Meeting Minutes
Department of Health and Human Services
Public Health Service
National Diabetes and Digestive and Kidney Diseases Advisory Council
September 22-23, 2004

I. CALL TO ORDER

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Director, Dr. Allen M. Spiegel, called to order the 166th National Diabetes and Digestive and Kidney Diseases (NDDK) Advisory Council meeting on September 22, 2004, at 8:30 a.m. in Conference Room 10, C Wing, 6th Floor, Building 31, National Institutes of Health (NIH), Bethesda, MD.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Janis Abkowitz
Dr. Robert Alpern
Mr. David Baldridge
Dr. Roberto Coquis
Dr. Robert Eckel
Dr. Richard Goodman
Dr. Earl Harrison (*Ex officio*)
Dr. Carolyn Kelly
Dr. Sum Lee
Dr. Rudolph Leibel
Dr. Daniel Porte (*Ex-officio*)
Dr. Linda Sherman
Dr. E. Darracott Vaughan
Dr. W. Allan Walker

Council Members Absent:
Dr. Jose Caro
Ms. Mary Clark
Dr. Raymond DuBois
Ms. Nancy Norton
Dr. Vicki Ratner
Dr. Ronald Ruecker

Also present:
Dr. Allen Spiegel, Director, NIDDK and Chairperson, NDDK Advisory Council
Dr. Griffin Rodgers, Deputy Director, NIDDK
Dr. Robert Hammond, 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
Beena Akolkar, NIDDK
Roberta Albert, NIDDK
David Badman, NIDDK
Michele Barnard, NIDDK
Terry Bishop, NIDDK
Rochelle Blaustein, NIDDK
Olivier Blondel, NIDDK
Sharon Bourque, NIDDK
Josephine Briggs, NIDDK
Timya Callahan, NIDDK
Francisco Calvo, NIDDK
Joan Chamberlain, NIDDK
Arlene Chiu, NIDDK
Tynia Conley, NIDDK
John Connaughton, NIDDK
Florence Danshes, NIDDK
Maria Davila-Bloom, NIDDK
Christine Densmore, NIDDK
Patrick Donohue, NIDDK
Edward Doo, NIDDK
Michael Edwards, NIDDK
Thomas Eggerman, NIDDK
Gayla Elder-Leak, NIDDK
Jody Evans, NIDDK
Richard Farishian, NIDDK
Ned Feder, NIDDK
Frances Ferguson, NIDDK
Olaf L. Fonville, NIDDK
Judith Fradkin, NIDDK
Lisa Gansheroff, NIDDK
Sanford Garfield, NIDDK
Mark Geanacopoulos, NIDDK
Christine Gill, NIDDK
Carol Goter-Robinson, NIDDK
Janet Gregory, NIDDK
Carol Haft, NIDDK
Frank Hamilton, NIDDK
Barbara Harrison, NIDDK
Trude Hilliard, NIDDK
Eleanor Hoff, NIDDK
Jay Hoofnagle, NIDDK
Donna Huggins, NIDDK
James Hyde, NIDDK
Donna James, NIDDK
Stephen James, NIDDK
Ann Jerkins, CSR
Teresa Jones, NIDDK
Tonia Jones, NIDDK
Robert Karp, NIDDK
Christian Ketchum, NIDDK
Robert Kuczmarski, NIDDK
Maren Laughlin, NIDDK
Todd Le, NIDDK
Ellen Leschek, NIDDK
Maxine Lesniak, NIDDK
Barbara Linder, NIDDK
Helen Ling, NIDDK
Pamela Love, NIDDK
Saul Malozowski, NIDDK
Denise Manouelian, NIDDK
Ronald Margolis, NIDDK
Dan Matsumoto, NIDDK
Michael K. May, NIDDK
Elizabeth Mayer-Davis, NIDDK
Julie McDermott, NIDDK
Catherine McKeon, NIDDK
Catherine Meyers, NIDDK
Carolyn Miles, NIDDK
David Miller, NIDDK
Megan Miller, NIDDK
David Mineo, NIDDK
Marva Moxey-Mims, NIDDK
Christopher Mullins, NIDDK
Neal Musto, NIDDK
Leroy Nyberg, NIDDK
D.G. Patel, NIDDK
Aretina Perry-Jones, NIDDK
Judith Podskalny, NIDDK
Sharon Pope, NIDDK
N.M. Rao, NIDDK
Rebekah Rasooly, NIDDK
Tibor Roberts, NIDDK
Patricia Robuck, NIDDK
Paul Rushing, NIDDK
Lakshmanan Sankaran, NIDDK
Sheryl Sato, NIDDK
Ross Shayice, CSR
Salvatore Sechi, NIDDK
Leonard Seeff, NIDDK
Jose Serrano, NIDDK
Viviana Simon, Society for Women's Health Research
Elizabeth Singer, NIDDK
Philip Smith, NIDDK
Lisa Spain, NIDDK
Myrlene Staten, NIDDK
Alison Strock, Health & Medicine Counsel of Washington
Patrick Sullivan, NIDDK
Karen Teff, NIDDK
Rebecca Torrance, NIDDK
Marcia Vital, NIDDK
Dorothy West, NIDDK
Elizabeth Wilder, NIDDK
Gina Wrench, NIDDK
Susan Yanovski, NIDDK
Jeffrey Young, Blue Sheet
Charles Zellers, NIDDK

II. CONSIDERATION OF SUMMARY MINUTES OF THE 165th COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 165th NDDK Advisory Council (May 2004) as submitted.

III. FUTURE COUNCIL DATES

Dr. Spiegel asked Council members to take note of future Council meeting dates as follows:

February 23 and 24, 2005
May 19 and 20, 2005
September 14 and 15, 2005
February 15 and 16, 2006
May 31 and June 1, 2006
September 20 and 21, 2006

IV. ANNOUNCEMENTS

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

With regard to NDDK Advisory Council members: This is the last NDDK Advisory Council meeting for the following Council members: Mr. David Baldridge, Dr. Jose Caro, Dr. Carolyn Kelly, and Dr. Vicki Ratner. The NIDDK acknowledges their dedication and hard work, and thanks them for their service to the Institute.

Within the NIDDK:

New staff to the Division of Diabetes, Endocrinology, and Metabolic Diseases include:

- Dr. Olivier Blondel was previously with Human Genome Sciences, Inc. Formerly a Senior Scientist in the Department of Preclinical Development, Dr. Blondel designed functional genomic screening programs for diabetes and obesity, developed therapeutics, and discovered new secretory factors with growth inhibitory and anti-angiogenic properties. He will be involved in managing the NIDDK bone endocrinology program, contributing his genomics expertise to several consortia in the diabetes programs, and bringing his skill in bioinformatics to trans-NIH activities related to national centers for biomedical computing.

- Dr. Lisa Spain formerly served as Associate Professor of Immunology at Holland Laboratory of the American Red Cross, and Adjunct Associate Professor of Immunology at George Washington University Medical School. She worked on T-cell receptor structure and function in thymocytes and regulation of early T-

cell development. She will manage research on the autoimmune process in type 1 diabetes and serve as advisor to TrialNet, a type 1 intervention trial network.

- Dr. Karen Teff, who was Assistant Director of Patient-Oriented Research at the Penn Diabetes Center and Associate Program Director at the University of Pennsylvania General Clinical Research Center. She has studied many aspects of diabetes, obesity, and appetite regulation, particularly the role of the parasympathetic nervous system in regulation of glucose homeostasis. She will manage research portfolios on the neurobiology of appetite regulation, metabolic alterations in HIV, hypoglycemia, and glucose sensors.

New staff to the Division of Digestive Diseases and Nutrition include:

- Dr. Edward Doo joins the Liver Disease Research Branch as a Project Officer. Dr. Doo trained in digestive diseases at the University of California in Los Angeles, and in hepatology in the NIDDK intramural Liver Diseases Section. He worked as a transplant hepatologist at the California Pacific Medical Center in San Francisco.

- Ms. Rebecca Torrence is a master's-prepared nurse who brings extensive research experience as a Principal Investigator, Coinvestigator, and Project Manager on research projects with the Army. She joins the Division as a Clinical Trials Specialist and will assist with multicenter clinical trials, notably with data safety and monitoring boards.

New staff to the Division of Kidney, Urologic, and Hematologic Diseases include:

- Dr. Mark Geanacopoulos as a Technical Writer for the Division. Dr. Geanacopoulos worked on nucleoprotein complexes in the National Cancer Institute's Laboratory of Molecular Biology before developing an interest in communicating science to the public. His career as a journalist includes recent contributions to educational outreach efforts of the American Association for the Advancement of Science.

Joining NIDDK's Review Branch as a Scientific Review Administrator is:

- Dr. Carol Goter-Robinson, who has conducted research in immunotoxicology and human cytotoxic T-cell maturation. She was trained in molecular biology and immunology at the Johns Hopkins University, and has worked at the Food and Drug Administration (FDA). Among her accomplishments are advances related to mouse models of mercury- and gold-induced autoimmunity.

Joining the Office of Communications and Public Liaison is:

- Ms. Marcia Vital as the Deputy Director. During her seven years with the NIH, Ms. Vital was a medical writer, editor, and press officer in the NIH news media

branch, with responsibility for oversight of NIH and HHS clearance procedures for all NIH news releases. She also served the NIH as liaison to the public, news media, and HHS scientific and congressional communities. She has worked with the National Institute of Neurological Disorders and Stroke (NINDS) and, most recently, the Office of Communications in the NIH Office of the Director.

Finally, with sadness, the NIDDK says farewell to Dr. David Badman, who will retire after 30 years of exceptional service to the NIH and NIDDK. Dr. Badman joined the NIH in 1974 and came to NIDDK the following year as Director of the Hematology Program of the Division of Kidney, Urologic and Hematologic Diseases. He shepherded this program through a period of remarkable scientific advances--shaping it into a program of great breadth and scientific strength. He has been recognized by the NIH community and by the investigative communities he has served, including the American Society of Hematology and the zebrafish community. The latter honored him for his work to sponsor NIH support for zebrafish genomic resources that have helped to propel this field forward. Notably, many of Dr. Badman's contributions have advanced translational activities at NIH, one of the themes of the NIH Roadmap for Medical Research in the 21st Century. Under Dr. Badman's close stewardship, for instance, the iron chelator program developed into a model for translational research in terms of interacting with the private sector to conduct toxicology and other studies that address problems of iron overload. Dr. Badman also fostered development of NIH orphan drug efforts generally. Dr. Badman's contributions to the NIDDK and the larger scientific community have been vital; he will be deeply missed by his colleagues.

For more detailed information on new or departing NIDDK staff, please refer to the Institute's new electronic newsletter, the NIDDK Director's Update. Approximately twice a year, this update is sent to NDDK Advisory Council members and to constituency organizations, including patient advocacy groups, disease-specific organizations, and professional organizations. In addition to staffing updates, the Director's Update will include information on NIDDK-specific plans, Council issues, and trans-NIH issues of importance to the Institute.

B. CONFIDENTIALITY AND CONFLICT OF INTEREST
Dr. Robert Hammond, Director, Division of Extramural Activities

Dr. Hammond 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.

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

Availability of the *Strategic Plan for NIH Obesity Research*

The *Strategic Plan for NIH Obesity Research* is now available in hard copy and online at: http://www.obesityresearch.nih.gov/About/strategic-plan.htm.
A living document, the Strategic Plan was developed by an NIH Obesity Research Task Force established by the NIH Director and co-chaired by the NIDDK Director and the NHLBI Acting Director with representatives from across the NIH. It was informed by input from NIH Institutes, Centers, and Offices, as well as many external sources including obesity researchers and clinicians, scientific and health advocacy organizations, leaders of voluntary and professional health advocacy organizations, lay leaders, and other stakeholders. This document reflects the hard work of many individuals throughout the NIH, including Drs. Sue Yanovski and Phil Smith, the co-directors of the NIDDK Office of Obesity Research, and Dr. Lisa Gansheroff of the NIDDK's Office of Scientific Program and Policy Analysis.

The Institute of Medicine (IOM) report on prevention of childhood obesity is expected to be published by the end of September 2004. For more information, please visit: http://www.iom.edu/report.asp?id=22596.

NIDDK Clinical Obesity Research Panel

On September 21, 2004, the NIDDK Clinical Obesity Research Panel (CORP) met to discuss treatment of pediatric obesity, which is now widely recognized as a national epidemic. Specific topics of discussion included low glycemic index diets, residential treatment drugs, and surgery. The group also discussed upcoming obesity-related initiatives. Council members are encouraged to provide suggestions for future CORP initiatives and workshops to Dr. Robert Eckel, the Council representative to CORP, or to Dr. Rudolph Leibel, a scientific member of CORP.

Draft *NIH Action Plan for Liver Disease Research*

A draft of the *NIH Action Plan for Liver Disease Research* is available online at: http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm.
The ambitious trans-NIH plan was developed by the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Committee, which is chaired by the NIDDK. The plan includes 16 chapters covering topics ranging from liver transplantation to

imaging and biotechnology. Drs. Jay Hoofnagle and Leonard Seeff of the NIDDK Liver Disease Branch made significant contributions to this important effort, as did many investigators from the external community who chaired contributing subgroups, and from representatives from patient advocacy groups and the public, who provided input in response to the posting of the draft plan on the Internet for comment. Dr. Megan Miller of the NIDDK Office of Scientific Program and Policy Analysis played a key role in coordinating the plan's production. The draft will be forwarded to the NIH Director, Dr. Elias Zerhouni, and all NIH institute and center directors, and will serve as a platform for guiding future directions in NIH-wide liver diseases research. More information about this planning process can be found at: http://liverplan.niddk.nih.gov

Update on NIH Roadmap for Medical Research in the 21st Century

September 22, 2004, marked the one-year anniversary of the launch of the NIH Roadmap for Medical Research in the 21st Century—a major initiative of the NIH Director. A number of awards made in FY04 reflect priorities set forth in the Roadmap and demonstrate the effectiveness of NIH Institutes and Centers in working synergistically to achieve common goals. Several of the currently funded Roadmap initiatives will be reannounced for FY05, and several new initiatives will be launched, including opportunities for funding related to translational research.

Update on NIH Conflict-of-Interest Policies

An NIH Blue Ribbon Panel was convened in March 2004 to address concerns about NIH's conflict-of-interest policies. The Panel presented its recommendations to the NIH Director, Dr. Elias Zerhouni, who testified at a series of congressional hearings earlier this year. Discussion on this topic continues within the scientific community. As an example, an article titled, "Conflicts of Interest at the NIH--Resolving the Problem," written by Robert Steinbrook, appeared in the September 2, 2004, issue of *The New England Journal of Medicine* and detailed many of the pending issues.

VI. REPORT FROM THE NIDDK DEPUTY DIRECTOR
Dr. Griffin Rodgers, Deputy Director

Budget for Fiscal Year 2005

The FY05 President's Budget request for the NIH was revised by the Administration to add three Centers of Excellence in translational stem cell research and a National Stem Cell Bank. It is expected that the Centers of Excellence will be administered by NIDDK, National Institute of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung, and Blood Institute (NHLBI) at a total funding level of $4.5 million annually. The National Center for Research Resources (NCRR) will administer the Stem Cell Bank competition at $3 million annually. Research solicitations (Request for Applications and Request for Proposals) for these competitions will be released shortly.

The House completed action on the HHS appropriations bill and, like the President's original budget, called for a 2.6 percent increase in funding for the NIH overall and an approximate 3.25 percent increase in funding for the NIDDK. The Senate approved the HHS appropriations bill at the subcommittee and full committee level, and called for a 4 percent increase in funding for both NIH and NIDDK. At the time of the Council meeting, full Senate action was pending. Because of the upcoming elections and recess, non-defense agencies will likely begin this year with at least one continuing resolution. In light of these circumstances, the NIDDK plans to carry out funding strategies in a conservative manner through early FY05.

NIH Policy on Open Access to Literature

On September 3, 2004, the NIH released a draft policy aimed at increasing public access to the results of NIH-funded research. Informed by input from patient advocates, journal publishers, professional organizations, and other stakeholders, the policy requests that NIH-funded investigators provide the NIH with electronic copies of all final-versions of their manuscripts upon acceptance for publication, if the research was supported in whole or in part by NIH funding. Manuscripts would be archived in PubMed Central (PMC), the NIH's digital repository for biomedical research. Within six months of a research study's publication, the manuscript would be made available freely to the public through PMC.

The following clarifications were offered in response to concerns raised by Council:

- The draft open access policy would not violate copyright laws.
- The manuscript to be archived in PMC would be the author's version resulting after all modifications due to the peer review process.
- PMC is expected to be fully searchable to enhance retrieval.
- Submission of the electronic versions of final manuscripts would be monitored as part of the annual grant progress review and closeout process.

Patient advocates and others have long maintained that taxpayers should have easier access to the results of Government-funded research. On the other hand, publishing companies and several scientific societies have expressed concern about the financial impact that this new policy may have on them. For further discussion on this topic, Council members are encouraged to read the editorial titled, "Public Access to Biomedical Research," in the September 23, 2004, issue of *The New England Journal of Medicine* (http://content.nejm.org/cgi/content/full/351/13/1343), as well as an article by Jocelyn Kaiser in *Science* titled, "NIH Proposes 6-Month Public Access to Papers."

The NIH will take public comments on its draft policy until early October 2004. For more information or to view the draft online please visit: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-064.html.

Dedication Ceremony

The Mark O. Hatfield Clinical Research Center (CRC) was dedicated in a ceremony held September 22, 2004. Named in honor of former Senator Mark O. Hatfield of Oregon, who attended the dedication, the CRC will promote translational research. This focus will extend the bench-to-bedside approach adopted in 1953 with the opening of the Warren Grant Magnuson Clinical Center. The new 870,000 square foot complex includes 242 inpatient units, 90 day-hospital stations, and 250,000 square feet of laboratory and vivarium space, and connects to the existing Magnuson Clinical Center. The first patients are scheduled to arrive in early December 2004.

VII. EXTRAMURAL PROGRAMS REPORT
Dr. Robert Hammond, Director, Division of Extramural Activities

NIH Extramural Loan Repayment Programs

The NIDDK is continuing to support two relatively new extramural Loan Repayment Programs authorized by the Congress--one for pediatric research and the other for clinical research. The purpose of these programs is to recruit and retain qualified investigators in pediatric and clinical research by offering to repay qualifying educational loans over a two-year period, during which time the investigator continues to devote at least 50 percent of his or her effort to the conduct of research in a specific pediatric or clinical project. The programs were launched in FY02 and are thus in their third year.

Of the pediatric Loan Repayment Program applications assigned to the NIDDK from FY02 through FY04, the success rate was, on average, 50 percent. Looking only at FY04 data, NIH-wide success rates for this program were about the same as NIDDK rates, at about 50 percent. Of the clinical Loan Repayment Program applications assigned to the NIDDK from FY02 through FY04, the success rate ranged from 65 percent in FY02 to 41 percent in FY04. Looking only at FY04 data, NIH-wide success rates for this program were at 59 percent. Likely reasons for the difference between NIDDK and NIH-wide success rates include: (1) the number of applications received for NIDDK review – approximately 180 across the two programs – is high, relative to the budget available, (2) NIDDK applicants may have had more debt than those applying for loan repayment through other Institutes, and (3) approximately one-quarter of the 2004 applicants were reapplying for loan repayment after initially applying in 2002, thus inflating the total number of awards made. Ultimately, however, the difference between NIH and NIDDK success rates probably reflects the NIDDK's need to weigh the investment in this program with the research needs and opportunities in the many other high-priority programs within the Institute's mission.

Over the next few years, data will be collected regarding this program's effectiveness in meeting its objective of drawing investigators into careers in pediatric or clinical research. Based on these data, the NIH will consider modifications to the administration of this program. More information about these and other NIH Loan Repayment Programs can be obtained at: http://www.lrp.nih.gov/About/5lrps.htm

Award Mechanisms and Funding Considerations

In FY05, the NIDDK remains committed to supporting the greatest number of meritorious research project grant (RPG) applications possible, while participating in new initiatives and responding to emerging opportunities. Proposed RPG strategies for FY05 include:

1. Continued Support of Programmatic Adjustments from Advisory Council-approved Levels: These adjustments are based on the overall scientific and technical merit of the applications, as well as their overall cost. The NIDDK averages a 12 percent programmatic reduction from the recommended level.

2. Continued Use of Special Emphasis Program Announcements (SEPAs): The Institute identifies a subset of active Program Announcements of sufficiently high priority to warrant Special Emphasis funding of applications beyond the payline. This approach permits up to nine receipt dates--three per year for three years--and thus provides ample time for application preparation and review.

3. Flexible Use of Special Emphasis Funds: If an application is just outside the projected NIDDK payline and meets one or more of the following criteria, it may be nominated for Special Emphasis funds:

- The applicant is a new investigator.
- The applicant is an outstanding investigator new to NIDDK.
- The application proposes research that: (1) demonstrates translational potential, (2) will engender enabling technology, (3) responds to a current initiative (RFA or PA), (4) addresses an underfunded area or disease, or (5) addresses an issue of congressional interest.
- The application proposes research that investigates health disparities, involves an underrepresented minority institution, or is from a minority investigator.
- There are other extenuating factors (e.g., the application is final revision).

The Council was asked to consider whether to abolish differential paylines in favor of more flexible use of Special Emphasis funds for new investigators (type 1 applications) and for competing continuations (type 2 applications). The Council considered data indicating that the number of new investigators who benefit from Special Emphasis funds far outweighs the number who benefit from the two-percent differential payline. Furthermore, of the investigators submitting competing continuations, the number who benefit from the two-percent differential has been, on average, only about a dozen per year. The Council also considered the importance of: (1) maintaining transparency in the scientific review process; (2) providing uninterrupted funding for continuing grants, (3) encouraging new investigators, and (4) supporting innovation. The Council also weighed the psychological impacts of a policy change against its practical impacts and reached a tentative conclusion: The Council recommended that the NIDDK abolish differential paylines for competing continuations, but not for applications from new investigators.

4. Use of Smaller, Short-duration Research Project Grants (RPGs) to Balance and Complement Existing Grant Portfolios: Among proposed RPG strategies for FY05 is the use of smaller, short-duration RPGs to complement existing grant portfolios. Such RPGs include the NIH Exploratory/Developmental Grant (R21); the NIH Small Grant (R03); and the NIH High-Priority, Short-Term Project Award (R56). The latter is new to NIH for FY05 and will fund, for one-to-two years, high-priority, new or competing renewal R01 applications with priority scores or percentiles that fall just outside the funding limits of participating Institutes, Centers, and Offices. The Advisory Council input on this new funding mechanism will be sought during the February 2005 meeting. For more information on R56s, please visit:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-047.html

Program Project Grants

The NIDDK is considering how to maximize its investment in Program Project (P01) grants. The successful P01 addresses a range of scientific questions, has a clear central focus, and demonstrates unity and interdependence among its multiple projects. The Council was asked to consider the current process for accepting, scoring, and funding P01s. Topics for discussion over the upcoming fiscal year include whether to:

- Establish a targeted number of P01 applications that will be accepted each year;
- Establish a minimum percent effort for the Principal Investigator (PI) of the overall P01;
- Discontinue percentiling in the scoring of applications; and
- Replace percentile-based P01 paylines with targeted numbers of P01 awards for the year.

Among the reasons for considering these changes are: (1) to better manage the number of applications in order to enhance the quality of the scientific peer review, and (2) to provide a more thoughtful mix of applications for review.

The following clarifications were offered in response to concerns raised by Council:

- Investigators on continuing program projects approaching renewal would not be barred from submitting renewal applications; however, before acceptance, renewals would be reviewed to ensure that they continue to reflect a level of interaction and collaboration that justifies the use of the P01 funding mechanism.

- Though the NIDDK hopes to designate a minimum percent effort for all Principal Investigators on P01 grants, the total budget for a P01 still could not exceed the designated budget cap. In some cases, this could mean that a Principal Investigator could not charge his/her effort to the grant.

Discussion on this topic will continue by email. Guidelines for NIDDK P01s are available online at: http://www.niddk.nih.gov/fund/divisions/dea/review_branch/p01guidelines.htm.

VIII. SCIENTIFIC PRESENTATION

Molecular Basis of Urinary Tract Infections: More to the Picture Than Meets the Eye

Dr. Scott J. Hultgren
Helen L. Stoever Professor of Molecular Microbiology
Washington University School of Medicine, St. Louis, Missouri

Dr. Hultgren presented the results of research on the pathogenic cascade of *Escherichia coli* urinary tract infections (UTIs). Uropathogenic *E. coli* invade and multiply within superficial bladder cells, which can lead to the recurrence of symptoms. The interaction between these bacteria and the mammalian immune response can determine the outcome of an infection. These insights could affect the ways that UTIs are evaluated, treated, and prevented.

IX. ADJOURN FOR LUNCH

Dr. Spiegel thanked all of the presenters and adjourned the open session of the full Council.

X. SUBCOMMITTEE MEETINGS

From approximately 1:00 to 5:30 p.m., separate meetings were convened by the Subcommittees for Diabetes, Endocrinology, and Metabolic Diseases; Digestive Diseases and Nutrition; and Kidney, Urologic, and Hematologic Diseases. The Subcommittees met again on Thursday, September 23, 2004, from 8:00 to 9:30 a.m.

XI. REPORTS OF SUBCOMMITTEES: CONSIDERATION OF APPLICATIONS (CLOSED SESSION)

XII. ADVISORY COUNCIL FORUM: UPDATE ON TRANSLATIONAL RESEARCH

General Discussion and Concept Clearance for FY 2005 Initiatives
Dr. Myrlene Staten

The NIDDK staff presented FY05 trans-NIDDK concepts for translational research initiatives, which are intended to complement activities under the NIH Roadmap for Medical Research in the 21st Century. The Council uniformly endorsed each of the seven concepts, which are described briefly below, and presented some comments and recommendations.

1. Development of Biomarkers: Drs. Maren Laughlin, Myrlene Staten, Robert Star, José Serrano, and John Connaughton

The purpose of this initiative is to develop biomarkers for well-defined human diseases for which there are no or very few biomarkers, or for which standard biomarkers are currently prohibitively invasive or expensive. This initiative would be used to stimulate bench-to-bedside translation by providing measures of the biological effects of potential new treatments. Examples of target biomarkers include a noninvasive marker of fibrosis, markers of early diabetic neuropathy, markers of disease activity for inflammatory diseases such as inflammatory bowel disease, markers of beta-cell mass and function, and tissue-specific markers of insulin resistance and angiogenesis.

Council Input: While this is a timely and important initiative, candidate biomarkers have not been identified. To identify candidates, researchers with knowledge of proteomics and genomics need to be linked with those researchers who have samples from well-characterized populations.

Additional questions for NIDDK staff to consider are: How should NIDDK leverage results from funded discovery projects? Who are the best investigators to target and how should the Institute target them? What are the relevant review criteria?

2. Development of New Imaging Methods: Drs. Catherine Meyers, Maren Laughlin, Elizabeth Wilder, Leroy Nyberg, and José Serrano

The purpose of this initiative is to stimulate the translation of new methods or imaging reagents for evaluation of diseases and disorders of the solid abdominal organs (liver, pancreas, kidney) and the urinary tract. Potential areas with promise include imaging methods to: (1) assess hepatic and renal fibrosis, (2) validate new technology in settings where protocol biopsies are being performed, (3) evaluate markers for hepatic or kidney inflammation, (4) evaluate vesicoureteral reflux in children without the need for bladder catheterization or radiation exposure, and (5) use robust techniques to readily assess the progression of cyst growth in polycystic kidney disease.

Council Input: While this initiative is admirable and timely, it may be difficult to: (1) identify a methodology upon which to focus, and (2) identify the appropriate collaborators in industry. The Council also encouraged the NIDDK to consider the following points in further defining this initiative: (1) expanding this initiative to include investigations into the bladder and the prostate; (2) broadening its scope to reach beyond the solid organs to, for example, skeletal muscle and adipose tissue; and (3) collaborating with the nanoscience community, device manufacturers, and bioengineers.

It was generally recognized that collaboration will be critical to the success of this initiative. Fortunately, a framework for collaboration among Institutes is already in place under the NIH Roadmap for Medical Research, wherein investigators across NIH are currently pursuing work in nanotechnology. Furthermore, with this initiative, the

NIDDK hopes to foster collaborative relationships external to the NIH as well--for example, with centers with outstanding pre-existing imaging and clinical expertise.

3. Animal Models for Preclinical Testing in NIDDK-Relevant Diseases: Drs. Kristin Abraham, Christian Ketchum, and Robert Karp

The purpose of this initiative is twofold: (1) to develop new animal models of NIDDK-relevant diseases where animal models are either inadequate or lacking, and (2) to validate specific animal models as surrogates for human disease through rigorous comparison with human clinical data. Disease-focused research areas that would benefit from new or improved animal models include, for example, research on irritable bowel syndrome, autoimmune liver disease, incontinence, thalassemias, cystic fibrosis, and type 1 diabetes.

While the Council did not have comments on this initiative at the meeting, NIDDK staff stressed that Council input would be sought throughout the process. Questions for further consideration include: What areas are in greatest need of animal models? How does one validate human disease in a new model? What are the most promising approaches for mono- and polygenic diseases?

4. Angiogenesis and Diabetes: Drs. Teresa Jones, and Terry Bishop

This initiative is informed by ideas presented during a two-day NIH workshop on angiogenesis, held May 2004. This workshop involved experts in angiogenesis, as well as diabetes and other diseases. The purpose of this initiative is to enhance the understanding of effects of type 1 diabetes on new blood vessel growth (angiogenesis), in order to exploit its therapeutic potential for diabetic complications and pancreatic islet transplantation. Objectives include: (1) promoting collaborative research projects between experts in angiogenesis and diabetes, (2) enhancing understanding of the effects of diabetes on angiogenesis, (3) developing biomarkers or imaging tools for assessing abnormalities with angiogenesis, and (4) promoting development of new angiogenic therapeutics or the evaluation of existing angiogenic therapeutics for diabetic complications or islet transplantation.

While the Council did not have comments on this initiative during the meeting, NIDDK staff stressed that Council input would be sought throughout the process.

5. Mitochondrial Oxidative Stress from Hyperglycemia: Drs. Teresa Jones, Edward Doo, and Christopher Mullins

With the goal of preventing diabetic complications and non-alcoholic steatohepatitis (NASH), the purpose of this initiative is to develop therapeutics that prevent the intracellular accumulation of reactive oxygen species (ROS) in the cells' mitochondria--induced by hyperglycemia. Research topics might include studies of: (1) agents that decrease the production of ROS, (2) agents that increase the degradation of intracellular

ROS, (3) strategies to target drugs into the mitochondria, and (4) the ability of FDA-approved drugs to decrease intracellular ROS levels. Among the challenges are: attracting new researchers to the field, translating promising new agents to therapeutics, and developing *in vivo* measures of oxidant accumulation to test efficacy.

Council Input: Pioneering techniques for imaging ROS are currently available and, combined with endoscopy and other devices, could be used to study animal models of NASH. While such animal models are not available, three models are under development. With this example, one begins to see the intersection of multiple NIDDK translational initiatives: imaging methods, animal models, and ROS fluctuation. This represents the type of research NIDDK would like to be supporting.

6. Therapeutic Agents for Diseases of Protein Misprocessing or Misfolding: Dr. Carol Haft

Informed by ideas presented during a two-day NIH conference on protein misfolding and misprocessisng in disease held May 2004, this initiative will invite applications to identify siRNA or small molecule reagents that specifically ameliorate a protein misprocessing defect in NIDDK-relevant diseases. Research activities appropriate to this initiative include, for example, development of robust and reliable primary and secondary assays, screening (low- or high-throughput), synthesis and testing of related compounds for enhanced efficacy, and animal model testing of efficacious compounds. Challenges include limited funding for research in rare diseases, industry's reluctance to invest in this area, and logistical barriers to gathering patients with rare diseases and disorders for clinical study.

While Council did not have comments on this initiative during the meeting, NIDDK staff stressed that NDDK Advisory Council input would be sought throughout the process.

7. siRNA Delivery, Processing, Stability, and Efficacy in Specific Cell Types, Tissues, or Organs: Dr. Rebekah Rasooley

The purpose of this initiative is to optimize RNAi technology for preclinical and clinical uses in organs and diseases relevant to the NIDDK's mission. Objectives are to: (1) solicit tissue- and organ-specific siRNA research projects to improve delivery, characterize factors mediating stability/half-life, improve efficacy, and identify ways to minimize or eliminate off-target or side effects; (2) emphasize *in vivo* projects; and (3) encourage disease-specific research.

NIDDK offered the following clarifications in response to questions raised by Council about this initiative:

- Outstanding libraries of molecules for siRNA experiments do already exist, and the NIDDK is interested in developing them further. Current NIH efforts in this area are directed through the Cancer Genome Anatomy Project. A trans-NIH effort still under

development will solicit grants to improve the efficacy of these interfering RNA treatments.

- The goal of this initiative is siRNA delivery as either a drug or a gene product.

- While research in this area is currently being carried out in small, private laboratories, these investigators may be using suboptimal techniques.

Conclusions and Closing: The Council uniformly endorsed the seven translational research concepts for implementation. The NIDDK's Office of Scientific Program and Policy Analysis is documenting all meetings, workshops, and Council deliberations leading up to these translational research initiatives. This information, as well as the initiatives themselves, will be compiled and provided to the Council. For further information about the translational research concepts, as well as other concepts for research initiatives, and general NIDDK research funding opportunities, please visit: http://www.niddk.nih.gov/fund/fund.htm

XIII. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1,115 grant applications, requesting support of $255,895,339 were reviewed for consideration at the September 22-23, 2004 meeting. Funding for these 1,115 applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 424 applications requesting $117,146,783 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 23, 2004 meeting.

XIV. ADJOURNMENT

Dr. Spiegel thanked the Council members for their attendance and efforts. There being no other business, the 166th meeting of the NIDDK Advisory Council was adjourned at 12:00 p.m., September 23, 2004.

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