DRAFT

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

September 14-15, 2005

I. CALL TO ORDER

The Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Dr. Allen Spiegel, called to order the 169th National Diabetes and Digestive and Kidney Diseases (NDDK) Advisory Council meeting at 8:30 a.m., Wednesday, September 14, 2005, in Conference Rooms E1/E2 at Natcher Center, NIH, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Janis Abkowitz
Dr. Robert Alpern
Dr. Janice Arnold
Ms. Janet Brown
Ms. Mary Clark
Dr. Raymond DuBois
Dr. Robert Eckel
Dr. Jeffrey Flier
Dr. Richard Goodman
Dr. Earl Harrison (*Ex officio*)
Dr. William Henrich
Dr. Sum Lee
Dr. Rudolph Leibel
Dr. Brian Monahan *(Ex-officio)*
Ms. Nancy Norton
Dr. Jerry Palmer (*Ex-officio*)
Dr. Ronald Ruecker
Dr. Linda Sherman
Dr. W. Allan Walker

Also present:

Dr. Allen Spiegel, Director, NIDDK and Chairperson, NDDK Advisory Council
Dr. Griffin Rodgers, Deputy Director, NIDDK
Dr. Brent Stanfield, Executive Secretary, NDDK Advisory Council

B. NIDDK STAFF AND GUESTS

In addition to Council members, others in attendance included NIDDK staff members, representatives of the NIH Office of the Director (OD), Center for Scientific Review (CSR) Scientific Review Administrators, and other NIH staff members. Some NIDDK staff listed below attended via Videocast from 2 Democracy Plaza, Room 701. Guests were present during the open sessions of the meeting. Attendees included the following:

Kristen Abraham, NIDDK
Lawrence Agodoa, NIDDK
Syed Amir, CSR
Michael Appel, NIDDK
Sara Arnold, IFFGD
Guillermo Arreaza-Rubin, NIDDK
David Badman, NIDDK
Michele Barnard, NIDDK
Terry Bishop, NIDDK
Olivier Blondel, NIDDK
Josephine Briggs, NIDDK
Bonnie Burgess-Beusse, CSR
Francisco Calvo, NIDDK
Joan Chamberlain, NIDDK
Debuene Chang, NIDDK
Michelle Cissell, Juvenile Diabetes Research Found.
Jennifer Curry, NIDDK
Florence Danshes, NIDDK
Christine Densmore, NIDDK
Andrea DeSanti, Fisher Bioservices
Patrick Donohue, NIDDK
Edward Doo, NIDDK
Michael Edwards, NIDDK
Gayla Elder-Leak, NIDDK
Thomas Eggerman, NIDDK
Jody Evans, NIDDK
Richard Farishian, NIDDK
Ned Feder, NIDDK
Frances Ferguson, NIDDK
Olaf Fonville, NIDDK
Judith Fradkin, NIDDK
Lisa Gansheroff, NIDDK
Sanford Garfield, NIDDK
Mark Geanacopoulos, NIDDK
Carol Goter-Robinson, NIDDK
Reed Graves, CSR
Xiaodu Guo, NIDDK
Carol Haft, NIDDK
Mary Hanlon, NIDDK
Mary Harris, NIDDK
Barbara Harrison, NIDDK
Jay Hoofnagle, NIDDK
Mary Horlick, NIDDK
Joyce Hunter, NIDDK
James Hyde, NIDDK
Donna James, NIDDK
Stephen James, NIDDK
Ann Jerkins, CSR
Farrah Jolly, NIDDK
Teresa Jones, NIDDK
Robert Karp, NIDDK
Christian Ketchum, NIDDK
Mustaq Khan, CSR
Sooja Kim, CSR
Ted Kotchen, CSR
Robert Kuczmarski, NIDDK
Molly Laas, RPA
Maren Laughlin, NIDDK
Todd Le, NIDDK
Ellen Leschek, NIDDK
Maxine Lesniak, NIDDK
Monica Liebert, Amer. Urological Assoc.
Barbara Linder, NIDDK
Helen Ling, NIDDK
Karl Malik, CSR
Saul Malozowski, NIDDK
Denise Manouelian, NIDDK
Ronald Margolis, NIDDK
Winnie Martinez, NIDDK
Dan Matsumoto, NIDDK
Michael K. May, NIDDK
Julie McDermott, NIDDK
Melissa McGowan, NIDDK
Catherine McKeon, NIDDK
Rebecca Menso, NIDDK
Catherine Meyers, NIDDK
Carolyn Miles, NIDDK
David Miller, NIDDK
Megan Miller, NIDDK
David Mineo, NIDDK
Walter Mitton, NIDDK
Laura Moen, NIDDK
Marva Moxey-Mims, NIDDK
Christopher Mullins, NIDDK
Neal Musto, NIDDK
Leroy Nyberg, NIDDK
D.G. Patel, NIDDK
Ralph Paxton, CSR
Aretina Perry-Jones, NIDDK
Bobbie Peterson, CSC
Chris Peterson, SRI
Judith Podskalny, NIDDK
Sharon Pope, NIDDK
Rebekah Rasooly, NIDDK
Vaddie Reese, NIDDK
Tibor Roberts, NIDDK
Patricia Robuck, NIDDK
Michele Rodrigues, SRI
Mary K. Rosenberg, NIDDK
Paul Rushing, NIDDK
Atul Sahai, NIDDK
Karen Salomon, NIDDK
Lakshmanan Sankaran, NIDDK
Sheryl Sato, NIDDK
Jane Schriver, NIDDK
Jose Serrano, NIDDK
Nancy Sheard, CSR
Viviana Simon, SWHR
Elizabeth Singer, NIDDK
Paul Smedberg, American Society of Nephrology
Philip Smith, NIDDK
Lisa Spain, NIDDK
Karen Teff, NIDDK
Dietmar Tietz, NIDDK
Rebecca Torrance, NIDDK
Marcia Vital, NIDDK
Rachel Weinstein, NIDDK
Robert Wellner, NIDDK
Anita Wilkerson, NIDDK
Susan Yanovski, NIDDK
Charles Zellers, NIDDK

II. CONSIDERATION OF SUMMARY MINUTES OF THE 168th COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 168th NDDK Advisory Council (May 2005) as submitted.

III. FUTURE COUNCIL DATES

Dr. Spiegel asked Council members to take note of future Council meeting dates as follows:
February 15 and 16, 2006

May 31 and June 1, 2006 (may be shortened to one day)
September 20 and 21, 2006
February 21 and 22, 2007
May 30 and 31, 2007
September 19 and 20, 2007

IV. ANNOUNCEMENTS

A. APPOINTMENTS, AWARDS, AND ACKNOWLEDGEMENTS
Dr. Allen Spiegel, Director

New Council Members: Dr. Spiegel thanked Council members whose terms are completed and also announced the names of newly approved members of the Council, who will be joining the Council in February 2006. They are:

- *Dr. Mitchell Lazar*, Chief of the Division of Endocrinology, Diabetes, and Metabolism; and Director of the Penn Diabetes Center, at the University of Pennsylvania (Division of Diabetes, Endocrinology, and Metabolic Diseases Subcommittee).
- *Dr. Juanita Merchant*, Professor of Internal Medicine and Integrative and Molecular Physiology at the University of Michigan (Division of Digestive Diseases and Nutrition Subcommittee).
- *Dr. David Perlmutter*, Chief of Pediatrics at the Children's Hospital of Pittsburgh (Division of Digestive Diseases and Nutrition Subcommittee).
- *Ms. Margery Perry*, Chair of Research for the Juvenile Diabetes Research Foundation International (JDRF); and Head of the JDRF's International Board of Directors (Division of Diabetes, Endocrinology, and Metabolic Diseases Subcommittee).

New NIDDK Staff: Dr. Spiegel introduced several new NIDDK staff members.
Joining the Division of Extramural Activities is:

- *Dr. Brent Stanfield,* the Director of the Division of Extramural Activities. Dr. Stanfield served as Acting Director of the NIH Center for Scientific Review (CSR) since October of 2003. Prior to that, he was Deputy Director of CSR. His scientific training is in the neurosciences.

Joining the Division of Kidney, Urologic, and Hematologic Diseases is:

- *Dr. Laura Moen,* the Director of the Renal and Urology Training Programs. Dr. Moen served with the National Institute of General Medical Sciences. Her scientific training is in biochemistry.

Joining the Division of Digestive Diseases and Nutrition is:

- *Dr. Mary Horlick,* the Director of the new Pediatric Clinical Obesity Program, Division of Digestive Diseases and Nutrition. Dr. Horlick served previously as a pediatric endocrinologist at Columbia University's Children's Hospital and at Saint Luke's-Roosevelt Hospital in New York City. Her scientific expertise is in measurement of body composition in children.

B. CONFIDENTIALITY AND CONFLICT OF INTEREST

Dr. Brent Stanfield, Director, Division of Extramural Activities

Dr. Stanfield outlined the procedures to guarantee confidentiality and avoid conflicts of interest, discussed the scope and applicability of these procedures, and requested Council compliance. Members were asked to sign and return a conflict-of-interest statement and were reminded that materials furnished are considered privileged information and are to be used only for the purpose of review and discussion during the closed portions of the meeting. The outcome of the closed-session discussions may be disclosed only by staff and only under appropriate circumstances; all communications from investigators to Council members regarding actions on applications must be referred to NIDDK staff.

Furthermore, Council members should recuse themselves when individual applications from their institutions are discussed in order to avoid an actual or perceived conflict of interest. This is unnecessary with *en bloc* votes, for which all members may be present and may participate. Council members from multi-campus institutions of higher education may participate in discussions of any particular matter affecting one campus of that multi-campus institution if their disqualifying financial interest is employment at a separate campus of the same multi-campus institution and is in a position with no multi-campus responsibilities.

Dr. Stanfield noted that the NIH and NIDDK are working with institutions and researchers in areas where Hurricane Katrina damaged the research infrastructure. There is a special Website for this purpose, and Dr. Carol Alderson in the NIH Office of Extramural Activities is the principal contact. Dr. Stanfield also noted that the NIDDK portfolio includes about 40 grants to research institutions in New Orleans, and plans to work with affected members of the research community to help get them through this crisis.

V. REPORT FROM THE NIDDK DIRECTOR
Dr. Allen Spiegel, Director
NIDDK Extramural Leadership Retreat

Dr. Spiegel summarized issues addressed at an NIDDK Extramural Leadership Retreat, August 22-24, 2005. This effort built upon an earlier retreat in 2003—at the end of the NIH five-year budget doubling.

Translational Research: The August 2005 retreat reprised a major theme struck at the earlier 2003 retreat, that is, the importance of translational research, which is intended to directly benefit patients by furthering the movement of laboratory discoveries into the clinical arena. Not only is translational research vitally important in its own right, but it is also of great concern to the Congress and the public, who appropriately ask: "Now that we've doubled the NIH budget, what impact has that made on public health?" Dr. Spiegel noted that, in consultation with the National Advisory Council, the NIDDK successfully implemented a number of important translational research initiatives following the 2003 retreat.

In the post-doubling era, key challenges the research community must meet are to support the critical and innovative basic research that is the underpinning of progress; to convey this work in an intelligible and compelling way to patients, the public and the Congress; and to be accountable in terms of furthering translational research. While it is still too early to see the full fruits of the NIH doubling, it is critical, at a minimum, to demonstrate an acceleration of progress, as well as some early tangible outcomes. Importantly, the NIDDK can point to productive investments in a number of major initiatives, including clinical trials and large genetics consortia, whose launch was made possible by the budget doubling. Concomitantly, the Institute sustained a strong foundation of investigator-initiated research.

Changing Budget Landscape: Dr. Spiegel emphasized the impacts of the new, post-doubling budget climate, which formed the backdrop to discussions at the August 2005 retreat. The research community cannot assume that steady increases in the NIH budget will continue. For example, a 2002 study in *Science* indicates that the effects of the 1999-2003 NIH budget doubling could be offset by 2007, if annual budget increases are on the order of slightly over two percent—a likely prospect. Thus, in somewhat of a "budget paradox," this type of post-doubling scenario would essentially erode the positive effects of the doubling period, and require difficult trade-offs among competing scientific efforts and research mechanisms.

Dr. Spiegel displayed NIDDK actual budget data for fiscal years (FY) 1995 through 2005, as well as projections for 2006, which are based on the President's budget request. These data show the effect on the NIDDK of the overall NIH budget doubling period. Although the NIDDK budget did not double during this period due to other NIH commitments to areas such as biodefense, it did expand substantially over earlier funding levels, and is now nearing $1.87 billion (including a separate Congressional appropriation for type 1 diabetes research). However, NIH and NIDDK funding is reaching a plateau in terms of current dollars, and may be falling in terms of constant (inflation-adjusted) dollars. Budget fall-off can also be seen when one looks at the recent history of NIDDK appropriated funds expressed in terms of annual percentage growth. These trends appear to be similar to a situation that occurred during the early 1990s when low grant paylines (peer-review-based percentiles to which the NIDDK was able to fund) caused great concern in the academic research community. That earlier downturn discouraged many talented investigators from entering biomedical research. Thus, there is a concern that current trends along these same lines could have a similar dampening effect.

It is also important to realize that the 1999-2003 NIH budget doubling was accompanied by a disequilibrium because of the time lag between the point at which increased resources became available and the point that researchers sought them. This disequilibrium can be seen by contrasting the slope of budget growth during the NIH doubling period with the slope of numbers of grant applications received for review by the NIH Center for Scientific Review. A similar disequilibrium exists now, in that the investigative community's demand on resources continues to increase, even though budget growth has tapered off.

At the NIDDK, paylines for both new and established investigators increased after FY 2000 for at least three years (and there were also many new Requests for Applications, or RFAs, during this period that generated applications not included in payline calculations). These higher paylines generally continued through FY 2004. However, maintaining these robust paylines will probably no longer be possible. It will be a major challenge to keep the payline for FY 2006 from falling below the 15th percentile for all investigators. Leaner budgets mean that difficult decisions will need to be made regarding large-ticket initiatives, and about programs such as research training. While training programs are not research *per se*, they are vitally important to sustaining creative human capital for the research enterprise.

Establishing Goals and Objectives: Within this budgetary context, staff members at the August 2005 retreat explored NIDDK goals, objectives and evaluation approaches for assessing the Institute's research investments. In follow-up, Dr. Spiegel has asked NIDDK Division Directors to develop a set of both Division-specific and Institute-wide goals, and has invited Council members to help in this process. A working group is being established for NIDDK goal- and priority-setting. Other working groups will evaluate the results of NIDDK funding decisions--including a program implemented in FY 2000 to provide funding for areas of "special emphasis" identified by the NIDDK, with Council concurrence, including funding for new investigators. Also to be addressed through this working-group process is the development of principles/approaches for assessing ongoing clinical trials, optimizing their efficiency, and enhancing decision-making regarding the initiation of new, large-scale clinical trials and other clinical research efforts.

Draft NIH Reauthorization Proposal: Another point of discussion at the August retreat was the draft proposal for reauthorizing the NIH. This proposal has been developed by the committee that has jurisdiction over NIH statutory base—the House Energy and Commerce Committee. The NIH Director addressed this proposal in his testimony before this Committee on July 19, 2005. (http://olpa.od.nih.gov/hearings/109/session1/testimonies/reauthorization.asp). While a reauthorization bill has not yet been introduced, the Committee has proposed reorganizing the NIH by grouping some Institutes according to their focus on diseases, organs or stages in the lifespan, while grouping others according to their focus on enabling the research enterprise to move forward. Another aspect of the reauthorization proposal is language to establish in statute a new organizational unit in the Office of the NIH Director—a Division of Program Coordination, Planning, and Strategic Initiatives. This proposed Division would be along the lines of a new unit the NIH Director has proposed for administrative creation—the Office of Portfolio Analysis and Strategic Initiatives (OPASI).

Whether administrative or statutory, the new unit is expected: (1) to address the need for enhanced information and methods, such as knowledge management, for analyzing the complex NIH research portfolio; (2) to coordinate NIH strategic scientific initiatives, such as the NIH Roadmap for Medical Research, that are beyond the purview or

resources of any one NIH component, but need to be undertaken by NIH as a whole; and (3) to spearhead the use of sound evaluation methods and data to aid informed decision-making. A major objective is to help to formalize coordination and collaboration across the NIH. Recent *ad hoc* coordination processes have led to the NIH Roadmap for Medical Research, the Neuroscience Blueprint, and the *Strategic Plan for NIH Obesity Research*, which was generated by the NIH Obesity Research Task Force. Importantly, the new organizational unit would pursue strategic planning with a "common fund" established *ex ante*, and would therefore have a formal budget envelope. Scientific areas selected for pursuit would be identified through a broad, consultative process involving external scientific and lay stakeholders and the leadership of the NIH. It should be noted that the IC Directors have already committed *de facto* to a common fund for the NIH Roadmap; however, the neuroscience and obesity efforts mentioned previously have had no formal budget, and were really intended to aid prospective coordination of research planning, especially to avoid redundancy and promote synergy.

Council Questions and Discussion

Possible Clustering of Institutes: Would the Proposed Clustering Concentrate Fiscal Authority in the NIH Director? According to Dr. Spiegel, legislative analysts have advised that, under the draft congressional proposal now under consideration, there does not appear to be any language that would preclude the appropriations committees from continuing to make appropriations to individual Institutes and Centers, with the NIH Director retaining one percent transfer authority. As noted previously, Institute and Center Directors have already committed to pooling resources for certain initiatives, such as the NIH Roadmap. In an October 20, 2005, presentation to NIH stakeholders, the NIH Director indicated his intent that current Roadmap funds serve as the baseline for the common fund. He indicated that Roadmap funds, which are projected to represent 1.1 percent of the NIH budget in FY 2006, are expected to grow to an estimated 1.7 percent of the NIH budget in FY 2008. Assuming that the NIH budget grows at a rate higher than the rate of inflation in the biomedical research sector of the economy, he has suggested that a "common fund" for such cross-cutting initiatives, including the Roadmap, might grow gradually to total as much as five percent of the NIH budget; however, these types of specifics are not included in the current draft congressional proposal. Whatever the ultimate dimensions of the common fund, it is expected that there would be broad stakeholder input for the initiatives it would support, in addition to key input from the Directors of the Institutes and Centers. Moreover, a "Council of Councils," whose members would include representatives from the existing National Advisory Councils, would contribute to this process.

What Constitutes Success in Training Programs? What Training Mechanisms Are the Most Effective in Producing Independent Investigators on Regular Research Grants? Dr. Spiegel said that it is difficult to obtain key metrics for tracking the success of clinical investigators. Assistance is needed from professional groups and research institutions in this regard. One possible approach would be to scan PubMed to determine which former trainees continue to publish research papers. This type of career tracking is clearly needed.

Research Training for Specific Areas That Are Under-Represented in Research:
Dr. Spiegel said that growth was substantial in specialty areas such as urology. It is also important to support surgical researchers, and the NIDDK has been working with the American Urological Association to see how K23 awards might be modified to incentivize their use, not only by urologic surgeons, but also by transplant surgeons generally. Surgical researchers are clearly among the most translationally-oriented in the community. We also need to attract gastroenterologists and other specialists to research. An overarching issue is how to use NIH resources most effectively to train people to do clinical research.

VI. REPORT ON MULTIPLE PRINCIPAL INVESTIGATORS
Dr. Elizabeth Wilder, Division of Kidney, Urologic, and Hematologic Diseases

Dr. Wilder described a proposal for recognizing multiple principal investigators (PIs) from single projects as a way of providing them with more appropriate professional recognition than they now receive. A critical issue is that R01 grants are used as a metric for promotion and tenure at academic institutions, even though PIs are tending to collaborate more frequently and in meaningful ways. This lack of congruence makes it difficult to evaluate the individual performance of PIs as researchers. The White House Office of Science and Technology Policy recently mandated that all federal funding agencies recognize team leadership on given projects. Council input would be useful in the development of this policy.

Council Questions and Discussion

Allocation of Funds to Individuals or Institutions: There are pros and cons as to whether to disburse funds proportionately on the basis of annual progress reports from each of the PIs, or flexibly, as determined by the institution(s), among the PIs. Under the latter scenario, some institutions will still consider the funds per individual in making some decisions. Perhaps multiple PIs could be treated independently, with each having a separate award, even though they are working on a single project. It was noted that individual PIs might be considered members of a consortium, with each PI having his or her own set of funds, or as subcontractors, with resources allocated among PIs, even though a single PI has lead responsibility and control. However, such approaches may be inequitable or divisive. The complexity of handling the funds could have unanticipated adverse effects on collaborations. Changes in the way that funds are awarded could affect both departmental and institutional rankings.

Relative Contributions of Investigators: Council members noted the need for a mechanism that defines the role of each investigator on each multi-PI grant. Moreover, it will still be important to recognize the individual who is the driving force for the existence of the research project.

Dr. Spiegel invited Council members to express their opinions on how best to implement the policy change by sending email comments or by responding to an NIH Request for Information posted on the NIH Website:
http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-05-055.html

VII. REPORT FROM THE NIDDK DEPUTY DIRECTOR
Dr. Griffin Rodgers, Deputy Director
Budget and NIH Extramural Loan Repayment Program

Dr. Rodgers noted that the FY 2006 President's Budget requested a 0.5 percent increase for the NIH. For the NIDDK, the President's budget proposed a similar 0.5 percent increase, which would translate into total funding of $1.722 billion (does not include a separate Congressional appropriation for type 1 diabetes research) in FY 2006, an increase of $9 million over FY 2005. The House bill is consistent with the President's budget for the NIH and the NIDDK. The Senate bill calls for a 3.9 percent overall increase for the NIH or about $905 million more than the President's request. It is not yet known how these differences will be reconciled in conference between both chambers, and one or more continuing resolutions may be needed to fund operations until a decision is reached.

The NIH's implementation of the President's budget would likely not provide any inflationary increases for non-competing research projects grants, or any increase in the average size for competing research grants. It would give modest selected tuition increases for postdoctoral fellows; hold the NIH Intramural Research Program and general administrative functions to an increase of 0.5 percent; and increase funding for Roadmap initiatives from about $235 million to $333 million, of which the NIDDK portion would rise from about $10.8 million to $15.4 million in FY 2006.

The NIH Loan Repayment Programs continue to encourage individuals to pursue research careers. The NIDDK participates in two of the four extramural components of the program, namely, the components for clinical research and for pediatric research. Overall, the Institute received a total of 240 applications and awarded funds to 83 of them for a 35 percent success rate (compared to a 48 percent success rate for the entire NIH). For both the NIDDK and the NIH, the success rates were higher for recompeting applicants who still have qualifying indebtedness than they were for new applicants. On the clinical side for NIDDK, the applicants primarily come from the diabetes, endocrinology, and metabolism areas; whereas on the pediatric side, they more often come from the digestive diseases area.

Council Questions and Discussion

Tracking Applicants and Evaluating the Program; Which Applicants Should Be Favored and How Fast Should This Program Grow? Dr. Rodgers said that the extramural component began five years ago, but tracking for evaluation purposes began in 2002. Mentors must report that individuals are still engaged in research in order for them to continue receiving loan repayment checks each quarter. Dr. Spiegel said that the NIDDK

now allocates $4 million per year for this program. The NIDDK share was initially $2 million, a target that resulted from a formula based on each IC's clinical research portfolio. Because it is too early to evaluate the program, Dr. Spiegel decided against elevating the base above $4 million. That, and the disproportionately larger number of applicants assigned to NIDDK explain why the NIDDK applicant success rate falls below the NIH average. Another issue is whether to favor researchers who are seeking renewals because they already are engaged successfully in doing research, *versus* those applying for the first time. As with other programs, there are difficult trade-offs in times of limited resources. Currently, individuals who already hold research training or career development awards from the NIH or another source, and thus are already committed to research, are heavily represented among NIDDK awardees under this program.

VIII. ADVISORY COUNCIL FORUM--PART I
Promoting, Supporting, and Prioritizing Clinical Research

Dr. Spiegel noted that the Institute is seeking to identify and address major barriers to clinical research, particularly investigator-initiated studies. Key issues under discussion in the research community include difficulties in recruiting and retaining clinical researchers, the increasing regulatory burden and costs of clinical research, fragmented research training programs, shifts in priorities toward providing clinical services at academic medical centers, and challenges in recruiting human subjects for studies. In addition to identifying barriers that need to be addressed, the NIDDK is exploring a range of practical questions. For example, are there specific clinical resources or infrastructure in particularly short supply for which NIDDK support would be cost-effective? Also, what evaluation criteria should the Institute use to assess the quality of its portfolio of investigator-initiated clinical studies? The NIH has been working to lessen some barriers to clinical research through efforts of the NIH Roadmap to develop interdisciplinary research teams and to re-engineer the clinical research enterprise. For example, the National Center for Research Resources will be releasing a request for applications (RFA) in October, entitled "Clinical and Translational Science Awards." Dr. Spiegel introduced several Council members and invited discussants who were asked to address specific issues.

Discussants from the National Advisory Council
Identifying and Overcoming Barriers to Clinical Research

Dr. Robert Eckel - University of Colorado Health Sciences Center: Dr. Eckel described several barriers including the complicated processes of Institutional Review Boards (IRBs), technology limitations, inappropriate study section membership for peer review of clinical research applications, lack of incentives to human subject participation, prohibitive cost of clinical research, and time burden on investigators. For example, there is a complex process for review of clinical research protocols for the General Clinical Research Center (GCRC) that he heads at his institution. Three separate IRBs exist for the different clinical sites involved, and their operations are not standardized. Furthermore, in addition to IRB review, the clinical protocols must also be reviewed by a GCRC scientific advisory board and, depending on geographic considerations, a hospital

review committee. These multi-level reviews can be an administrative challenge for investigators. Other examples are the obstacles investigators face with respect to gaining access to new technology and other research resources, and the increasing reluctance of individuals to participate in clinical trials, particularly if they will not be paid. In addition, the costs in money and time for clinical research are substantial, including efforts directed toward retaining study participants for long-term follow-up. It was noted that Ph.D.s often serve as PIs on clinical protocols—raising questions about the role of M.D.s—who participate, but typically have other clinical-care responsibilities at their institutions.

Dr. Allan Walker - Harvard Medical School: Dr. Walker emphasized lack of infrastructure as a significant barrier to clinical research because of the time it takes to ramp up for clinical studies. An approach that deserves exploration as a possible model is the Glazer Foundation Network, a consortium of five medical schools that provides an efficient means for reviewing proposals and quickly accumulating large numbers of study participants. Dr. Walker also noted his nutrition research center gives high priority to K23 awardees who use the NIH-supported General Clinical Research Center to more efficiently address clinical questions and thus maximize the use of investigators' time.

Dr. William Henrich - University of Maryland College of Medicine: Dr. Henrich said that it might be helpful to centralize IRB reviews because, under the present system, there are so many points at which clinical research efforts may be delayed after many years spent on planning for and designing of the trial. Clinical research efforts can also be slowed when clinical fellows sometimes arrive without appropriate training in areas such as biostatistics and epidemiology. Furthermore, dealing with other federal agencies, particularly the Food and Drug Administration, when an investigational new drug or a new device is being evaluated, can complicate efforts to conduct clinical research. The NIH is to be commended on efforts to aid investigators in this regard, and in its efforts to promote interdisciplinary research. In nephrology specifically, clinical researchers would like to address other health issues, such as heart disease, which affect patients on dialysis. An additional concern among nephrologists is that consolidation in the dialysis industry, with fewer providers, may hamper research.

Dr. Rudolph Leibel - Columbia University College of Physicians and Surgeons: Dr. Leibel discussed challenges in recruiting clinical investigators at medical centers that are being run increasingly as businesses, with little attention paid to research training and to understanding that current clinical know-how derives from clinical research. Providing students and fellows with examples of the impacts of clinical research can show them the extraordinary rewards to be derived and spark their enthusiasm and dedication. In addition, medical schools might, in a flexible way, centralize aspects of medicine and science that are related to clinical investigations, thus making it easier for new fellows to participate in clinical research as part of their overall training. For example, it would help if training efforts were coordinated with programs such as General Clinical Research Centers and other centers that have clinical investigation as part of their mission.

Ms. Janet Brown - Albert Einstein College of Medicine: Addressing the issue of human subject recruitment to clinical trials, Ms. Brown identified several barriers. These include: recruitment costs, training of staff, community outreach, difficulties in obtaining information about particular trials, the geographic distance of potential study participants from the clinical trial sites, and challenges in developing trust among community members.

Dr. Robert Alpern – Yale University School of Medicine; Dr. Jerry Palmer – VA Puget Sound Health Care System: Both of these Council members were asked to discuss steps that academic medical centers can take to support clinical research and ways that the NIH can contribute to this. Dr. Alpern underscored that clinical trials can lead to a loss of revenue for academic medical centers, so institutions need to know that they are at least supporting successful research. To this end, clinical investigators need to be well trained before they join an academic faculty, and the institution needs to be able to single out the stellar researchers on their faculties. It is essential that institutions provide these investigators with core research resources and appropriate facilities—for which more NIH support is warranted. Dr. Palmer stressed the importance of encouraging academic medical centers to want to be places of strength for clinical research. One help in this regard is that many of these institutions already house NIH General Clinical Research Centers. It was also noted that any means of defraying the costs of clinical research for institutions, such as industry support, would help to incentivize them to undertake more clinical research.

Council Questions and Discussion

- *Centralized IRB Processes:* Such processes, similar to those being used by the National Cancer Institute (NCI) or others used in the private sector, could expedite multiple-institutional reviews. However, it can take a long while to set up these processes, and academic centers and universities need to be willing to accept this type of change. For example, institutional IRBs will often stress the importance of having "local context"—that is, personal knowledge of the facilities, investigators, etc.—that central IRBs cannot possess. In addition, institutions may have concerns about how any type of misconduct in a single site would be handled in a centralized IRB process, and the potential for cascading effects on other participating institutions which were not involved. Clearly, lessons can be learned from the NCI experiences, and the use of commercial IRBs might also be explored. The new NIDDK clinical trials working group will be examining the pros and cons of centralized IRBs.
- *Patient Recruitment:* Recommendations of personal physicians or other local establishments can help develop trust, while use of dispersed physician networks can help subjects to participate. Bidirectional communication between clinical trial leaders and community physicians is important. Continuing medical education might be a means for encouraging physicians to inform their patients about clinical trial participation; patient voluntary groups can also play a constructive role. Study volunteers also need to know that they are partners in

research that will benefit people. It was noted that the NIH is currently supporting efforts to build public trust in research.

- *Harmonization Efforts:* The NIH is trying to harmonize with FDA more effectively with respect to clinical trials, and has made progress in the specific area involving pancreatic islet transplantation. The NIH is also taking steps to better integrate its clinically-oriented training programs. Clinical training requirements are more extensive and formalized today than in the past.

Dr. Ted Kotchen – Medical College of Wisconsin – A Special Advisor on Clinical Research to the NIH Center for Scientific Review (CSR)
Peer Review of Clinical Research

In an invited presentation, Dr. Kotchen said that NIH continues to assess whether clinical grant applications are disadvantaged in peer review compared to applications for basic research. A review of applications from 1994 to the present indicates that clinical grant applications score somewhat less favorably than non-clinical applications, leading to a five-percent lower funding rate. The CSR has looked at a number of factors to discern what may account for this difference. While peer review is not perfect, analyses of data from 1994 show that the composition of study sections and the percentages of clinical grants that they review do not explain the lower success rate for clinical research proposals. The lower funding rate for clinical research is also not attributable to whether the reviewers themselves have experience in clinical research, and data in this regard have been accepted for publication in the *Journal of Investigative Medicine*. While costs should not be considered in the assignment of a priority score, it is true that clinical research is more expensive than basic research. However, the priority scores and funding rates for the more expensive applications were more favorable—which may suggest that more senior, experienced researchers are seeking support. The recent revamping of study sections within CSR aimed to prevent clinical research proposals from being reviewed in an "isolated" way. This will likely be beneficial to clinical research. Moreover, the January 2005 changes in review criteria to emphasize the importance of clinical research are expected to have positive impacts, but it is too early to measure the effects of these changes.

Dr. Kotchen said that differences in funding success for basic *versus* clinical research appear to be attributable to the investigators and the applications they submit. For example, investigators who have previously participated in certain clinical research training programs fare much better in terms of subsequent NIH funding than those who have not had such training. Potential grant-application factors may include weaker science, more difficult research to present, and/or inadequate preparation of grant proposals. Clinical research tends to be more complex than basic research, with special concerns about safety and privacy for human subjects. Data show that applications for which concerns were raised about safety and privacy scored considerably less well that those without such stated concerns.

IX. SCIENTIFIC PRESENTATION

Dr. Vikas Sukhatme, Victor J. Aresty Professor of Medicine, Harvard Medical School -- "Vignettes in Vascular Biology: Fun Working Across Borders"

Dr. Sukhatme described several examples of translational research in vascular biology.

X. ADVISORY COUNCIL FORUM--PART II

Promoting, Supporting, and Prioritizing Clinical Research

Dr. Rodgers introduced this session by emphasizing strengthened partnerships between the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI). He then turned the program over to Dr. Terry Manolio, Director of the NHLBI Epidemiology and Biometry Program, who discussed major NHLBI-supported clinical research programs, The NHLBI encourages these programs to support ancillary studies—recognizing the cost-effectiveness in leveraging research on established cohorts to maximize research investments and productivity.

Dr. Terry Manolio, National Heart, Lung, and Blood Institute

Ancillary Studies to Major NHLBI Clinical Trials

The Framingham Heart Study begun in 1948 has expanded to several ancillary studies that examine cardiovascular risk factors in the young, atherosclerosis in middle age, and disease in the elderly. The Strong Heart study focuses on American Indians, while the Women's Health Initiative includes 161,000 participants in an observational study, and the Jackson Heart Study focuses on African Americans in or near Jackson, Mississippi. The Multiethnic Study of Atherosclerosis (MESA), in partnership with the NIDDK, is adding a Hispanic cohort and will look also at renal disease and outcomes.

Participants in the Framingham Heart Study, of whom about 600 of the original 5,000 still participate, have been examined every two years since 1948. Members of an offspring cohort were examined at regular intervals since the 1970s, and a third generation was recruited recently. Although this study helped define the major risk factors for cardiovascular disease, its ancillary studies address many additional diseases. For instance, recent genetic studies helped to map renal diseases to chromosomes 3 and 4.

The Coronary Artery Risk Development in Young Adults (CARDIA) Study looks at cardiovascular risk factors in young adults, including predictors of subclinical atherosclerosis. Recent findings show that elevated excretion of albumin, a response to hypertension, is higher among African Americans than Caucasians. The Atherosclerosis Risk in Communities (ARIC) Study, from the late 1980s, of a middle-aged cohort finds a strong relationship between atherosclerosis and platelet inflammatory factors. This study also shows that the incidence of heart attacks is rising among African Americans. Further, it includes a large sample of people with diabetes, many of whom have reduced lung function.

The Cardiovascular Health Study is investigating risk factors for development and progression of coronary heart disease and stroke in approximately 5,700 people aged 65

years and older. It shows a high incidence of subclinical disease. The study provides a means for tracking risk associations and clinical outcomes. It also is tracking diabetes status, showing that diabetes patients have high rates of cardiovascular disease and that glucose-intolerant individuals also are at elevated risk.

The Strong Heart Study, whose cohort of American Indians was recruited from the Southwest and West during the 1980s, shows that there is a high incidence of obesity in this population and that diabetes is the most important determinant of cardiovascular disease. More generally, this and other studies show that such cohorts can be used for much more than studying heart disease.

The Jackson Heart Study includes 5,300 African Americans and is in the early stages of evaluating risk factors for heart disease and stroke. The Multi-Ethnic Study of Atherosclerosis (MESA) has nearly 7,000 participants, including many Chinese and Hispanic Americans. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial is aimed at preventing cardiovascular events in individuals with type 2 diabetes through intensive glycemic control, as well as hypertension and lipid control.

Dr. Manolio noted that proposals to establish ancillary clinical studies to these ongoing efforts are subject to one or more reviews. Investigators proposing such studies are encouraged to build on the unique aspects of the main studies. In general, investigators apply through NHLBI, need to receive IRB approval, and must agree to comply with established policies and procedures.

Council Questions and Discussions

How Extensive Are the Ancillary Studies and What Is the Nature of New Collaborative NIDDK-NHLBI Efforts? Dr. Manolio said that number of ancillary studies vary. The Jackson study has the fewest; Framingham has had more than 100; and MESA also has a large number. The Cardiovascular Health Study (CHS) is moving from a contract to a grant mechanism, with workshops to inform investigators of research opportunities. Dr. Briggs said that the NIDDK-NHLBI partnership with regard to the CHS is very new. In addition, Dr. Briggs said that, although efforts are under way to inform investigators about the ARIC and other kidney studies, investigators tend to learn of these new opportunities through informal communications in the community.

Analyzing the Genetics of Complex Human Phenotypes: Questions Raised about Efficient Approaches. Because analysis of a single phenotype may require studying as many as 100,000 individuals, it may be necessary to establish repositories for genotyping information—probably basing each one on single nucleotide polymorphisms (SNPs), a stored dataset for "controls," and a questionnaire that will help to classify participants. These repositories could also help in efforts to identify biomarkers for particular phenotypes. The NIDDK established a repository for samples and datasets for all U01 (Cooperative Agreement) programs more than two years ago, and this collection continues to grow. Investigators involved in such projects are expected to vouch for sample reproducibility in grant proposals that they submit for review.

XI. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 960 grant applications, requesting support of $241,077,187 were reviewed for consideration at the September 14-15, 2005 meeting. Funding for these 960 applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 692 applications requesting $148,986,737 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 on September 15, 2005.

XII. ADJOURNMENT

Dr. Spiegel thanked the Council members for their attendance and efforts. There being no other business, the 169th meeting of the NDDK Advisory Council was adjourned at 11:55 a.m., September 15, 2005.

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

Allen M. Spiegel, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases,
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council