

Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Diabetes and Digestive and Kidney Diseases Advisory Council
September 9, 2009

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 181st meeting of the NIDDK Advisory Council at 8:30 a.m., Wednesday, September 9, 2009, in Conference Room 10, Bldg. 31, NIH, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

CHAIRPERSON

RODGERS, Griffin P., M.D., M.A.C.P.
Director, NIDDK

FRESTON, James W., M.D., Ph.D.
Professor of Medicine Emeritus
Boehringer Ingelheim Chair of Clinical
Pharmacology
University of Connecticut Health Center
Farmington, Connecticut

MEMBERS

ALTSHULER, David, M.D., Ph.D.
Professor of Genetics and Medicine
Simches Research Facility
Boston, Massachusetts

GLASS, Christopher K., M.D., Ph.D.
Professor
Department of Cellular & Molecular
Medicine
Department of Medicine
University of California, San Diego
La Jolla, California

ANDREWS, Nancy C., M.D., Ph.D.
Dean
Duke University School of Medicine
Vice Chancellor for Academic Affairs
Durham, North Carolina

LAZAR, Mitchell A., Ph.D., M.D.
Sylvan H. Eisman Professor of Medicine &
Genetics
Chief, Division of Endocrinology, Diabetes,
and Metabolism
Director, Institute for Diabetes, Obesity and
Metabolism
University of Pennsylvania
Philadelphia, Pennsylvania

BURTON, Laverne
President and CEO
American Kidney Fund
Rockville, Maryland

ELSON, III, Charles O., M.D.
Professor of Medicine and Microbiology
Division of Gastroenterology and
Hepatology
University of Alabama at Birmingham
Birmingham, Alabama

MAGNUSON, Mark A., M.D.
Earl W. Sutherland, Jr., Professor of
Molecular Physiology and Biophysics
Director, Center for Stem Cell Biology
Vanderbilt University School of Medicine
Nashville, Tennessee

MERCHANT, Juanita L., M.D., Ph.D.
Professor of Internal Medicine and
Molecular and Integrative Physiology
Division of Gastroenterology
University of Michigan Medical School
Ann Arbor, Michigan

MITCH, William E., M.D.
Gordon A. Cain Professor of Medicine and
Director, Division of Nephrology
Baylor College of Medicine
Houston, Texas

PERRY, Margery D.
Consultant
Aspen, Colorado

PERLMUTTER, David H., M.D.
Vira I. Heinz Chairman of Pediatrics
Department of Pediatrics
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

SCHAEFFER, Anthony J., M.D.
Professor and Chairman
Department of Urology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

SCHLICHT, James P., MPA
Arlington, Virginia

SEDOR, John R., M.D.
Associate Chair for Research
Department of Medicine
Case Western Reserve University
Cleveland, Ohio

TSO, Patrick P., Ph.D.
Professor
Department of Pathology/Genome Research
Institute
University of Cincinnati College of
Medicine
Cincinnati, Ohio

EX-OFFICIOS

KLURFELD, David M., Ph.D.
National Program Leader, Human Nutrition
Human Nutrition Research Center
USDA-Agricultural Research Service
Beltsville, Maryland

MONAHAN, Brian P., M.D., FACP Captain
MC USN
Associate Professor of Medicine
Program Director and Specialty Leader,
Hematology and Medical Oncology
National Naval Medical Center
Bethesda, MD

PALMER, Jerry P., M.D.
Director, Division of Endocrinology,
Metabolism & Nutrition
VA Puget Sound Health Care System
Director, Diabetes Endocrinology Research
Center
Professor of Medicine
University of Washington
Seattle, Washington

EXECUTIVE SECRETARY

STANFIELD, Brent B., Ph.D.
Director, Division of Extramural Activities
National Institute of Diabetes and Digestive
and Kidney Diseases
Bethesda, Maryland

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:

Abankwah, Dora – NIDDK
Abraham, Kristin – NIDDK
Agodoa, Lawrence-NIDDK
Akolkar, Beena – NIDDK
Appel, Michael – NIDDK
Barnard, Michele – NIDDK
Betha, Gina-NIDDK
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Bloom-Davila, Maria – NIDDK
Calvo, Francisco – NIDDK
Carrington, Jill – NIDDK
Castle, Arthur – NIDDK
Chamberlain, Joan – NIDDK
Chen, Yuan-Who R – NIDDK
Chon Lee, Angie – NIDDK
Cowie, Catherine – NIDDK
Curtis, Leslie – NIDDK
Doherty, Dee – NIDDK
Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Edwards, Michael – NIDDK
Eggerman, Thomas – NIDDK
Eggers, Paul – NIDDK
Evans, Mary – NIDDK
Everhart, James – NIDDK
Farishian, Richard – NIDDK
Feldman, Blair – AMERICAN COLLEGE OF
SPORTS MEDICINE
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gansheroff, Lisa – NIDDK
Germino, Greg – NIDDK
Goter-Robinson, Carol – NIDDK
Grey, Michael – NIDDK
Guo, Xiaodu – NIDDK
Haft Renfrew, Carol – NIDDK
Hanlon, Mary – NIDDK
Harris, Kimberly – NIDDK
Harris, Mary – NIDDK
Hilliard, Trude – NIDDK
Hoofnagle, Jay – NIDDK
Hogan, Michelle – NEPHROLOGY TIMES
Horlick, Mary – NIDDK
Hoshizaki, Deborah – NIDDK
Howards, Stuart – NIDDK
Hubbard, Van – NIDDK
Hunter, Christine – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jenkins, Ann – CSR
Jones, Teresa – NIDDK
Jones, David – NIDDK
Karp, Robert – NIDDK
Keersmaekers, Christine – AMERICAN SOCIETY
OF NEPHROLOGY
Ketchum, Christian – NIDDK
Kim, Sooja – CSR
Kimmel, Paul – NIDDK
Klausing, Thomas – NIDDK
Kranzfelder, Kathy – NIDDK
Kuczarski, Robert – NIDDK
Kusek, John – NIDDK
Laughlin, Maren – NIDDK
Linder, Barbara – NIDDK
Magra, Amy – NIDDK
Malik, Karl – NIDDK
Manouelian, Denise – NIDDK
Margolis, Ronald – NIDDK
Martinez, Winnie – NIDDK
McGowan, Melissa – NIDDK
McKeon, Catherine – NIDDK
Miles, Carolyn – NIDDK
Miller, David – NIDDK
Moxey-Mims, Marva – NIDDK
Mullins, Christopher – NIDDK
Narva, Andrew – NIDDK
Nabel, Betsy – NHLBI
Newman, Eileen – NIDDK
Ngwu, Ezuma – NIDDK
Nicholson, Katherine – NIDDK
Patel, D. G. – NIDDK
Paterson, Beth – NIDDK
Papier, Wendy – NIDDK
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Podskalny, Judith – NIDDK
Pope, Sharon – NIDDK
Rada, Beth – XOMA
Rankin, Tracy – NIDDK
Rasooly, Rebekah – NIDDK
Roberts, Tibor – NIDDK
Robuck, Patricia – NIDDK
Rosenberg, Mary Kay – NIDDK
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – CSR
Sagan, Rebekah – HHS
Sahai, Atul – NIDDK

Salomon, Karen – NIDDK
Scanlon, Elizabeth – NIDDK
Sankaran, Lakshmanan – NIDDK
Sato, Sheryl – NIDDK
Savage, Peter – NIDDK
Schneider, Donald – CSR
Sechi, Salvatore – NIDDK
Seeff, Leonard – NIDDK
Sheard, Nancy – CSR
Smedberg, Paul – AMERICAN SOCIETY OF
NEPHROLOGY
Silva, Corrine – NIDDK
Smith, Philip – NIDDK

Spain, Lisa – NIDDK
Star, Robert – NIDDK
Tatham, Thomas – NIDDK
Tinkler, Emily – NIDDK
Torrance, Rebecca – NIDDK
Trepod, Allison-SRI INTERNATIONAL
Wallace, Julie – NIDDK
Weinberg, David – CSR
Williams, Will – NIDDK
Woynarowska, Barbara – NIDDK
Wright, Daniel – NIDDK
Wright, Elizabeth – NIDDK
Yanowski, Susan – NIDDK

C. PERSONNEL ANNOUNCEMENTS

Dr. Rodgers made the following announcements.

Council Members

- *Drs. Mitchell Lazar, Juanita Merchant, and David Perlmutter, Ms. Margery Perry, and Ms. Lisa Richardson* will rotate off the Council after this meeting. Dr. Lazar and Ms. Perry served on the Division of Diabetes, Endocrinology, and Metabolic Diseases subcouncil, and Drs. Merchant and Perlmutter and Ms. Richardson served on the Division of Digestive Diseases and Nutrition subcouncil. Dr. Rodgers thanked these members for their time and service and looked forward to their continued advice and involvement at NIDDK.
- *Dr. William Mitch* received the 2009 John P. Peters award from the American Society of Nephrology. This award recognizes individuals who have made substantial research contributions to nephrology and sustained achievements in one or more domains of academic medicine, including clinical care, education, and leadership. Established in 1983, the award is named for one of the founders of the field of nephrology and is very prestigious. Dr. Rodgers congratulated Dr. Mitch on his award.

NIDDK Staff Members

- *Dr. Kristin Tarbell*, of the Intramural Program, Diabetes Branch, Immune Tolerance Section, was one of 12 NIH-supported scientists who received the Presidential Early Career Award for Scientists and Engineers (PECASE) for 2008. The PECASE is one of the highest scientific awards for investigators at the early stages of their careers. Dr. Tarbell's work focuses on the roles of dendritic cells and regulatory T cells in peripheral T-cell tolerance induction and particularly how this mechanism is affected by autoimmune diseases such as type-1 diabetes.
- *Dr. Ken Jacobson* was inducted into the American Chemical Society Medicinal Chemistry Division Hall of Fame. Dr. Jacobson serves as Acting Chief of the NIDDK Laboratory of Bioorganic Chemistry and as Chief of Molecular Recognition Section. He

received his Ph.D. in Chemistry from the University of California, San Diego and was a Bantrell Fellow at the Weizmann Institute of Science. He has received several awards, including the 2003 Hillebrand Prize of the Chemical Society of Washington, and the 2009 Pharmacia ASPET Award in Experimental Therapeutic. His research interests include the structure and pharmacology of G protein-coupled receptors.

- *Dr. Leroy Nyberg*, Director of the NIDDK Urology Program, recently retired from Federal service. Dr. Nyberg received his Ph.D. from Columbia University and an M.D. from the University of Massachusetts. He conducted his residency in surgery and urology at Johns Hopkins University. Before joining NIDDK, Dr. Nyberg held faculty positions at the Medical University of South Carolina and the University of Connecticut Medical School and was Chief Urologist at the Charleston Memorial Hospital and the U.S. Department of Veterans Affairs (VA) Medical Center in Hartford, Connecticut. Dr. Nyberg joined NIDDK in 1988 as a urology program director, and during his 21 years of federal service he served as a program director or scientific officer for several urology clinical trials, including Medical Therapy of Prostate Symptoms, Urinary Incontinence Treatment Network, Interstitial Cystitis Network, and Complementary and Alternative Medicine for Urinary Centers. He also served as project officer for the Urologic Diseases of America compendium and for the Boston-Area Community Health (BACH) Study. While at NIDDK, Dr. Nyberg was recalled to active duty as a medical officer in the U.S. Navy during the first Gulf War. Dr. Rodgers thanked Dr. Nyberg for his service.
- *Mr. Thomas Klausing* has joined NIDDK as Budget Officer. Mr. Klausing worked for 10 years as a budget officer at the National Institute of Standards and Technology, where he led staff responsible for planning, review, development, justification, and reporting on the NIST budget and annual performance plan. He earlier served as the Chief of the Budget Review and Coordination Branch of the U.S. Immigration and Naturalization Service and as a senior budget analyst at the Department of Justice. Mr. Klausing received his bachelor degree in political science from West Virginia University and a Masters in Public Management and Policy from Carnegie Mellon University.
- *Mr. Will Williams*, a program analyst for the Division of Kidney, Urologic, and Hematologic Diseases, is leaving NIDDK. Mr. Williams was integral in program efforts and served as a valuable resource for budget, contracts, and sub-Council presentations. He received the You Make a Difference Award for his work.
- *Dr. Yuan-Who (Richard) Chen*, has joined the biostatistics group in the NIDDK Office of the Director. Dr. Chen received his Ph.D. in biometry from the University of Texas Health Sciences Center and worked at the U.S. Food and Drug Administration (FDA) for 8 years, where he reviewed investigational new drug protocols, biological license applications, and nondisclosure agreements in several areas.

Anniversary Celebration

Dr. Rodgers reminded the Council that NIDDK will celebrate its 60th anniversary in 2010. Throughout the year, the Institute will conduct several activities, which will culminate on Tuesday, September 21, 2010, with an anniversary scientific symposium and an anniversary celebration dinner at the Marriott Bethesda North. Dr. Rodgers noted that the September celebration will take place the day before the September 2010 Council meeting, and he invited Council members to save the date.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 180th COUNCIL MEETING

Following a motion, the Council approved the Summary Minutes of the 180th Council meeting by voice vote.

III. FUTURE COUNCIL DATES

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

2010

February 24-25 (Wednesday and Thursday)

May 12-13 (Wednesday and Thursday)

September 22-23 (Wednesday and Thursday)

2011

February 16-17 (Wednesday and Thursday)

May 11-12 (Wednesday and Thursday)

September 7-8 (Wednesday and Thursday)

Dr. Rodgers noted the expectation is that most meetings in 2010 and 2011 will take place on Wednesday and last a single day. However, he asked Council members to hold both days to ensure flexibility should a longer meeting be required.

IV. ANNOUNCEMENTS

Dr. Stanfield

Confidentiality

Council members were reminded that material furnished for review purposes and discussion during the closed portion of the meeting is considered confidential. The content of discussions taking place during the closed session may be disclosed only by the staff and only under appropriate circumstances. Any communication from investigators to Council members regarding actions on an application 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

Dr. Stanfield emphasized that advisors and consultants serving as members of public advisory committees, such as the NIDDK Advisory Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist each Council member to help ensure that he or she 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 an 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 drew the Council's attention to a statement within each member's folder regarding conflict of interest issues in review of applications. Each Council member was asked to read it carefully, and to sign and return it to NIDDK before departing the meeting.

At Council meetings when applications are reviewed in groups without discussion, that is, "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.

Dr. Stanfield addressed multi-campus institutions of higher education as follows: An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education, if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities.

Submission Dates for Council Members

Dr. Stanfield announced that CSR had extended the special, late, "ongoing" grant applications submission dates to Advisory Council members. This extension was previously granted only to reviewers. Council members should submit cover letters explaining their service along with their applications. CSR has committed to review these applications within 120 days of receipt. Dr. Stanfield noted, however, that these reviews most likely would take place in *ad hoc* meetings, not in regular standing meetings. He encouraged Council members to read the notice regarding the extended submission dates in the *NIH Guide* (see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-155.html>) and decide what is best for their applications.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Rodgers

Congress has extended the special appropriations for the type 1 diabetes program through 2011, which has allowed the Institute to extend several important ongoing activities such as the

Clinical Islet Transplantation Consortium. In addition, the action allowed NIDDK to re-compete the Clinical Center for the Type 1 Diabetes Trial Net and solicit R01 and R21 proposals for research on closed-loop technologies for clinical and behavioral approaches to type 1 diabetes. NIDDK has also solicited Small Business Innovation Research (SBIR) applications for new technologies contributing to an artificial pancreas. Furthermore, NIDDK is working with NEI to solicit SBIR applications related to diabetes, diabetes-related retinopathy, and telemedicine.

The President's proposed budget for 2010 calls for an increase of 1.5% for NIH, but much of this boost is focused on cancer research through a 3.6% increase in the National Cancer Institute budget. The budget also requests an increase for autism research, to be distributed proportionately to institutes involved in this research. Both the House and the Senate have acted on the 2010 budget, but no conference committee has yet taken place to resolve differences between the two reports.

The Senate proposal, like the President's request, recommends a 1.5% increase to the NIH budget. However, the Senate has rejected the additional funding for cancer and autism, because of concerns that advocates for other diseases and conditions would demand similar treatment. Instead, the Senate version would reduce some central accounts and use the additional flexibility to provide most institutes with an increase of 1.7% over 2009 levels. The Senate also notes the enormous budgetary increase for research from the American Reinvestment and Recovery Act (ARRA) in 2009-2010 and expresses concern that FY2011 funding will "fall off a cliff."

The House is willing to increase the NIH budget by 3.1% over the 2009 level by adding \$500 million to the President's proposed budget for FY2010. By making reductions to some central accounts the House proposes an increase of 3.6% to almost all Institutes. The House expects these funds to cover the inflation in biomedical research; to increase the number and size of research project grant awards; to allow a 2% increase in training stipends; to allocate about \$300 million for the Global Fund for AIDS, malaria, and tuberculosis; to continue the National Children's Study with \$194 million; and to support a Common Fund in the Office of the Director with \$534 million. Like the Senate, the House has expressed concern about requests for disease-specific funding levels.

There is speculation that Congress will act to finalize the budget within the first few weeks of the next fiscal year, by early November at the latest.

NIH has received \$10.1 billion in ARRA funds, and after funds were deducted for NCRR building projects, the remaining funds have been distributed to Institutes and Centers (ICs) in the normal percentages. NIDDK has received its share, \$445 million, to be spent over 2 years. Approximately eighty percent of this allocation has already been committed, and 20% has been held in reserve for consideration in FY2010. The ARRA funds available for FY2010 might increase depending on what opportunities for co-funding from the NIH Office of the Director come to fruition.

Among the ARRA-related activities, the ARRA Challenge Grant program has seen the highest demand. NIH received 22,000 applications for Challenge grants, and of those, 1,600 were assigned to NIDDK. Regarding other ARRA activities, the Institute is also considering

approximately 184 competitive revisions, 2,200 administrative supplements, and 220 summer research experience supplements. NIDDK is also considering roughly 837 R01 and 281 R21 applications that had been submitted in 2008-9 and had just missed the payline. With respect to totals committed to ARRA funding to date, approximately 32% has been focused on R01/R56 awards, 29% for administrative supplements, 21% for Challenge grants, 9% for R21 awards, 7% for competitive revisions, and 2% for Summer Research Experience supplements.

Dr. Rodgers provided examples of NIDDK's ARRA commitments:

- A Challenge grant in urology to use nanotechnology for intravesicle treatment of urological diseases. This project involves nanotechnology beads specifically recognized by bladder umbrella cells. The beads would act as a Trojan horse, delivering small interfering RNAs that would disrupt abnormal cellular processes in these cells. The technology could address a wide array of bladder diseases and hopefully minimize systemic toxicity to patients.
- A Challenge grant to explore hepcidin-based screening for infantile iron deficiency. This method, which would use a newly discovered iron regulator, could prove to be a more accurate blood screening method to detect iron deficiencies at a preclinical stage. About 12% of children have an iron deficiency, and 3% have anemia. Iron is important for both blood formation and brain development and infants with iron deficiencies can have lifelong problems.
- An NIDDK signature project on novel cell therapies and regenerative medicine for diabetes. This is supported primarily through supplements to the Beta Cell Biology Consortium, which has developed peer-reviewed programs through a coordinating center to seed collaborative research. Five applications to this program have been selected for support by ARRA funds.
- A set-aside for a Summer Research Experience program at Vanderbilt University. This program provides high school students from rural areas in Arkansas, Kentucky, and Tennessee an opportunity to perform research at the university. This program has been well received and even covered by a local news broadcast.

VI. ADVISORY COUNCIL FORUM I

Comparative Effectiveness Research

Dr. Rodgers introduced Dr. Elizabeth Nabel, Director of the National Heart, Lung, and Blood Institute (NHLBI) and co-chair of the NIH Comparative Effectiveness Research Coordinating Committee. Dr. Nabel earned her M.D. degree at Cornell University and completed her residency in internal medicine, as well as a clinical research fellowship in cardiovascular medicine, at the Brigham Women's Hospital at Harvard University. Before joining NHLBI, she was a professor of internal medicine and physiology, director of the Cardiovascular Research Center, and director of the Division of Cardiology, at the University of Michigan. She joined NHLBI as a scientific director for the intramural program in 1999 and became Director of NHLBI in 2005. Dr. Nabel's research focuses on the molecular and cellular mechanisms that cause vascular disorders, particularly the pathways that regulate cell growth, remodel the vasculature following injury, and lead to genetic susceptibility to vascular disease.

Dr. Nabel

The Federal Coordinating Committee of DHHS defines comparative effectiveness research (CER) as “the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in ‘real world’ settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective under which settings.” CER must assess an array of health-related outcomes for 1) diverse patient populations and subgroups, and 2) defined interventions including medications, procedures, medical and assistive devices, diagnostic tools, behavioral change, and delivery system strategies. It should be noted that CER does not constitute phase I-IV clinical research, but compares the effectiveness of procedures that are standard practice or FDA-approved and efficacious.

CER is needed because only a limited amount of evidence is available regarding treatments that work best for patients and the health care costs associated with different interventions. For example, a review of guidelines for cardiovascular disease prevention found that only half of the guidelines were supported by established evidence. The remaining guidelines were backed by observational data or experience, but not evidence-based medicine. A popular and widely referenced article by Dr. Atul Gawande in the *New Yorker* notes that physicians tend to agree on interventions when the right course is well established. However, when the best intervention is not as clear, physicians vary in their practice; with much of this variation depending largely on where the physicians were trained and where they currently practice.

In working to fulfill its mission, NIH has long supported CER and thus has substantial CER infrastructure, including trial networks, cooperative groups, the NIH Consensus Program, the National Library of Medicine (NLM), and the Clinical and Translational Science Award (CTSA) program. Ongoing CER projects include a variety of intervention comparisons—such as drug versus drug, surgery versus medical, lifestyle versus medical, surgery versus surgery, and screening versus usual care, as well as analysis of different health care delivery systems. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) supported by the National Institute of Mental Health has found that newer-generation antipsychotic drugs are no more effective than conventional agents for schizophrenic patients, while the conventional agents were much less expensive. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a community-based study of 35,000 hypertensive individuals, has found that generic the thiazide diuretic is just as effective as more expensive angiotensin-converting enzyme (ACE) inhibitors in treating hypertension and reducing risk for heart disease and stroke. The Diabetes Prevention Program has demonstrated that lifestyle changes and exercise are more effective than metformin alone in controlling diabetes.

Other NIH CER efforts include large consortiums or networks, such as the Health Maintenance Organization Research Network of 15 integrated health systems, which allows NIH to look at health outcomes and associated costs over 11 million covered individuals. These sorts of networks allow NIH to perform what are called practical clinical trials, which are based upon observational data built around electronic health records accrued through these health systems. Likewise, NLM has been very active in the CER arena with clinicaltrials.gov in which all

clinical trials in the country must be registered. New legislative language will require NIH-supported scientists to enter positive and negative results into clinicaltrials.gov.

In keeping with its long history of supporting CER, NIH aims to articulate its commitment to the best science, continue its leadership role to enhance returns for the public, work closely with other DHHS agencies, involve all health care stakeholders, and generally demonstrate its value to the public.

There has been unanimous support for moving forward with CER by all NIH Institute and Center Directors. Over the past year, Congress has appropriated \$1.1 billion toward CER—\$400 million for the Office of the Secretary, \$400 million for NIH, and \$300 million for the Agency for Healthcare Research and Quality (AHRQ)—and NIH has participated in the Federal Coordinating Council to help guide how this appropriation is spent. CER is a hot topic in public policy discussions and health care reform bills. Among these discussions is a proposal, in one of the health reform bills, for a public-private partnership that would make decisions about research areas that should be supported by public funds. NIH is keen to participate should such an entity arise. NIH funds the largest amount of CER research at HHS—the dollar amount would be ten-fold greater than any other DHHS component. Given this stake, it is important that NIH continue to play a major leadership role.

The Institute of Medicine (IOM) has published a report listing 100 national CER priorities. In addition, AHRQ has published several reports on evidence gaps. The NIH ICs are reviewing these reports to determine how best to move forward. At the request of DHHS, NIH is conducting a formal analysis of in-house CER projects that align with IOM priorities, and preliminary results demonstrate that NIH projects are already addressing 88 of the 100 priorities. NIH has also mapped its CER activity to the evidence gaps identified by AHRQ.

In the spring of 2009 NIH established a Coordinating Committee, co-chaired by Dr. Nabel and by Dr. Richard Hodes, Director of the National Institute on Aging. This committee has established: 1) A spending plan for the \$400 million ARRA CER appropriation; 2) Working groups to coordinate with AHRQ, the VA, and FDA; and 3) A set of criteria to evaluate requests from ICs.

In summary, NIH believes that we are the entity that can generate research that can inform medical decision-making based on quality and value.

Council Questions and Discussion

Where does FDA responsibility end and CER begin? The general paradigm is that FDA approves new therapies based on efficacy—to gain approval therapies must be equal to or better than comparators. Is there a vision for new studies following FDA approval? The new leadership of FDA is still considering CER but has not yet issued a statement on how it will take CER under advisement. There does not appear to be a clear cut answer to this question right now.

Do you see something becoming “unadopted” as a result of CER? This is not clear. The controversy surrounding CER has focused on how CER outcomes would be implemented. In some cases, implementation would mark a dramatic shift and might conflict with existing economic incentives. For example, the research outcomes of the CATIE study have not been adopted in medical practice, perhaps because of resistance by a variety of stakeholders.

Given the complexity of CER research, how do you design studies that give you an answer? Study design and sufficient statistical power are extremely important, and new research methodologies form an emerging area of CER.

NIH’s focus on the importance of education is a good one. It is often not clear to the public how much time and money goes into CER research. NIH has participated in several discussions about the tension between good clinical research and patient-centered medicine, as well as the need to educate the public about the importance of CER. The responsibility for educating the public will fall to all DHHS agencies. In addition, there have also been discussions about educating new CER investigators, because CER could represent the next generation of health services research. NIH is funding new centers and academic institutions to work on research methodologies and education.

What about the possibility that effectiveness might depend on the population? Do you fund international studies? DHHS has not tackled international studies yet, because ARRA funds focus on domestic efforts. However, as the field of CER matures, it could become an international effort, for example because many efficacy trials are already done internationally.

CER studies will identify treatments that are most effective for most people, but what about outliers? What about people who don’t respond to the usual treatments? NIH recognizes that most of what is observed in CER is median or mean responses and that some subgroups and individuals might exhibit different responses. Thus, one aim of CER is to define what works best in diverse and distinct populations; that is, “getting the right treatment to the right person in the right setting at the right time.” There is a recognition that aggregate studies are not going to provide a complete answer. This point has been the focus of pushback from entities responsible for reimbursements.

What about an infrastructure of clinical research centers to facilitate CER? NIH recognizes that for CER, doing research in an *ad hoc* way will not generate an answer. NIH has discussed a broad push toward understanding the basis for disease, and it is interested in sharing cohorts and data. The use of an extensive network that aggregates health systems is one approach.

VII. NIDDK CLINICAL OBESITY RESEARCH PANEL

Dr. Rodgers reminded the Council that the NIDDK Clinical Research Panel (CORP), successor to the National Task Force on the Prevention of Obesity, is composed of leading researchers focused on prevention and treatment of obesity. Organizationally, CORP is under the auspices of the NIDDK Advisory Council and serves in an advisory capacity for the Weight Control Information Network. NIDDK Advisory Council Member Patrick Tso, Ph.D., serves as a liaison

to CORP. Dr. Rodgers introduced Dr. Susan Yanovski, Co-Director of the NIDDK Office of Obesity Research and Executive Director of CORP.

Dr. Yanovski

CORP holds two meetings a year: one around the time of the February Council meeting, and a single-topic seminar in September. At the February 2009 meeting, CORP welcomed Dr. Matt Gillman of Harvard University, Dr. Lee Kaplan of Harvard University, and Dr. Alan Shuldiner of the University of Maryland Medical School as new members. Dr. Shuldiner also gave a scientific presentation.

The next CORP meeting will be held on September 24, 2009, on the NIH campus in conjunction with the NIH Obesity Research Task Force seminar series. The core meeting will be held from 8:30 a.m. to 9:30 a.m., and the seminar will take place from 9:30 a.m. to 2:00 p.m. in the Lister Hill Auditorium. The seminar, titled “Non-traditional Risk Factors for Obesity,” will feature four speakers: Dr. Nikhil Dhurandhar, who will discuss obesity of infectious origin; Dr. Jerry Heindel, who will discuss the role of environmental toxins; Dr. Elissa Epel, who will discuss stress pathways to obesity; and Dr. Jeffrey Gordon, who will discuss the human gut microbiome.

VIII. ADVISORY COUNCIL FORUM II

Challenge Grant Review and Lessons Learned Thus Far from the Editorial Board Review Model

Dr. Rodgers introduced Dr. Donald Schneider, Director, Division of Basic and Integrative Biological Sciences, Center for Scientific Review (CSR).

Dr. Schneider

The Challenge Grant program was one of the first ARRA programs announced to the scientific community. Since it was one of the first ARRA program announcements there was an expectation that there would be considerable interest in the Challenge Grant program—perhaps a thousand or so applications. NIH was stunned by the greater than 20,000 applications received for Challenge Grants.

The timeline to review these applications was very compressed; CSR received applications in late April and delivered scores and summary statements by the end of July—this schedule is compressed by approximately two-fold compared to the standard review schedule. To manage this tight timeline CSR planned and used a two-phase editorial board approach. Stage 1 was completed by a large number of “spot-on” experts who submitted written critiques and criteria scores evaluating the scientific and technical merit of the applications. In general, three stage 1 reviewers were assigned to each application. Stage 2 was performed by individuals with broad expertise across a range of scientific fields. In addition to the applications, Stage 2 reviewers had access to Stage 1 reviews and scores. Stage 2 reviewers used these materials to assess the overall impact and scientific merit of applications from a broader perspective; they identified and

discussed the best applications in special emphasis panel meetings and provided final overall impact/priority scores.

The editorial board review approach used to review Challenge Grant applications had been piloted over the past year at CSR. It held the advantage of being easy to scale up, which was necessary in light of the overwhelming response to the program. To review the 20,000 Challenge Grant applications, CSR used more than 15,000 stage 1 reviewers. There were 450 stage 2 reviewers, about 25 per special emphasis panel meeting. About 750 applications were assigned to slightly more than 30 meetings, but only the top 100 of these applications were discussed at each of the meetings. However, all applications were reviewed closely by two or three stage 1 reviewers and then further examined by three stage 2 reviewers. So, each application was considered by five or six people and reviewed carefully—even if it was not discussed in a meeting.

Dr. Schneider noted that the requirements associated with reviewing so many Challenge Grant applications combined with the compressed review timeline created logistics problems for CSR staff and put a tremendous strain on NIH's electronic peer review records system. For example, staff members were forced to enter study section rosters into NIH's electronic system at essentially the same time, which overloaded and slowed the system to the point of nearly failing. CSR asked all Integrated Review Groups to recruit stage 1 reviewers ahead of time. Recruiting stage 1 reviewers was manageable, however the logistics of assigning 700 or more applications to 500 or more reviewers was beyond what any one person could manage so teams of staff members worked on this together—which complicated balancing reviewer workload considerations. Also, the process of managing three critiques for 20,000 applications and entering these into NIH's electronic review system was complicated from a human factors standpoint and the activity also put extraordinary burden on NIH's electronic systems. Some additional factors that made managing review of the Challenge Grant applications “challenging” included: 1) applications were received as NIH was implementing changes associated with its “*Enhancing Peer Review*” initiative; and 2) that CSR did not have time to hire extra staff to manage additional work. In short, existing CSR staff had to contend with extremely heavy workloads paired with complex (logistics and electronic systems) circumstances—a perfect storm.

Dr. Schneider concluded by noting that applicants who were not awarded a Challenge Grant have the option to rewrite their applications and submit them as R01 or R21 applications in future. He cautioned that it is not clear how this will play out and that CSR might face overwhelming workloads if all the revised applications come back to NIH within a compressed timeframe.

Council Questions and Discussion

How does the quality of the summary statements compare with those emerging from the usual review process? Were they abbreviated? The Challenge Grant review process occurred while NIH is implementing portions of its “*Enhancing Peer Review*” initiative. Specifically, NIH is now encouraging reviewers to make their review statements more telegraphic and concise by featuring bullet points instead of prose. Although there was some unevenness across summary

statements (with more than 18,000 reviewers there was bound to be some variation), the quality of the message overall was good. While some of the stage 1 reviewers were relatively inexperienced, the stage 2 reviewers/editors were much more senior and helped level the playing field.

What proportion of Challenge Grant applications were thoughtful and serious, with good ideas, versus those that appeared to be hastily cobbled together and submitted at the last minute? Recently, R01 applications overall have been very high quality, but there was a sense that the quality of Challenge Grant applications was somewhat diminished. This may be because the applications were somewhat rushed and the sense that some felt there was nothing to lose by throwing out a wild idea that just might pan out.

When the editorial process was pilot-tested, what was the distribution of scores compared with those from the traditional approach? CSR had pilot-tested the editorial review with small business applications because of their heterogeneity and the resulting broad range of science. Approximately six study sections used the two-tier model where written critiques were received from typically three stage 1 reviewers, and then stage 2 reviewers (or “editors”) assigned overall scores. The scoring appeared to be less compressed than that for the traditional approach, perhaps because scores were assigned only by the editors, who looked at a large number of applications—not just half a dozen. It seems that the editorial board process results in broader perspective in scoring and less score compression.

Did the editors adjust scores? Only “editors” or second stage reviewers voted scores. Stage 1 reviewers could suggest scores, but only those assigned by the editors counted.

Dr. Stanfield

Dr. Stanfield closed the discussion of the Challenge Grant process by noting that the Challenge Grants certainly had the greatest impact on CSR staff and review operations. However, the impact of Challenge Grants on NIH program staff was also considerable. Because of the compressed schedule, NIH program officers had little time to familiarize themselves with the Challenge Grant applications in their portfolios before reviews were scheduled. The Challenge Grant reviews then took place on an extremely compressed timescale—over one week—resulting in difficult choices for program officers regarding which review meetings to attend (since many program officers had applications in several meetings that were taking place simultaneously). There was also the problem of considering all the scores and summary statements in a very short amount of time before awards needed to be made. In summary, while the bolus of work fell on CSR, the huge number of Challenge Grants presented hurdles and increased work across the NIH extramural program.

Dr. Stanfield then provided some information about the new NIH scoring system, which was implemented in response to concerns that the old scoring method suggested a false precision in the rating of applications. The latest round of applications reviewed by NIH (for September/October 2009 Council) were, for the first time, scored with the new system. Data from the NIH Office of Extramural Research (OER) indicate that a median of approximately 65 applications were reviewed across standing study sections during this latest review round. The

data also show that using the new scoring system, although there are now fewer scores available, study sections generally used a broader range of the available scale (score compression appeared to be reduced with implementation of the new scoring system). Because the new scoring system has fewer possible scores, the frequency of percentile ties were expected to increase and the observed data very closely matched the expected outcome.

Council Questions and Discussion

Was reducing the number of ties one of the goals of the new scoring system? No. When the percentile formula was applied, it was inevitable that with fewer scores to give, the number of ties would increase. This was of concern to ICs that rely very strictly on paylines for making funding decisions; they worried that they would have multiple applications at the payline and would thus have to make decisions regarding which applications receiving the same percentile ranking to fund.

Do we know where the payline used by NIDDK falls with respect to impact scores? No. The payline is usually established with percentiles, not primary scores. The correspondence of percentile rankings to scores would vary across study sections, depending on the scores within those study sections.

The interpretation that reviewers are using a broader range of the new scale may not hold up over time. There might be a “newness effect,” where reviewers score more broadly because they do not yet know what scores will be funded. Once more experience is gained, however, there might be a return to scores clustered around fundable levels. That is likely. This is still a learning process. Study section reviewers have always been encouraged to use a broad range of scores, but even though they do not make funding decisions, they tend to identify fundable scores and cluster their scoring around them.

Will the two-stage editorial board style review continue? CSR is eager to continue the pilot, but the future plans for expanding it are not now known.

IX. SCIENTIFIC PRESENTATION

A Critical Developmental Switch Defines the Kinetics of Kidney Cyst Foundation after Loss of Pkd1

Dr. Rodgers introduced the presentation by Dr. Gregory Germino, new Deputy Director of NIDDK. Before joining NIDDK, Dr. Germino was a Professor of Medicine at Johns Hopkins University in the Division of Nephrology and the Division of Molecular Biology and Genetics. He earned his bachelor degree in biology from Loyola University in Chicago and an M.D. from the Pritzker School of Medicine at the University of Chicago, then went on to an internship and residency in internal medicine at Yale University, followed by a clinical fellowship in nephrology and a research fellowship at Oxford University. In addition to serving as Deputy Director at NIDDK, Dr. Germino will continue his research on polycystic kidney disease in an appointment in the NIH intramural program. His interests have focused on the molecular basis of renal cystic disease and renal tubular morphogenesis, and his research has generated several high-quality

antibody cell lines, cell culture systems, and genetically altered mouse models that closely mimic human polycystic kidney disease. He has authored more than 70 peer-reviewed journal articles and dozens of book chapters and mentored more than 20 postdoctoral fellows.

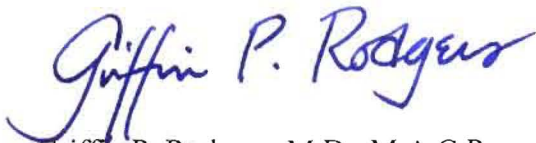
X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 3,420 grant applications, requesting support of \$1,000,152,629 were reviewed for consideration at the September 9, 2009 meeting. Funding for these 3,420 applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 2,538 applications requesting \$803,116,740 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 September 9, 2009 meeting.

XI. ADJOURNMENT

Dr. Rodgers thanked the Council members for their attendance and valuable discussion. There being no other business, the 181st meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m.

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



Griffin P. Rodgers, M.D., M.A.C.P.
Director, National Institute of Diabetes and Digestive and Kidney Diseases
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council