations process has been much more streamlined than the Fiscal Year 2008 cycle, during which there were several NIH theme hearings. However, following Dr. Zerhouni's testimony, the NIH was visited by Congressman David Obey, the Chairman of the full House Appropriations Committee, as well as the Chairman of the Subcommittee with jurisdiction over the NIH--along with several other committee members. This visit provided the NIH with an additional opportunity to highlight recent accomplishments. Formal presentations were made by Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI); Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID); Dr. Betsy Nabel, Director, National Heart, Lung, and Blood Institute (NHLBI); and others. Presentations focused on several topics including: recent genetic discoveries linked to a wide range of diseases--including some strongly linked to kidney cancer; new surgical techniques for minimally invasive therapies; and new diagnostic techniques for heart attacks and strokes. Dr. Rodgers joined with a few other Institute Directors who gave brief remarks and met with the Members and their staff during their visit to the NIH Clinical Center.

Dr. Rodgers noted that as a newly appointed Institute Director he has taken the opportunity to make several introductory visits to Members of appropriations and authorizing committees that have the NIH within their jurisdiction. He has visited close to three dozen House and Senate Members, and additional visits are scheduled. During these visits, the Members have generally shown a great interest in learning more about both the NIDDK and the NIH. They have been receptive to Dr. Rodgers' message that research plays an essential role in the public health and in the economic health of the Nation. About 20 percent of these visits have led to an invitation to Dr. Rodgers to join the Members locally in their communities to speak further about areas of interest to their constituents.

Paylines

For Fiscal Year 2008, the NIDDK has been able to achieve the goal of raising its R01 payline from 13 percent to 17 percent for all applicants, and from 15 to 19 percent for new investigators. As reported at the last Council meeting, several factors have enabled these payline increases.

Numbers of New Investigators

New R01 investigators continue to be an NIH-wide priority, with Institute-specific goals set for their support. The NIDDK goal is 166 for Fiscal Year 2008, which is slightly fewer than last year's goal of 188. These goals include individuals who will be funded within the general payline, as well as some individuals who score beyond that payline. Dr. Rodgers thanked the Council and the NIDDK staff for helping to identify the individuals to receive this funding.

Bridge Awards

The NIH Director's Bridge Award Program is continuing for a second year. This Program provides for one-year funding through an R56 grant for established investigators whose peer-review score on a competing application was near, but not quite within, the fundable range, and whose other means of support were considered insufficient to enable them to continue their efforts until they could re-compete for an R01 grant. The continuity of funding provided by a Bridge Award permits the Principal Investigator additional time to strengthen an application for resubmission. Each Institute and Center is permitted to nominate eligible and worthy candidates for a first round of funding decisions. The NIDDK has been notably successful in participating in this Program.

Special Statutory Funding Program for Type 1 Diabetes Research

The Congress has extended funding for this Program for one additional year—through Fiscal Year 2009. Because this Program was approaching the end of its statutory funding envelope, the NIDDK previously requested and received permission to use multiyear funding authority to establish a new Type 1 Diabetes Pathfinder Award. This award was established to support exceptionally creative new investigators who propose innovative research projects that have the potential for unusually high impact in type 1 diabetes and its complications. It also complements ongoing NIH efforts to fund new investigators. Based on the large numbers of applications submitted, the Type 1 Diabetes Pathfinder Award has been well-received by the community. The NIDDK plans to make eight awards each of which may total up to $1.5 million in direct costs over a five-year budget/project period.

With the recent extension of the Special Statutory Program, the NIDDK is seeking to apply a multiyear funding approach again—this time for other new efforts that will not be limited to new investigators. The aim is to encourage groups of investigators to apply jointly for complex projects related to the complications of diabetes and to the genetics of

type 1 diabetes. These research solicitations will be announced shortly, with the designation of "DP3" awards. Given that there is no guarantee of further Program extensions, multiyear funding approaches provide the NIH with the greatest flexibility for managing this Special Statutory Program. At the same time, Dr. Judith Fradkin, the Director of the NIDDK's Division of Diabetes, Endocrinology and Metabolic Diseases, arranged for an extensive external review of the clinical research studies that are already under way so that priorities can be established for either a possible Program close-out, or alternatively, a further funding extension, should that be provided by the Congress. On April 29 and 30, 2008, the NIDDK convened thirteen scientific leaders whose collective expertise encompassed clinical trial design, epidemiology, biostatistics, transplantation, genetics and immunity. They rendered a thoughtful analysis of nine large, multi-site clinical studies that are currently under way. A similar review is planned to analyze the basic research component of the Program, as well as activities focused on the development and use of animal models. The observations and recommendations from these processes will be of great assistance in the NIDDK's continuing management of this Program, which is vested in the Secretary of Health and Human Services and involves multiple NIH components and the CDC.

Funding Prospects for Scored vs. Unscored Applications Upon Resubmission

Dr. Rodgers presented a slide in follow-up to a question posed by a Council member at the last meeting regarding the percentage of unscored (streamlined) initial applications (A0 applications) that are eventually funded through a resubmission process. For both the NIH and the NIDDK, the slide presented 1996-2006 data in a line graph showing the percentage of both scored and unscored grant resubmissions (A1 and A2 applications) that were eventually funded (as a percentage of submitted A1 applications).

Dr. Rodgers noted the similarity of the NIH and NIDDK data, which is not surprising given that the NIDDK is the fifth largest NIH component and thus can have a large effect on NIH summary data. NIDDK-assigned grants represent about ten percent of all the grants processed by the NIH Center for Scientific Review, and are considered in well over 60 percent of the NIH Study Sections.

Although there is some yearly variation in the data, the overall picture is relatively stable. Of the NIDDK-assigned initial applications (A0) that are scored, roughly 55 percent are eventually funded through the resubmission and re-review process. This funding profile closely matches that of the NIH proper for scored applications. Of the NIDDK-assigned initial applications (A0) that are considered streamlined or unscored, only about 15-20 percent have received eventual funding—again closely matching the NIH data. The most recent, reliable data for the NIDDK unscored applications show that 15 percent receive eventual funding. The take-home message is that applications that receive scores upon initial submission have a much greater probability of eventual funding than those that are unscored.

VI. UPDATE: ACCORD Trial (ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES TRIAL)

Dr. Peter Savage, Special Advisor on Clinical Research
Division of Diabetes, Endocrinology and Metabolic Diseases

In introducing Dr. Savage, Dr. Rodgers noted that the NIDDK has been one of several co-sponsors of the ACCORD trial. Led by the NHLBI, this large trial is being conducted in a group of adults with established type 2 diabetes who are at especially high risk for cardiovascular disease. The NHLBI stopped one of the treatment arms in this trial--the intensive glycemic control (glucose-lowering) arm--18 months earlier than planned due to safety concerns that were raised following the review of available data. (Note: Information about the ACCORD trial can be found at: www.accordtrial.org/ *This website includes material published subsequent to the NIDDK Council meeting, i.e., the June 2008 article on ACCORD findings in the New England Journal of Medicine, as well as the June 2008 NHLBI Press Release.)*

Dr. Savage began by describing the complexity of the ACCORD trial, which has been a trans-NIH effort in many respects. In addition to receiving support from the NHLBI and the NIDDK, the trial is also supported by the National Institute on Aging (NIA), National Eye Institute (NEI), and the Centers for Disease Control.

ACCORD Trial Design

The ACCORD study is a multicenter, randomized clinical trial with a double-factorial design. The trial is conducted at 77 different sites around the country. The design of the trial included:

- Recruitment of over ten thousand patients with established type 2 diabetes, high glucose levels, and a high risk for cardiovascular disease events. The patients either had clinical cardiovascular disease (CVD) or they had at least two other CVD risk-factor abnormalities in addition to their diabetes.
- Testing of three separate treatment strategies to reduce cardiovascular disease: glycemic control, blood pressure control, and blood lipid control--according to specified targets.
- All interventions were with drugs approved by the FDA and on the market in the United States.
- Dr. Savage underscored that the primary focus of the trial is on the three treatment strategies and not on specific drug interventions. He described the strategies in general terms.
- For the glycemic control strategy, two targets were used for hemoglobin A1c (A1c) levels, which reflect an individual's average blood glucose level over the past three months. The targets were an intensive-control target of less than 6 vs. a standard-control target in the 7-7.9 percent range.
- For the blood pressure control strategy, a target systolic blood pressure of less than 120 millimeters of mercury was contrasted with a standard control of less than 140 millimeters of mercury. Physicians titrated the treatment to goal using a range of antihypertensive agents provided by ACCORD.

- For the lipid control strategy, all patients received statin therapy to reduce low density lipoprotein cholesterol (LDL-C) levels to less than 100 milligrams per deciliter. However, one group of patients also received fibrates to test their effects in increasing high density lipoprotein cholesterol (HDL-C) levels and in lowering triglyceride (TG) levels.

The trial design included the participation of all patients in the glycemic-control strategy. Half of them were randomized to the intensive control group and half were randomized to the standard control group. To participate in the study, patients needed to be eligible for either a blood pressure or lipid intervention and they were randomized to those strategies within the two large glycemic control strategy groups.

The primary outcome in the ACCORD design is a composite CVD outcome of non-fatal myocardial infarction, non-fatal stroke, and CVD deaths. Cases are adjudicated by a committee blinded to the assignment of the patients. Comparisons are between the marginal results in each of the arms of the trial. Direct comparisons are not possible between the blood pressure control and lipid control groups because they were not randomized to permit that type of analysis. The statistical power of the ACCORD design is about 89 percent power to detect a 15 percent effect for glycemic control; about 94 percent power to detect a 20 percent effect for blood pressure control; and about 87 percent power to detect a 20 percent effect for lipid control.

ACCORD Trial Monitoring

The monitoring of the trial has been extensive, particularly the oversight provided by an independent Data and Safety Monitoring Board (DSMB). A requirement for starting the trial was to test a vanguard of 1,000 patients for a year in order to assess safety, as well as the ability to achieve or come close to the treatment goals and to maintain separations among the groups. Several indicators were analyzed in the glycemic control strategy in addition to A1c levels. For example, one concern was whether these generally older patients (average age of 62 years) with significant co-morbidities were at risk for hypoglycemia. An external working group was established to review not only the frequency of hypoglycemia, but also the way the study responded to it. Other indicators that were monitored included the rate of hospitalized heart failure, heart failure symptoms, weight gain, and ALT levels. The trial design included following a whole series of adverse events, and the efficacy of the primary outcome. Several substudies also are underway. One of the objectives was to determine whether or not intensive glucose control is associated with improvement or deterioration in mental function, another was to assess diabetic retinopathy, a third was an economic substudy.

Termination of Intensive Glycemic Control Component of ACCORD Trial

In February 2008, the NHLBI announced that it was terminating the intensive glycemic control component of the trial based on the recommendation of the independent Data and Safety Monitoring Board (DSMB). (See NHLBI press release at: http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2551)

For several months, the DSMB closely watched a slowly developing trend in excess deaths in the intensive glycemic vs. the standard treatment glycemic intervention groups. After careful monitoring, review of additional data analyses, and deliberation, the DSMB recommended to the NHLBI Director that this part of the study be stopped because of concern for the participants' safety. A discussion then occurred as to whether the entire trial should be halted. Because of interest in the questions addressed in the other arms of the trial, the NHLBI determined that the best course of action was to continue the study, but to place all participants on the standard glycemia control group and follow them all to the scheduled conclusion of the study in 2009, with final results expected to be reported in 2010.

The excess deaths in the intensive glycemic control arm occurred despite a non-significant reduction in that group of overall cardiovascular events as compared with the standard glycemic control group.

Nevertheless, the DSMB concluded that any significant or major excess in deaths would counteract whatever other benefits were being seen in the intensive glycemic control arm of the trial. It should be noted that the death rates were lower in ACCORD than previously reported in most type 2 diabetes studies of comparable subjects--although it is difficult to make comparisons of ACCORD data with published data from other studies. The ACCORD patients tended to have better control of their glucose levels, better blood pressure levels, and better lipid levels than most patients in earlier studies.

Implications of ACCORD Trial Results for Diabetes Care

The excess deaths in the intensive glycemic control group appeared to be mainly cardiovascular, but the specific cause(s) has not been identified, despite extensive efforts on the part of the ACCORD Data Coordinating Center. Because the main design of ACCORD focuses on strategies for controlling glycemia, blood pressure and lipid levels, rather than on specific drug interventions, it is difficult to pinpoint the cause(s) of the excess deaths. Had the trial design been focused on assessing specific medical interventions, it would probably have been criticized for not reflecting the way that patients with diabetes are treated with multiple drugs in medical practice. Patients in ACCORD took several drugs because of their multiple risk factors and combinations of risk factors that were being addressed. To date, there has been no clear indication that rosiglitazone or any of the other medications used in the ACCORD trial are related to the excess deaths observed; however, the search for causes is continuing.

Several questions are raised by the finding that the overall CVD rate was lower (but not significantly lower) in the intensive glycemic control group, yet there was an excess of cardiovascular mortality. Is there something about the underlying cardiovascular disease in these patients? Is there something about the diabetes itself? Is a combination of factors responsible? While these questions are difficult, they are very important because the answers could illuminate whether there is a subset of patients for whom intensive glycemic control carries a risk for CVD death. If these patients could be identified, glycemic targets could be tailored to account for the specific risk of this subgroup,

whereas many other diabetes patients without such risk might be able to benefit from more intensive glycemic control. Although there is unequivocal evidence that more intensive glycemic control is beneficial in terms of the microvascular complications of type 2 diabetes, the hoped-for positive effect of this strategy on CVD rates has not been realized. Moreover, the question may be more complex than previously thought, because a serious question now exists as to whether or not there may be subsets of type 2 diabetes patients in terms of CVD risk.

An overriding treatment question is: For what types of patients do the results of the ACCORD trial have relevance or applicability? The results apply most directly to patients who are similar to the ACCORD patient population. The ACCORD patients have type 2 diabetes and existing CVD, or they are at high risk of developing CVD because they have multiple CVD risk factors in addition to their diabetes. The ages of ACCORD participants at entry to the study ranged from around 40 to around 80 years, with an average age of 62 years. The average duration of their diabetes at entry to the study was 10 years, and, in general, they had been treated with some type of drug therapy before joining the study.

With respect to A1c levels, the ACCORD participants attained a median of 6.4 percent in the intensive glycemic control group and around 7.5 percent in the standard glycemic control group. At the present time, it is not believed that the findings of the ACCORD trial would invalidate the A1c guidelines of the American Diabetes Association (ADA), which continues to advise people with diabetes to strive for an A1c level of less than 7 percent. (Note: The following is a link to the ADA statement related to the ACCORD trial. http://www.diabetes.org/for-media/pr-ada-statement-related-to-accord-trail-announcement-020608.jsp) However, the ACCORD findings do raise a question about how widely applicable intensive therapy should be. When all the ACCORD data are available and published (with the first publication expected in June 2008), there may be a need to revisit the current guidelines and consider whether modifications may be necessary. Importantly, guidelines about A1c levels currently have a statement underscoring the need to individualize therapy in diabetes patients and this requires greater emphasis. However, the ACCORD patients were relatively indistinguishable from other type 2 diabetes patients with CVD or at high risk of developing CVD.

It is possible that the ACCORD findings of excess deaths associated with intensive glycemic control may not apply to type 2 patients who do not share the characteristics of the ACCORD participants, for example, those with recent-onset diabetes and/or low CVD risk. However, the study wasn't designed in a way to answer that question. One can look at other studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), in which there was no excess mortality in the intensive glycemic control group in type 2 diabetes patients who were in the early stages of diabetes. However, in making comparative analyses, one must consider differences between the ACCORD trial and other studies with regard to the level of treatment and the degree to which glucose was controlled. Light may be shed on these issues by other ongoing trials, along with discussions at the American Diabetes Association meeting in June, 2008.

The ACCORD findings reinforce the importance of randomized controlled clinical trials to determine the optimal treatment for patients with diabetes and other chronic diseases. They also illustrate a need for better systems to monitor the effects of drug interventions. In many cases, these interventions have become very complex because of the multiple risk factors in patients with long-standing chronic diseases such as type 2 diabetes. *(Note: Dr. Savage recognized the contributions of Dr. Denise Simmons-Morton, the Project Officer for the ACCORD trial, who was unable to attend the Council meeting.)*

Council Questions and Discussion

What proportion of the patients in the intensive glycemic control group actually reached a target of 6 or lower on their A1c levels? While he could not provide the exact percentage, Dr. Savage responded that there were some patients whose A1c levels were in the 5's. In general, the A1c levels came down to the 6.4 range at the end of the first year and then remained essentially flat after that. However, there was a spectrum of A1c levels that ranged from normal into the mid 7's--with most patients clustered around the median.

Were there more cardiovascular events at the really low A1c levels? Dr. Savage noted that there were some details of the study that he couldn't provide prior to publication of the main results of the glycemic intervention. However, there was no evidence that attaining a lower A1c level, in and of itself, was a risk factor. On the other hand, patients whose type 2 diabetes was of shorter duration found it easier to lower their A1c levels. Epidemiologic studies may be performed on the all the data when they are published; however, the trial wasn't designed to answer the question posed by the Council in the intensive glycemic control group.

Could you elaborate on whether there has been some movement to A1c guidelines that are lower than the ADA guidelines? Dr. Savage responded that there is a European guideline of 6.5 percent and that the Association of Clinical Endocrinologists in the U.S. has recommended 6.5 percent. As continuous glucose monitoring and feedback devices are developed further, it may be appropriate to look at guidelines again, because more intensive glycemic control with less variation in glucose levels than is currently possible may provide a benefit to some patients. Researchers would be in a better position to know the answer if they had the technology to replicate with precision the normal metabolic control of glucose and to avoid excursions in patients that inevitably occur when administering drugs whose effects may be delayed by several hours. For now, however, treatment approaches depend on the drug regimens available and on consideration of the results obtained from large, multisite research efforts such as the ACCORD trial and other studies.

Has the ACCORD trial raised questions in the public's mind more broadly? For example, is it possible that diabetes patients might not take medications to get their A1c levels into the 7's because of concerns they have about the excess CVD deaths in ACCORD, even though these excess deaths were only seen in the intensive glycemic control group for which the A1c target was 6.4? Also, might patients ease off on efforts

to control their blood pressure and lipid levels—even though those components of the ACCORD trial did not involve excess deaths as seen in the intensive glycemic control group? Among type 2 diabetes patients who might meet the standards of this trial in America, is it known what fraction is anywhere near the 7.5 A1c target level of the standard glycemic control group in ACCORD?

Dr. Savage responded that one of the studies that will emerge from the ACCORD trial will look at data from the National Center for Health Statistics to try to determine whether A1c levels are coming down among diabetes patients in America. The CDC has reported that levels have dropped recently. However, the average A1c level in the overall U.S. diabetes population is still in the high 7 percent range, so there is not a large group of patients whose levels are in the area of the 6.0 percent A1c target of the intensive glycemic control group of the ACCORD trial. Nevertheless, if intensification of glycemic control becomes more prevalent using current regimens, there may be a susceptible group of patients at risk because of some genetic or toxic consequence of their diabetes or another factor. The Chair of the ACCORD study group has said that there may be a significant danger in attempting to lower A1c levels to values around the 6.4 percent achieved in the intensive treatment group in ACCORD.

At the same time, however, patients with type 2 diabetes and their physicians should consider the established benefits of glycemic control and recognize the progress that has already been made. It is very important to emphasize that several studies have shown the benefits of good glucose control on the microvascular complications of diabetes. Also, studies have shown the advantages of blood pressure control and intensified LDC cholesterol lowering in type 2 diabetes. If pursued collectively, these strategies should change the overall risk of microvascular and cardiovascular complications in diabetes. The 50-year data analysis of the Framingham study suggests that diabetes patients have had a decline in the CVD risk rate that parallels the major decline, but still remains 2-3 times higher, than the general population of non-diabetics--although there are some data suggesting that diabetes patients, particularly women, may not have done as well during the last decade. Other data accumulating from interventions that do not involve glycemic control indicate that much can be done for diabetes patients. Importantly, there is no evidence that the excess deaths seen in the intensive glycemic control group of the ACCORD trial would occur in individuals with recent-onset type 2 diabetes. In fact, it may be very important to do more studies in the earlier stages of type 2 diabetes to see if it is possible to prevent or reverse the deterioration in health that occurs over time, especially in populations with very high rates of diabetes, such as the American Indians or other high risk minority groups in the U.S.

VII. ADVISORY COUNCIL FORUM: Part 1
Update on Peer Review Enhancement
Dr. Lawrence Tabak
Director, National Institute of Dental and Craniofacial Research

Dr. Rodgers noted that Dr. Tabak's presentation would provide an update on the NIH peer review self-study that has resulted in an 88-page final draft report. Dr. Tabak has had a leadership role in the internal and external working groups involved in the self-study. He previously briefed the NIDDK Council on this effort.

Dr. Tabak set the stage for his presentation by noting that the increasing breadth, complexity, and interdisciplinary nature of science creates new challenges for the peer review function, which is essential to the NIH mission. Funding trends can also aggravate stresses on the peer review system. In response to these factors, the NIH initiated a self-study of the peer review system with the goal of enhancing it. Since July 2007, the NIH self-study of peer review has proceeded through several phases, under the leadership of two working groups—one internal and one external. The charge of the NIH Director to the working groups was to find ways to fund the best science, by the best scientists, with the least administrative burden. However, it was recognized that the term "best"--when used in assessing research applications--is context-dependent, including many factors such as the scientific quality, public health impact, and mission relevance of the scientific proposals, as well as their relationship to the existing NIH portfolio.

The phases of the peer review self-study have included diagnosis of the issues; design of an implementation plan; and the start of phased implementation of several actions. The diagnosis phase involved broad outreach to the external and internal NIH communities, including five regional town hall meetings around the country, as well as a Request for Information that received a robust response. A dialogue was also begun with most of the National Advisory Councils. Based on these and other sources of input received, a Final Draft Report was submitted to the NIH Director issued on February 29, 2008. This report is on the NIH website at: http://enhancing-peer-review.nih.gov

Seven Challenges

The report articulates seven sets of challenges along with recommended actions to address them. The challenges include reducing the administrative burden on stakeholders; enhancing the rating system; enhancing the quality of both review and reviewers; optimizing support at different career stages; optimizing support for different types and approaches of science; reducing stress on the support system of science; and meeting the need for continuous review of peer review. Based on feedback, a skeletal framework for implementing all of the recommendations was provided to the NIH Director on April 15, 2008. The self-study is now in its final stages in which implementation approaches are being vetted in several ways, including a presentation by Dr. Zerhouni to the Peer Review Advisory Committee (PRAC) and by internal NIH discussions with the NIH Steering Committee members and other Institute and Center Directors. Discussions will also take place with several Study Section chairs and

members of the Advisory Committee to the Director, NIH (ACD). In June, a public meeting is planned to provide details regarding the ways that some specific recommendations have been selected for further implementation.

Core Themes

The NIH has looked at the big picture to decide which of the major challenges need to be tackled first. In implementing changes, some general principles have been established to guide the process. The first general principle is to do no harm. The second principle is to continue to maximize the freedom of scientists to explore. A third is to place emphasis on a subset of changes that are most likely to add significant value to the system, but at a reasonable cost-benefit ratio. As a result of this process, four interdependent core themes have emerged.

Excellence of Reviewers: It is recognized that the excellence of peer review is directly correlated to the ability of the NIH to recruit, retain, and motivate the most accomplished, broad-minded, and creative scientists to serve on Study Sections. Therefore, key goals are to reduce the burden on reviewers, to recruit additional distinguished reviewers to serve on Study Sections, and to recognize and compensate the efforts of distinguished NIH review service. The NIH wants to acknowledge those scientists whose efforts extend well beyond expectations in terms of their excellence in review service. It will also be important to use common best practices to enhance the training of NIH Scientific Review Officers, Study Section Chairs, and members of review panels.

Fairness and Clarity of Review: Peer review requires the consistent identification of the relative merit, potential for scientific and/or public health impact, and feasibility of research applications. Thus, the NIH seeks to enhance the process for providing applicants and NIH Program Officers alike with clear and purposeful review feedback through informative Summary Statements, and a rating system that is comparable across Study Sections and fields of science. To accomplish this, the NIH plans to modify the research application structure and to align it with a new rating system and Summary Statement format that will emphasize the five specific review criteria: (1) impact, (2) investigator, (3) innovation or originality, (4) project plan and feasibility, and (5) environment. In the new system each review criterion will be given its own score. The NIH plans to pilot new models of review, including the editorial board model—a two-stage system similar to the review process used for the publication of articles by scientific journals.

Support for Scientists at Different Stages of Their Careers: The peer review system clearly needs to provide an unbiased evaluation of applications from all scientists, irrespective of their disciplines or where they are in their career paths. Moreover, the NIH should not favor the funding of conservative scientific approaches at the expense of innovation and originality.

A major goal will be to reduce any bias in the review of early-stage investigators. For example, the NIH needs to ensure that there is no bias toward subsets of investigators

regarding the opportunity for full discussion during the review process. This issue became apparent to the NIH when it observed the adaptation of Study Section behavior to changes in funding policy. When the Study Sections understood that the NIH was committed to funding more early-career investigators, the scores for these applicants began to drift upward, and an increasing percentage of their applications were left unscored--without the benefit of discussion. It has also become clear that a subset of investigators who had been considered "new," are very accomplished researchers with other sources of support--even though they may not have received an NIH R01 grant. In the future, the NIH will delineate those "new" investigators (new to NIH funding, but not to research success) from those who are truly early-stage in their careers, that is, within ten years from receipt of their last degree or clinical training. The NIH plans to continue its efforts to fund more new-to-NIH and early-stage investigators. An effort will also be made to expand transformative research pathways--for example, expanded use of the Eureka Award—and also to enhance the overall system used to support research.

A second example relates to the balancing of retrospective and prospective review. It is important to evaluate both the science produced and the science proposed. Recognizing that past performance is the best predictor of future success, the NIH has determined that the review of applications from established investigators--who have had the opportunity to establish a track record--will include increased emphasis on retrospective assessment.

Dr. Tabak noted that a third issue related to stages of a scientist's career concerns the success rates for initial submission of a research grant--the A0 submission--relative to the success rates for subsequently amended and resubmitted applications (A1 or A 2 applications), as previously mentioned by Dr. Rodgers. An analysis of data has shown that, over time, there has been a drop in A0 funding rates and an increase in the funding of applications at the stage of first or second resubmission (A1 or A2, respectively). Dr. Tabek showed several slides to illustrate the changes that have occurred. For example, in 1998, slightly over 60 percent of R01s-equivalent grants that were awarded were made in response to A0 applications. However, by 2007 the percentage of R01-equivalent grants made in response to A0 applications fell to about 30 percent. During this same 1998 to 2007 time period, the percentage of R01-equivalent grants made in response to A1 applications rose from slightly under 30 percent to nearly 40 percent. The corresponding percentage of R01-equivalent grants awarded in response to A2 applications rose from slightly under 10 percent to about 30 percent. Corollary data indicate that, in 1998, nearly all A0 applications at about the 15th percentile were funded. However, over time, an increasing number of resubmissions have been required (through 2006) for an investigator to obtain funding.

These changes have increased the inefficiency of the peer review system, which must deal with processing the resubmissions. Concerns have even been raised anecdotally that some investigators may be purposefully planning for poor scores on their initial applications, with the expectation that they will go through a resubmission process that will likely culminate in funding. Although the funding rates for resubmissions are high and improvements in the quality of some applications probably do occur, there may be a subset of applications that really do not need to undergo this iterative review process,

which is burdensome to both investigators and reviewers. Moreover, it is not known if resubmissions produce better science. Thus, consideration has been given to the development of an NIH-wide policy statement regarding an intent to return to historical averages of funding rates for A0, A1 and A2 submissions.

Continuous Quality Control and Improvement for Peer Review: Continuous enhancement of the NIH peer review system needs to be based on rigorous and independent prospective evaluations that favor, rather than discourage, adaptive and innovative approaches to peer review and program management. The present self-study has identified steps the NIH will immediately begin to implement, along with actions that will not be pursued at this time. Dr. Tabak elaborated on a group of concepts that were considered during the self-study, but that are either not moving forward at all, or not in the form proposed.

- *Paying Reviewers for Their Time in Preparing for and Participating in the Review Process:* This idea is not being pursued because it probably would not make a great deal of difference in terms of recruiting and retaining excellent reviewers.
- *Relieving Reviewers of Administrative Reductions on Their Grants:* There is considerable unevenness in these reductions among the Institutes and Centers; therefore, this approach would have unintended disparate impacts.
- *Introducing a New Designation to Peer Review--"Not Recommended for Resubmission" (NRR):* This concept is based on the perspective that the science of some applications, no matter how much they are improved via the resubmission process, is unlikely to have a sufficient impact to warrant funding. Rather than having the investigator undergo the A1 and A2 process--and then possibly even change the content sufficiently to start the whole process over again with an A0 application--it may be better for the applicant to know at the outset that spending additional time and effort on the scientific concept will probably not result in funding. The NIH is not going to adopt this approach because the research community did not support it. Instead, by elaborating on the specific criteria that the reviewers will use and reflecting those criteria in the Summary Statements, the NIH will convey to the applicant information about his or her probability of eventual funding, without the starkness of an NRR designation.
- Permitting "Prebuttal" To Correct Factual Errors: Broadly endorsed, the general idea underlying this recommendation will be tested in a pilot manner through the two-stage, editorial-board model of review. However, this model will not be implemented extensively until the NIH has an opportunity to see how it works experimentally.
- *Overweighting the Research Environment for Early-stage Investigators:* While this concept had some support, it could introduce a bias against less research-intensive institutions.
- *Establishing Separate Reviews for New Investigators and for Clinical Research:* While the intent of this concept is to foster these two categories, its implementation could result in stigmatizing them.

- *Creating a New Mechanism for Transformative Team Science:* This action is not considered necessary at this time because of the existence of the Eureka Award, the Pioneer Award, and other similar mechanisms.
- *Considering all Applications as New (A0):* This idea met with great opposition in the research community.
- *Allowing NIH Salary Support for a Maximum of 50 Percent:* This action could favor some institutions more than others because of differences in the business models in academic institutions across the country.
- *Requiring a Minimum of 20 Percent Effort for Principal Investigators:* This idea raised enormous angst in the community, particularly among scientific professional organizations. While there is a need to determine whether investigators have sufficient time to realize the scientific aims of their grants, there could be unintended consequences because of differences in defining percent effort among academic research institutions. Therefore, the NIH will not pursue this particular route, but will seek alternative administrative approaches to ensure appropriate use and oversight of resources.

Currently, the NIH is beginning to discuss with stakeholders the parameters of the planned enhancements to the peer review system. The NIH will flesh out the details of various implementation strategies and Dr. Zerhouni will announce them in June to the Advisory Committee to the Director, NIH (ACD). He is also scheduled to have a commentary in *Science* in mid-June. For some enhancements, implementation can commence very quickly. Other changes may require more time for planning and execution. The NIH plans to evaluate the effects of the modifications that are introduced, as it indicated to the community at the beginning of the self-study process. It is expected that the results of those evaluations will ultimately lead to the development of new NIH policies.

Council Questions and Discussion

Has there been significant discussion about the length of research applications during this thoughtful self-study process? Dr. Tabak replied in the affirmative. As a result, the NIH will be implementing a shortened application for all R series research grants, for the F research training awards, and for the K research career and development awards. The precise length of the application is still under discussion; however, a seven-page application for R01 grants was recommended by a subset of the investigative community. Others favored a length of about fifteen pages. However, it was recognized that the presentation of complicated clinical trial proposals may need additional space. The final length will likely be between seven and fifteen pages--with an appendix for proposals that involve clinical trials, epidemiology and other areas requiring additional explication. When the final length is agreed upon for the R01 grant, the length of applications for other mechanisms will likely be scaled to it.

The report outlined the knotty problem of introducing a designation of "not recommended for resubmission (NRR)," which is not favored by the community for addressing the trends in A0, A1, and A2 applications. However, another difficult problem

is the skew that is introduced to peer review by the use of ad hoc reviewers who only vote on occasion, in contrast to the continuity of review provided by regular Study Section members. What can be done to eliminate that problem, perhaps with mathematical approaches? Dr. Tabak responded that the NIH will be addressing both of these issues. With regard to the former, all applications will be scored in the future by use of five criteria that will provide meaningful, practical feedback to investigators without resorting to an NRR designation. For applications that do not receive further discussion, the applicants will at least receive the average of the reviewers' scores on each of the five criteria. Thus, for example, they will have a sense of whether or not the potential scientific impact of their proposals was judged to be below an acceptable threshold. For applications that are considered further, the Study Section members will establish a global score that is informed by the scores on the individual criteria and the discussion about them, as led by assigned reviewers. The general consensus is that this process should not be driven by algorithms, but rather, that it should be informed by the results of peer review on the individual criteria. The NIH expects that these changes will help to address the issues raised.

The report is impressive and reflective of an incredible effort. Many of the approaches for which there is an action plan will be very positive. Two actions of particular note are efforts to address the unevenness of review, and also, to try to ensure funding for the most outstanding investigators. The increased focus on innovation is likewise extremely important. One question is whether some of the enhancements planned for Study Sections would lead to their being tasked with actual funding decisions? Also, what data exist regarding the degree of scattered results in the Study Sections? Dr. Tabak responded that the driver for the discussion about ranking applications at the conclusion of a Study Section meeting is the sense that there is unevenness in terms of the review of applications on the first day of a Study Section meeting *versus* the review of applications reviewed on the second day. Analysis shows that, if an investigator is among the first applicants reviewed, he or she will benefit. Many involved in the peer review self-study argued that a global re-examination and ranking of all the individual applications would enable the Study Section to provide a more even review process for the entire universe of applications it considers. Other ranking methodologies have been proposed, such as an up-front ranking. The NIH proposes to pilot different approaches to ranking. However, the new ranking process would not replace the vital role of National Advisory Councils in final funding decisions. While the NIH is trying to maximize its funding investments, including support for outstanding and innovative investigators, the agency also recognizes that the universities contribute enormous amounts of funding to the support of research. Because of the dynamics of the NIH budget-doubling period followed by a leveling-off period, many investigators are now at funding risk in many institutions. A dialogue should probably be established among stakeholders to come to grips with this issue so that ways can be found to sustain these investigators in their research careers.

Is there a way to reduce the burden on the peer review process by staggering the initiation of funding based on data showing that about 55 percent of applications will eventually be funded? Dr. Tabak replied that the NIH self-study included discussion of the relative value of having a funding queue so that investigators who were not within an

Institute's or Center's payline but scored close to it would not have to reapply and undergo the peer review process again. In general, the National Advisory Councils favored this idea, and it is likely that it will be pursued at the level of the individual Institutes and Centers. Such an approach would greatly reduce the burden of peer review on both applicants and reviewers, while preserving the critically important role of the Councils in funding decisions.

Will there be a process to reconsider at some future point the recommendations from the self-study process that are not being implemented? What was the process for differentiating between those recommendations that would go forward and those that would not? What will happen with some of the more innovative suggestions, including the one about "Not Recommended for Resubmission"? In keeping with the last core theme regarding the need for continuous quality control and review of peer review, Dr. Tabak noted that the issues and recommendations not pursued at this time may be revisited in the future if the enhancements being implemented are not as effective as hoped. The NIH recognizes the frustrations that investigators experience when revised and resubmitted applications still do not receive funding. Investigators might be spared that process if they knew, from an NRR designation on their initial application, that there was little probability of their work being funded, even with revision. However, the NIH received substantial feedback from the research community in opposition to the NRR concept, particularly because it could dishearten investigators. The NIH will therefore take a different approach to this issue through a more structured review built upon five explicit criteria and a Summary Statement in which the reviewers must address those criteria, with the impact of the application being a primary consideration. Thus, the applicant and the Program Officers at the Institutes and Centers will have much clearer feedback than they have had previously regarding whether the revision and resubmission of an application will improve its funding prospects. When the effects of this approach are analyzed through the continuous review of peer review, it is possible that the NIH could revisit previous recommendations about this issue or entertain suggestions for other, different approaches.

What about the cost to investigators of time spent rewriting grant applications—time that could be spent on doing the science? Wouldn't the NRR approach help avoid that problem? Dr. Tabak responded that the NRR approach was viewed as useful by the NIH, but that the community responded very negatively to it. However, as the issue of grant resubmissions continues to be discussed and the five criteria are rolled out, the NIH expects that investigators will realize that an application judged to have little potential for scientific impact will have little likelihood of funding upon re-review no matter how perfect the application may otherwise be. Thus, the effect of the five criteria is consistent with the underlying principle of NRR, without resorting to the use of that specific terminology.

Was any consideration given to whether there might be cost savings achieved from peer review enhancement that could be redirected to the budget available for funding research projects? Dr. Tabak said that this concept was considered extensively. Because the major cost of peer review is travel for the reviewers, the NIH will go forward with increased use

of electronic-assisted reviews. However, face-to-face meetings of Study Section members cannot be completely eliminated for several reasons, including differences among scientific disciplines and some technical problems with video-enhanced reviews. The NIH hopes to make some modest investments in electronic-assisted reviews that may diminish the expense of travel.

VIII. ADVISORY COUNCIL FORUM: Part 2
NIH Roadmap for Medical Research

Roadmap Initiative Update
Dr. Philip Smith
Deputy Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, and Co-Director, Office of Obesity Research

Dr. Smith reported that two new programs under the second cohort of the NIH Roadmap for Medical Research have begun to move forward: the Microbiome Project and the Epigenomics of Human Health and Disease Project. Both programs were highlighted at the February Council meeting. They are of great scientific interest to the NIDDK, which is actively participating in their management. Requests for Applications have been issued, and funding for the initial parts of the initiatives is expected to begin this year.

The NIH has also initiated a third wave of planning for Roadmap programs. New programs were recently recommended to the Directors of the Institutes and Centers, and several relate to specific interests of the NIDDK. Because concepts are still under consideration by the NIH Director, it will not be possible to report on them until final decisions are made.

New Roadmap Initiative Development Process
Dr. Betsy Wilder
Acting Associate Director
Office of Portfolio Analysis and Strategic Initiatives (OPASI), NIH

Dr. Wilder acknowledged the contributions of the NIDDK to keeping the Council apprised of Roadmap programs. It is important to NIH that Roadmap programs be based on community input. The Roadmap programs are intended to address severe, pressing needs within the scientific community without duplicating efforts in the Institutes and Centers. Importantly, Roadmap programs are intended to be transformative. Although it is difficult to predict transformation, approaches are being sought to further insightful decisions.

There are several groups that participate in the Roadmap process. At the NIH, these groups include:

- *NIH Leadership:* Collectively the 27 Institute and Center Directors make conceptual recommendations regarding concepts submitted for consideration. These recommendations are passed to the NIH Director for final approval.

- Director, Office of Portfolio Analysis and Strategic Initiatives: Under the authority of the NIH Director, the OPASI Director makes final decisions on detailed issues. His decisions are based heavily on the recommendations of a rotating group of three Institute and Center Directors and the OPASI Director called the ICOD. The ICOD is delegated the responsibility of reviewing programmatic details, such as approving RFAs and funding plans.

- *Working Groups:* Trans-NIH groups of program staff from the Institutes and Centers and from OPASI help to develop and implement new programs, and are responsible for managing ongoing ones. The primary workers in this process are the Institute and Center staff members, for whom OPASI serves as a supportive umbrella mechanism.

The development of Roadmap initiatives has involved input from many sources external and internal to the NIH, from portfolio analyses reflective of NIH current funding, from the Council on Councils, and from public meetings. The National Advisory Councils have a key role in informing NIH staff about pressing scientific needs in their respective research communities. A key mechanism for obtaining broad input has been and will continue to be the Request for Information (RFI). When NIH staff members submit ideas through an RFI, it is understood that they are reflecting extensive community input gathered in many ways. From such broad-based input, NIH staff members funnel ideas to OPASI, which, in turn, passes them along to senior program officials who review them for responsiveness to the Roadmap criteria. Are the ideas cross-cutting in scope, relevant to many diseases, relevant to the missions of the Institutes and Centers but not duplicative of their efforts? Do the ideas have the potential for being highly transformative? Although many ideas are potentially transformative, they need to be considered against the backdrop of the existing NIH scientific portfolio to see if they would help to fill research gaps. It is likewise important to identify the major hurdles to making scientific progress and the most effective ways to overcome them.

The Working Groups refine the submitted ideas into proposals for new programs, which are then sent to the Council of Councils, whose members include representatives from the National Advisory Councils of the Institutes and Centers. The Council of Councils meets in November and March and has two roles in the Roadmap process. First, in addition to participating in generating suggestions via the RFI, the Council of Councils can formulate and discuss much broader ideas, especially new approaches to be tested via the Roadmap and new ways to foster innovation and transformation. Second, the Council of Councils reviews proposals at its annual Fall meeting prior to the NIH leadership's selection process in February. If the Council deems that a proposal is not responsive to Roadmap criteria, it can provide comments and guidance regarding how it could be made responsive. Following The Council of Council's concept clearance, the proposals are sent to the NIH leadership for final approval.

The NIH would like to amplify the needs assessment process by the community because it is a critical part of developing new Roadmap programs. The currently active Request for Information, which is open until June 2, 2008, is the first means of needs assessment for new concepts. Moreover, for NIH staff members, the RFI will now be the only route for submitting new ideas for the next Roadmap cycle. Ideas from the National Advisory Councils will also need to come in through the RFI. The NIH expects that workshops, surveys and more detailed RFIs will be undertaken over the course of the summer by NIH teams before the most compelling of the submitted ideas are developed fully into proposals for concept clearance.

There is an increasing need for portfolio analysis to assess the research areas that are currently being funded by NIH. These analyses are an important context for the consideration of ideas submitted for possible Roadmap funding. The OPASI is working to develop new and more automated methods of portfolio analysis, but will also retain the human element in the assessment process.

In summary, the decision-making of the NIH leadership in the next stage of the Roadmap life cycle will be informed by input from many sources: responses to the RFI; the Council of Councils; analysis of the existing NIH research portfolio; and continuing assessment of community needs. Ideas submitted through the RFI solicitation mechanism will go to a group of senior NIH staff members, who will identify those that will go forward for further development into proposals over the summer. These proposals will be submitted to the Council of Councils in the Fall. Finally, the proposals will be considered by the IC Directors and NIH Director at their annual February retreat.

Council Questions and Discussion

What are the challenges to having truly innovative ideas identified and supported through these mechanisms? Dr. Wilder replied that the challenges are huge, but the process involves a great deal of consensus building. Currently, The Roadmap has programs that are very open-ended in their scientific content, such as the Pioneer Awards and the New Innovator Awards. Because it is difficult to recognize true innovation in advance, these types of mechanisms encourage the community to submit outstanding ideas and the NIH will find a way to fund them. These types of program have a heavy emphasis on the past research achievements of the applicants. The NIH is also discussing the possibility of having another open-ended approach that is based more on the project than on the investigator. There can be a tension between the goal of funding innovative ideas and the goal of addressing the specific needs that cut across many disease areas and the individual missions of the Institutes and Centers. Currently, there is a single funding pool for Roadmap efforts, and ideas that may be weighted more toward one direction or another must compete within that funding envelope.

Is it important to have clarity about which ideas are responsive to shared research needs versus which ones are innovative approaches that fall beyond the domain of any single IC? Dr. Wilder responded that clarity about these different types of ideas is definitely

important. However, targeting a specific allocation of funds for these different types of projects within the overall Roadmap funding envelope would probably not be well-received by the community.

How many concepts are submitted? How do you ensure that the individuals who screen the submitted ideas and filter out those that will not receive further consideration have sufficient scientific expertise to do that? Dr. Wilder said that the last time ideas were solicited, over 300 were submitted. The Institute and Center Directors triaged the ideas, with the assistance of a group of senior program staff members who provided their views about responsiveness of the ideas to the Roadmap criteria. However, for the next cycle of ideas, the Directors will designate a member of their scientific staff to represent them in this process. Like the Directors, their delegates will have broad knowledge of the research portfolios of their respective Institutes and Centers. For the NIDDK, Dr. Rodgers has nominated Dr. Philip Smith. Thus, collectively, the process should reflect the same type of expertise that is possessed by the Institute and Center Directors as a whole. It is also important to keep in mind that the RFI requests the submission of very broad conceptual problems and a way to approach them. Hence the filtering process is at a conceptual level that does not require scientific expertise about the details of the proposed ideas. Dr. Rodgers commented on the long, detailed, and deliberative process through which Roadmap ideas are broadly vetted. Extensive time is spent by the NIH scientific staff in performing portfolio analyses and in considering whether the submitted ideas represent transformative research that would unlikely be pursued by a single Institute or Center. Dr. Rodgers noted that the member of the NIDDK National Advisory Council who serves on the NIH Council of Councils is Dr. Juanita Merchant, who very recently was also recognized by the American Gastroenterological Association with an award for her outstanding mentorship in science. After the Council of Councils becomes fully operational, the NIDDK will invite Dr. Merchant to make a presentation to the NIDDK Council about its activities relative to the Roadmap.

The Roadmap process is logical, inclusive, and exciting. What is the cost of the Roadmap initiatives? Is there a danger that the Roadmap will raise unrealistic funding expectations in the research community? There is a growing cynicism about the ability of NIH to support costly initiatives given its current budget realities. For example, in one Roadmap initiative--the Clinical Translational Science Awards (CTSAs)—the awarded budgets were dramatically reduced from the original requests. In such circumstances, the investigators cannot deliver what they have proposed. What other research may need to be sacrificed if all the excellent Roadmap ideas are funded and come to fruition? Dr. Wilder replied that the total Roadmap budget is currently $500 million. Dr. Rodgers noted that the initial funding of the Roadmap included the NIH Director's funds and transfers from the ICs. However, by legislation, budgetary resources for support of the Common Fund, which includes the Roadmap, are now provided through a direct, separate congressional appropriation for that purpose. Hence, the ICs are no longer transferring funds from their own specific appropriations to support Roadmap activities and the issue of opportunity costs and trade-offs does not really arise. The ICs can now use the funds they would have transferred to the Roadmap initiative for other research activities. With regard to the CTSA program, Dr. Wilder noted that this initiative is jointly funded by the

National Center for Research Resources and the Roadmap, within a framework developed in conjunction with congressional staff input. Because the CTSA program is new, the NIH will need to see how it is functioning before it can determine the level of future budgetary commitments may be appropriate based on that program assessment. Dr. Rodgers also commented that the CTSAs are being rolled out in a relatively fast-paced, two-phase exploratory approach. Efforts are being made to reach the number of CTSAs that NIH set as a goal; however, accomplishing that goal within a fixed budgetary envelope is requiring some funding adjustments. Importantly, there is a recognition that many CTSAs are at institutions that house large clinical efforts funded by the NIH through other means. The ICs have been asked to identify one or two leaders of clinical research at institutions that have CTSA awards to see whether it may be possible to realize economies of scale if funded investigators could be involved in these CTSAs. The NIDDK has two such leaders who are Principal Investigators on currently funded CTSAs whom it would like to invite to a future Council meeting to present their ideas and seek feedback on ways to enrich and synergize the CTSAs with NIDDK's ongoing clinical research activities. Dr. Alving, the Director of NCRR, spoke to the Council about the CTSA program previously and it may be an appropriate time to invite her back for an update on the goals and directions of the program.

IX. SCIENTIFIC PRESENTATION

RNAi-based Therapeutic Strategies for Metabolic and Inflammatory Diseases
Dr. Michael Czech

Dr. Rodgers introduced Dr. Michael Czech, Professor and Chair of Molecular Medicine and Professor of Biochemistry and Molecular Pharmacology at the University of Massachusetts Medical School.

Dr. Czech gave an overview of his laboratory's work developing gene silencing strategies and demonstrated the therapeutic potential for strategies using Glucan Encapsulated siRNA Particles.

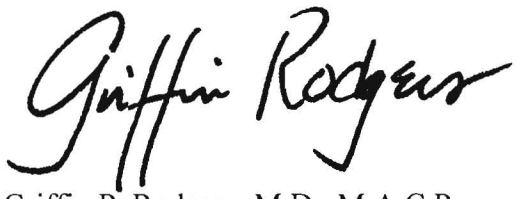
X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 2,001 grant applications, requesting support of $449,325,793 were reviewed for consideration at the May 23, 2008 meeting. Funding for these 2,001applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 1,015 applications requesting $244,050,102 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the May 23, 2008 meeting.

XI. ADJOURNMENT

Dr. Rodgers thanked the Council members for their attendance and valuable discussion. There being no other business, the 177th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m., May 23rd, 2008.

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



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