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

May 26 - 27, 2004

I. CALL TO ORDER

The Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Dr. Allen M. Spiegel, called to order the 165th National Diabetes and Digestive and Kidney Diseases Advisory Council meeting on May 26, 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. Robert Alpern
Mr. David Baldridge
Ms. Mary Clark
Dr. Roberto Coquis
Dr. Raymond DuBois
Dr. Robert Eckel
Dr. Richard Goodman
Dr. Earl Harrison (*Ex officio*)
Dr. James W. Kikendall (*Ex officio*)
Dr. Sum Lee
Dr. Rudolph Leibel
Ms. Nancy Norton
Dr. Daniel Porte (*Ex-officio*)
Dr. Vicki Ratner
Dr. Ronald Ruecker
Dr. Linda Sherman
Dr. E. Darracott Vaughan
Dr. W. Allan Walker

Council Members Absent:
Dr. Janis Abkowitz
Dr. Jose Caro
Dr. Carloyn Kelly

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 video cast 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
Beena Akolkar, NIDDK
Syed Amir, CSR
Sara Arnold, Health & Med Counsel
David Badman, NIDDK
Michele Barnard, NIDDK
Kevin Beverly, Soc. & Scien. Sys.
Terry Bishop, NIDDK
Sharon Bourque, NIDDK
Josephine Briggs, NIDDK
Francisco Calvo, NIDDK
Joan Chamberlain, NIDDK
John Connaughton, NIDDK
Catherine Cowie, NIDDK
Maria Davila-Bloom, NIDDK
Jane DeMouy, NIDDK
Christine Densmore, NIDDK
Dale Dirks, HMCW
Patrick Donohue, NIDDK
Michael Edwards, NIDDK
Thomas Eggerman, NIDDK
Paul Eggers, NIDDK
Gayla Elder-Leak, NIDDK
Nancy Emenaker, CSR
Steven Everett, NIDDK
Jody Evans, NIDDK
James Everhart, NIDDK
Richard Farishian, NIDDK
Ned Feder, NIDDK
Carol Feld, NIDDK
Frances Ferguson, NIDDK
Olaf L. Fonville, NIDDK
Judith Fradkin, NIDDK
Lisa Gansheroff, NIDDK
Sanford Garfield, NIDDK
Reed Graves, CSR
Janet Gregory, NIDDK
Carol Haft, NIDDK
Frank Hamilton, NIDDK
Mary Hanlon, NIDDK
Dana Harris, NIDDK
Barbara Harrison, NIDDK
Jay Hoofnagle, NIDDK
Ann Karen Howard, NIDDK
Van Hubbard, NIDDK
Joyce Hunter, NIDDK
Marc Hurlbert, JDRF
James Hyde, NIDDK
Donna James, NIDDK
Stephen James, NIDDK
Ann Jerkins, CSR
Teresa Jones, NIDDK
C. Ronald Kahn, Joslin Center
Melissa Kaplan, SWHR
Robert Karp, NIDDK
Christian Ketchum, NIDDK
Sooja Kim, CSR
Krish Krishnan, NIDDK
Robert Kuczmarski, NIDDK
Maren Laughlin, NIDDK
Amy Lavarda, Constella
Kim Law, NIDDK
Todd Le, NIDDK
Susan Lehman, NIDDK
Ellen Leschek, NIDDK
Maxine Lesniak, NIDDK
Monica Liebert, Am. Urol. Assoc.
Barbara Linder, NIDDK
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
Barbara Merchant, NIDDK
Catherine Meyers, NIDDK
Carolyn Miles, NIDDK
David Miller, NIDDK
Megan Miller, NIDDK
David Mineo, NIDDK
Marva Moxey-Mims, NIDDK
William Mitch, Univ. Texas
Christopher Mullins, NIDDK
Neal Musto, NIDDK
Diana O'Donovan, NIDDK
Bert O'Malley, Baylor College
D.G. Patel, NIDDK
Denise Payne, NIDDK
Chris Peterson, SRI
Judith Podskalny, NIDDK
Sharon Pope, NIDDK
Janet Reise, NIDDK
Tibor Roberts, NIDDK
Patricia Robuck, NIDDK
Dominica Roth, OD/NIH
Paul Rushing, NIDDK
Lakshmanan Sankaran, NIDDK
Sheryl Sato, NIDDK
Salvatore Sechi, NIDDK
Leonard Seeff, NIDDK
Roy Sewall, Soc & Scien. Sys.
Elizabeth Singer, NIDDK
Philip Smith, NIDDK
Jennifer Soloman, Constella Grp
Lisa Spain, ARC
Robert Star, NIDDK
Myrlene Staten, NIDDK
Dorothy West, NIDDK
Elizabeth Wilder, NIDDK
Joseph Woodill, NIDDK
Gina Wrench, NIDDK
Susan Yanovski, NIDDK
Charles Zellers, NIDDK

II. CONSIDERATION OF SUMMARY MINUTES OF THE 164th COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 164th NDDK Advisory Council (February 2004) as submitted.

III. FUTURE COUNCIL DATES

Dr. Spiegel asked Council members to take note of future Council meeting dates as follows:
September 22-23, 2004
February 23-24, 2005
May 19-20, 2005

September 14-15, 2005
February 15-16, 2006
May 31-June 1, 2006
September 20-21, 2006

IV. ANNOUNCEMENTS

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

With regard to extramural investigators:

▪ The NIDDK welcomes Dr. William Mitch, Chairman of the Department of Internal Medicine, University of Texas Medical Branch at Galveston, who joined the Council meeting as an *ad hoc* member of the Kidney, Urologic, and Hematologic Diseases Subcommittee. Dr. Mitch is President of the American Society of Nephrology and is an expert in nutrition and renal disease.

▪ Dr. Robert Alpern, currently Dean of the University of Texas Southwestern Medical Center, has accepted an appointment as Dean of Yale Medical School.

▪ Dr. Raymond DuBois, Vanderbilt University Medical Center, received the Dorothy P. Landon American Association for Cancer Research prize for translational cancer research. This prize recognizes his innovative research on the role of cyclooxygenase-2 (COX-2) in cancer.

▪ Dr. John Potts, Jackson Distinguished Professor of Clinical Medicine at Harvard Medical School, and Director of Research at Massachusetts General Hospital, was elected to the National Academy of Sciences in April 2004. He is recognized for his research on the structure and function of parathyroid hormone and its application to the successful treatment of osteoporosis.

▪ Dr. Eugene Butcher, physician at the Veterans Affairs Palo Alto Health Care System, and Professor of Pathology, Stanford University School of Medicine, is the co-recipient of the Crawford Prize in polyarthritis for his research on the molecular mechanisms involved in migration of white blood cells in health and disease.

▪ Dr. Robert Simpson, Professor, Department of Biochemistry and Molecular Biology, Pennsylvania State University, passed away in April 2004. Dr. Simpson contributed more than 25 years of service to the NIH, primarily as a laboratory chief at the NIDDK. He was a pioneer in the study of chromatin, the histones, and other proteins associated with DNA, and the regulation of chromatin structure, and ultimately, of gene expression.

Two NIDDK-sponsored researchers are recipients of the 2004 Presidential Early Career Awards for Scientists and Engineers. Dr. Susan Buchanan of the NIDDK's intramural Laboratory of Molecular Biology, works on membrane protein structural biology. Dr. David Cummings, an extramural investigator and Assistant Professor of Medicine at the University of Washington School of Medicine, received his award for research on body weight regulation.

Within the NIDDK:

▪ Dr. Frances Ferguson has joined the Office of Minority Health Research Coordination as a Program Director. Dr. Ferguson received her M.D. from Howard College of Medicine and her M.P.H. from Emory University. She has a strong interest in chronic disease prevention and health promotion, particularly in the prevention of type 2 diabetes.

▪ Dr. Carolyn Miles has transferred from the NIDDK Review Branch to the Division of Digestive Diseases and Nutrition, where she will be a Program Director in the Clinical Obesity and Nutrition Program.

▪ Dr. D.G. Patel has joined the Review Branch as a Scientific Review Administrator. He received his Ph.D. in pharmacology from the Medical College in Baroda, India, and has worked for the University of Cincinnati, Meharry Medical College, the Department of Veterans Affairs (VA), the Food and Drug Administration (FDA), and more recently, the Review Branch of the National Center for Research Resources. His field is carbohydrate metabolism and diabetes.

▪ Dr. Jane DeMouy, Deputy Director of the Office of Communications and Public Liaison, is retiring after 15 years with NIDDK. She has a special interest in health education projects for the Pima Indians. She has received multiple NIH Plain Language awards for her work involving the Gila River Indian community in Phoenix.

B. CONFIDENTIALITY AND CONFLICTS-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. They were reminded that materials furnished are considered privileged information, and are to be used for the purpose of review and discussion during the closed portions of the meeting only. 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 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 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. SCIENTIFIC PRESENTATION
The Amazing Biologic Diversity of Nuclear Receptor Coactivators

Dr. Bert W. O'Malley
Professor and Chair, Department of Molecular and Cellular Biology
Baylor College of Medicine

In 1995, a team of scientists led by Dr. O'Malley discovered a new molecule that is critical in regulating gene expression—the steroid receptor coactivator-1 (SRC-1). Soon, others uncovered SRC-2 and SRC-3. Together, these coactivators comprise a family of molecules that enhance the activity of a number of steroid hormone receptors, including the progesterone and estrogen receptors, and they also help regulate other receptors involved in the regulation of many other cellular processes, including carbohydrate and lipid metabolism. The discovery of these molecules revealed a previously unappreciated complexity in the regulation of gene expression, opened the door to a new field of research, and identified potentially powerful targets for the development of novel therapies.

This research was propelled by investigators who were seeking to answer several questions about fundamental issues in cellular metabolism: How does the cell regulate which genes are turned "on" or "off"? What factors coordinate the activation of genes that perform related functions—in response to changes in the cellular environment? How might disruptions of this coordination lead to disease? Could future therapies be developed based on approaches for targeting the molecules that influence this coordination?

Cells have a number of different proteins that dock onto sites on genes to turn the genes on. However, for many genes, additional accessory factors are required; these act as "power boosters" to help turn on the genes and also provide additional layers of regulation. A large number of these accessory proteins are termed "coactivators;" they help boost genetic activity. (Corepressors help dampen it.) Different cell types may have varying concentrations or different complements of coactivators—to which genes may respond in different ways. Very small changes in levels of these molecules or in the ratios of one to another, or other slight differences, may have an immense effect on gene expression over time.

The discovery of the SRC family is being translated into new insights about health and disease. SRC-3 is overproduced in many cases of human breast cancer, and the combination of an overabundance of SRC-3, together with a specific oncogene (*HER2/neu*), signals a particularly poor prognosis, as well as tamoxifen resistance, in women with breast cancer. Coactivators have been associated with many other cancers as well. SRC-3 (and other coactivators) may have potent effects on the development of cancer because it is involved in many different regulatory pathways within cells, including cell growth. Thus, when overabundant, a coactivator may adversely over stimulate many cellular functions, resulting in cancer.

The growing appreciation of the important role of coactivators has many implications. Coactivators make attractive targets for designing therapies that selectively affect certain types of cells. The unfolding of new knowledge about the roles of coactivators and corepressors is providing exciting opportunities for translational research.

VI. ADVISORY COUNCIL FORUM: TRANSLATIONAL RESEARCH
Moving New Ideas from Bench Research to the Patient

Dr. Myrlene Staten
Senior Advisor, Diabetes Research Translation
NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases

In follow-up to the discussion at the previous Council meeting, Dr. Staten shared with the Council the results of an assessment the NIDDK Translation Working Group has conducted. The assessment focused on primary translation, which was defined as the movement of discoveries from the basic sciences to human studies, as opposed to secondary translation, which involves the application of clinical findings in medical practice. The Working Group concentrated on research activities likely to have a practical application in human disease. To the extent possible, the activities examined included not only research funded solely by the NIDDK, but also research funded by other institutions, both public and private. Program staff gathered and displayed on Gant charts information from NIDDK portfolios, literature searches, and public meetings. They also developed a standard series of questions to help them summarize research efforts to date for each topic analyzed. In one part of the assessment, NIDDK staff identified translational success stories in the NIDDK programmatic divisions, outlined the major milestones, and determined the role of NIH support—with a view toward gathering "lessons learned" that might have current and future applications. In another part of the assessment, NIDDK staff analyzed the current status of translation activities for several specific diseases. Through this process, the Working Group has identified some emerging themes and roadblocks for further discussion with, and input from, the Council. With Council guidance, the NIDDK plans to undertake program enhancements to reduce or eliminate these roadblocks/barriers and to enhance progress in some of these areas.

Lessons Learned from the HbA1c Translation Success Story: To illustrate the process through which a finding from basic research can progress into a useful clinical tool, Dr. Staten described a translation success story. This story derived from the discovery of hemoglobin variants, which were first identified in the study of sickle-cell anemia in 1949. Eventually, the variant hemoglobin A1c (HbA1c) was identified. It was determined that HbA1c is formed by post-translational modification, and that the level of HbA1c correlates with degree of glycemia (blood sugar level). HbA1c was thus initially seen as a "biomarker," that is, a measurable indicator of disease activity or progression. However, based on further translation research, HbA1c is now used as a "surrogate outcome," that is, an end point that is accepted as sufficiently robust to be substituted for a clinical outcome in clinical trials.

In the 1980s, there had been controversy as to whether the common complications of diabetes were the result of hyperglycemia (high blood sugar levels), or whether underlying genetic

abnormalities predisposed a patient with diabetes to develop complications. To address this question, the NIDDK implemented the Diabetes Control and Complication Trial (DCCT) to study the relationship between glycemic control, as measured by HbA1c, and the microvascular complications of diabetes. In 1993, the DCCT proved that lowering HbA1c by 1 to 1.5 percent significantly reduced the onset and progression of diabetic microvascular complications (damage to the small blood vessels of the eyes, kidneys and nerves). This discovery was followed by the creation of a national program to standardize tests for HbA1c, so that clinicians could apply the DCCT findings and realize their practical benefits for patients. As a result, the FDA accepted HbA1c as a surrogate for diabetes outcomes, greatly reducing the cost of studies needed for approval of new drugs.

Other clinical benefits also flowed from the HbA1c discovery. The finding that treatment for hyperglycemia provided protection against long-term complications was a stimulus for the development of new therapeutic agents. Furthermore, the setting of goals for levels of HbA1c encouraged medical practitioners to use a combination of methods to control blood sugar. Although epidemiology studies have not yet demonstrated the achievement of a lower HbA1c nationwide, there clearly are pockets where progress is being made, and clinicians are trying to realize goals. Moreover, the impact of the DCCT extended beyond validation of HbA1c; it also supported the use of C-peptide as a measure of beta cell function and as a potential surrogate, based on the finding of better glycemic control and reduced hypoglycemia in those with significant C-peptide levels.

The “larger lesson” learned is that clinical trials can validate biomarkers that become surrogates for disease activity. They can also illuminate a clear biologic pathway, and this knowledge can then stimulate development of new therapies targeted to specific parts of that pathway. Furthermore, databases from the studies can be mined for multiple uses. However, it can take years, even decades, for successful translation to occur, and the NIDDK would like to speed this process for diseases within its research mission. (Council members were provided with information on other success stories where public funding contributed to at least part of the progress, including Forteo-rPTH, Adagen-peg adenosine deaminase, Fabrazyme-agalsidase beta, Aldurazyme-laronidase, proton pump inhibitors, and the Sensipar-calcium mimetic.)

Assessing the Status of Translation Research in Several Diseases as Informative Examples: To identify emerging themes for translational research and uncover roadblocks to translation, staff from the three programmatic NIDDK divisions conducted an evaluation of translational research efforts undertaken to date for certain diseases or disease-related research areas. For the Division of Kidney, Urologic and Hematologic Diseases, the topics were polycystic kidney disease, interstitial cystitis, oxalosis deposition, iron overload, diabetic nephropathy, and acute renal failure. For the Division of Diabetes, Endocrinology and Metabolic Diseases, the topics were cystic fibrosis, beta cell replacement, type 1 diabetes, and insulin resistance. For the Division of Digestive Diseases and Nutrition, the topics were intestinal failure, inflammatory bowel disease, liver regeneration, and gastrointestinal motility. Across NIDDK, obesity research was also examined. Program staff assessed the state of translation research for a subset of disease-related topics in order to gain insights into aspects of the translation process; this

assessment was not intended to be comprehensive for all the diseases within the NIDDK mission.

On Gant charts prepared by NIDDK staff, horizontal bars showed research activity in the translation pipeline, with color coding to differentiate between public and private sources of funding. Gaps in the bars indicated roadblocks, or unrealized opportunities. For each disease-oriented topic analyzed, the Working Group tried to answer the following questions:

- What is NIDDK's goal in translational research?
- What is industry's interest?
- What is the current assessment of the pipeline?
- What is the assessment of the roadblocks to basic research, preclinical development, and human studies?
- What are the priority steps to address these roadblocks?

Emerging Themes/Insights from NIDDK Staff Assessment: Dr. Staten summarized the main themes that have emerged thus far:

1. Gaps in Understanding the Role of Biological Pathways in Human Disease: Frequently, discoveries made *in vitro* or in animals lead immediately to pre-investigational new drugs (pre-INDs), especially when there is considerable industry interest. To increase the likelihood of long-range success in the development and application of therapeutics, better strategies should be established to assess the significance of such findings in human systems. One such strategy is a partnership among the NIH, the FDA, and industry so that the bench researcher--who often defines pathways through basic discoveries--can have access to tissues, human biologic samples, and/or patients who wish to participate in clinical research. The biological roles of pathways could then be explored at an early level. Genetic studies of extreme human cases of a given disease can sometimes lead to the exploration of new pathways. For most diseases there has been limited research of this nature.

2. Improved Animal Models: A more critical assessment needs to be made of how closely the progression of disease in existing models relates to what occurs in the corresponding human disease. In many cases, it is clear that improved models are necessary. In addition, standardization of laboratory protocols and procedures for the study of animal models would facilitate data comparison across laboratories--as would standardized approaches for using animal models to test the efficacy of potential therapeutic strategies.

3. Access to Pre-IND and Pre-clinical Development Resources: For some disease-oriented research, the pharmaceutical industry is not involved, either because the condition affects a small population, because market size is limited, or for some other reason. In these and similar cases, access to pre-IND resources may be an issue.

4. Difficulties in Early Human Testing: Many of the difficulties in early human testing could be overcome with: (a) improved imaging methods to diagnose disease and assess its progression during the early stages; (b) better biomarkers that determine whether or not a therapeutic agent is

having the desired effect; (c) more effective methods to identify subsets of patients who may be particularly responsive to therapeutic agents; (d) improved strategies for using the results from animal research and from *in vitro* methods to identify or predict toxicity in humans; and (e) regulatory expertise regarding requirements for pre-IND development/preparation and preliminary clinical studies. A clear path to regulatory approval is a potent stimulus for commercial development.

Dr. Staten concluded her presentation with a set of questions for Council members:
- Has our approach to the analysis of translation research included the right elements?
- Do the themes that we have identified seem to be the primary areas of need? If not, what are the areas with significant potential for impact on translation, which can help achieve the maximum benefit from our basic research portfolio?
- How should we prioritize translation research areas for enhancement?
- How can the NIDDK Central Repositories be used most effectively in translation research?
- How should we measure the impact of our efforts?

Discussion

Council members stressed the importance of bi-directional research. It is not only important to move ideas from the bench to studies in humans, but also from clinical observations back to the laboratory. Council members identified the need for an appropriately trained and interactive cadre of basic and clinical scientists; more useful animal models; better access to technologies and clinical resources; and more vigorous pursuit of research that will speed clinical trials, such as the development of biomarkers which can serve as surrogate clinical outcomes. Other topics discussed included the development of ways to characterize how diseases may progress differently in individual patients; the value of collaborative efforts among researchers, the NIH, other Federal agencies, and industry, with respect to sharing information and leveraging funding; and the need for NIH to communicate timely information about funding opportunities and peer review processes. Highlighted below are some of the discussion points:

Definitions
- Consideration should be given to what is meant by "disease" in the context of the NIDDK assessment materials. Risk factors (e.g., insulin resistance), therapeutic interventions (e.g., beta-cell replacement), and actual diseases (e.g., cystic fibrosis) are all similarly addressed.

Pursuing Bi-directional Translational Research
- Pursuit of bi-directional translational research can be slowed by many factors, including: access to clinical research resources, research manpower issues, the focus of the traditional regular research project award (R01), and regulatory requirements.

- The translational pathway might be shortened if the NIH encouraged basic scientists to focus on areas that lend themselves to translational research. For example, research on coactivators and corepressors is now proving clinically relevant in areas such as breast cancer. Similarly, research on fibrosis could lead to the development of an important biomarker so that interventions might be introduced to stave off related diseases of the liver, kidney and lung.

▪ Ph.D. scientists (rather than M.D. researchers) appear to be the driving force in NIH-funded research, and particularly, in General Clinical Research Centers (GCRCs), which some consider to be the best model environment for translation research. Also, the research workforce is changing from physician-scientists to graduate students, who are trained in molecular techniques, rather than in physiology or medicine. Therefore, it is important to find more ways to bring clinicians into the research process.

▪ The curricula offered by many academic institutions around the country may not be conducive to maintaining an adequate cadre of scientists trained in clinical research. A shrinking fraction of the research being done by M.D. researchers is focused on clinical projects. Typically, most of the research is being performed by either Ph.D. researchers or by M.D. scientists who do not practice medicine. In an attempt to resolve this situation, a recent multi-institute meeting focused on changing medical school curricula so that clinical research can be presented earlier to medical students. Some schools are developing Ph.D. programs in the clinical sciences—with emphasis on health services outcomes, informatics technology, or clinical investigation.

▪ A perceived stumbling block in the pursuit of translational research is that the R01 award mechanism is not uniquely positioned for this type of research. One remedy might be to encourage focused projects in which R01 basic research investigators are partnered with clinicians, and to ensure that the combined research team has access to a variety of technologies and research cores. This approach would facilitate corroboration or contradiction of findings via information-sharing among members of such a program-project-like research grant. Dialogue of this type could help ensure that ideas about the clinical application of findings are continually offered and considered during the lifetime of a grant, and would also foster longer-term cooperation and links between clinical and basic science researchers. Some institutes are now mandating that their Program Project Grants (P01s) have a translational component.

Dr. Spiegel noted the importance of fertilization of ideas across disciplines, NIH components, other Federal agencies, and industry. A new Forum on Drug Discovery, Development, and Translation begins in January 2005. This Forum is a successor to the Institute of Medicine's (IOM) Clinical Research Roundtable. The Forum will address problems related to the flow of research discoveries.

Improving Animal Models

▪ Most diseases are complex genetic disorders rather than single-gene abnormalities. Because current technology permits only comparatively simple genetic manipulation in mice, it is difficult, time-consuming and costly to make mouse models that accurately reflect complex diseases in humans. Future technologies may help to fill this void.

▪ Improved animal models would accelerate research at the critically important cross-over point between fundamental and applied science. Currently, it takes a very long time to establish animal models and use them for studies with final endpoints, after which they are sacrificed. The pursuit of new types of non-invasive, non-lethal laboratory assays could foster and accelerate translation research in model systems. Such assays could monitor gene, pathway, and metabolic

activities in animals. For example, it might be possible to develop, and to use for metabolic scanning in animals, an approach similar to the application of positron emission tomography (PET) in humans.

▪ Using the Small Business Innovation Research (SBIR) funding mechanism could accelerate the development of improved animal models because many companies are adept at knock-out and proteomic techniques.

Providing Access to Necessary Equipment/Resources-- and Setting Priorities

▪ A major roadblock to cutting-edge, field-furthering clinical research is the difficulty in obtaining funding for and access to sophisticated technology such as nuclear magnetic resonance (NMR). This difficulty can be a rate-limiting step in moving research forward. The need to harness technology has been recognized in the NIH Roadmap process (for example, with respect to integrating NIH-funded General Clinical Research Centers into translational efforts).

▪ As the NIH enters a period of greater resource constraints, it is important to synergize research around common themes, such as translation, and to leverage resources to support them. However, translation is very broad, and the NIDDK will need to focus its efforts in specific ways. Interdisciplinary meetings can help to identify compelling cross-cutting research themes that merit support. Also useful are meetings with other agencies, such as the FDA.

▪ One way to reduce the gap between basic and clinical studies on the research continuum would be for basic investigators to move more toward high throughput screening and the identification/validating of targets, while more clinically-oriented investigators move toward bringing their observations in humans to bear on laboratory studies. If each set of scientists moves a bit closer toward the other's central work focus, bridges would be built and gaps eliminated. The NIH Intramural Program may be well-suited to such bridging efforts, and to the development of a model prioritization process to facilitate effective resource allocation decisions.

▪ Thought should be given to maximizing the use of existing resources. For example, NIH studies of the high rates of type 2 diabetes among the Pima Indians have resulted in cohorts of patients and raw data that would be an extremely useful research resource for the broad diabetes research community.

Dr. Spiegel and Dr. Staten underscored the NIDDK's need for continuing Council input and guidance in setting priorities for translation research. As one example of the Institute's efforts to maximize its investments and speed translation, Dr. Staten and Dr. Briggs described how, with Council input, the NIDDK established a central repository for housing biologic samples from Institute-funded clinical trials, both completed and prospective. Led by Dr. Rebekah Rasooly, this repository will make samples readily accessible to scientists. In the future, banked samples could be used for the identification of new potential biomarkers to speed the process for validating targets for drug development. The repository has three sections: genetics, data, and biologic samples. Publicly available data from the DCCT is a similar resource, as is the NIH-supported hepatotoxicity drug network. The NIDDK hopes to be able to work with the FDA and industry--in synergistic, non-duplicative ways--to optimize these and other efforts. This

approach is consistent with the NIH Roadmap's emphasis on translation research, and with one of its key themes: Re-engineering the Clinical Research Enterprise.

Identifying Biomarkers

▪ Identification of biomarkers is considered a high-priority area for translation research. To identify biomarkers in obesity, for example, food-intake patterns must be quantified and qualified. An initiative led by the National Heart, Lung, and Blood Institute, *Bioengineering Approaches to Obesity and Nutrition*, will include small businesses and the engineering community to ensure the acquisition of more precise and quantitative measures of nutrition. In a similar vein, finding a biomarker for fibrosis could be a trans-institute translation initiative relevant to liver, kidney and lung diseases.

Fostering Collaboration

▪ The need for collaboration is critical and urgent. Delays in or the absence of collaboration are costly in terms of human life, time, and dollars. Sometimes studies are duplicated because existing data and resources are not shared. Such duplication results in delays in the development of needed therapies and the expending of energy and money that could have been used more effectively. The need for collaboration spans all levels of the research community, the NIH Institutes, the FDA, and industry.

▪ Limited resources--a problem not easily solved--could be addressed by synergies among organizations which are researching different aspects of the same diseases. The leveraging of resources would benefit all participants. For example, research to develop better models of the metabolic syndrome could be a cross-cutting effort of the NIDDK, the National Heart, Lung, and Blood Institute, the National Institute on Aging, and other NIH components.

▪ Clinical research is often conducted without considering what information beyond basic biological information about patients would be needed by the FDA and industry to arrive at the approval of new treatments and methods. Early interchanges with the FDA and the pharmaceutical industry could provide information to the clinical investigator, who could, in turn, provide input to the FDA and industry that would expedite the development of therapies.

▪ Within the NIH Institutes, regular interchanges could help to accelerate the timeframe for developing surrogate markers (which can take about 20 years from the first observation to validation to use in a clinical setting). Time could be saved if basic and clinical investigators get together sooner, rather than waiting for an observation, and then waiting several years for the marker to be applied clinically. Once collaborations have been established, cross-fertilization (the mutual exchange of scientific ideas and data) is possible.

Dr. Spiegel pointed to an example of collaboration and cross-fertilization—angiogenesis research. This research area was the topic of a recent meeting that included representatives from the NIDDK; the National Cancer Institute; the National Eye Institute; the National Heart, Lung, and Blood Institute; the National Institute of Neurological Disorders and Stroke; and others. Angiogenesis advances in the cancer field are highly relevant to diabetes complications and other diseases; hence, this meeting could lead to a synergistic trans-institute angiogenesis research

program. Likewise, Dr. Spiegel noted that meetings have spurred synergistic relationships between the NIDDK and the FDA with respect to facilitating the development of therapeutics for both diabetes and Crohn's disease. Such meetings help to pinpoint roadblocks to translational research and collaboration, and identify steps that can be taken to remove or reduce them. Dr. Spiegel called attention to a recent FDA report: *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,* which underscores the need for collaboration between government and the private sector. (This document can be accessed at: http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). As a case-in-point, Dr. Spiegel reported an estimate from a pharmaceutical company that puts the cost of clinical failures of drugs due to liver toxicity alone at over $2 billion in the last decade, money that could have been directed toward successful new product production. This example shows that it is very much in the interest of industry as a whole to work with the NIDDK and the FDA, so that existing data can be benefically accessed. Although competitive issues may arise, the resulting life-sparing and cost-saving opportunities would advance the goal of better patient care.

Dr. Spiegel noted yet another example of research synergy in a forthcoming paper in *Nature Medicine*, already described in the popular press. This paper reports that--when researchers induced endothelial apoptosis in adipose tissue of obese rodents--fat deposits could be reduced by as much as 30 percent--apparently with no untoward effects to the animal. Thus, an issue of fundamental importance to the cancer research community has led to a dramatic result in the study of obesity.

Investigating Extreme Phenotypes in Humans

- For some diseases, the focus on extreme phenotypes in humans is helpful for providing insights into underlying disease physiology. However, because the extreme phenotypes are often so serious, first-order relatives are sometimes a better group of research patients for gaining insights into the genetics and mechanisms underlying the disease being investigated.

Communicating Information about the NIH Review Process and Research Priorities

- It is important to keep study section members who perform NIH peer review abreast of current NIH policies so that applications proposing translational research will not be disadvantaged. Peer reviewers play key roles in disseminating information about NIH policies, directions, and priorities to their institutions and to the broader research community. The review panel orientation is an important means of keeping them informed, and reminding them that the NIH is accountable to the Congress and to the public for improving human health. *[Dr. Hammond explained that, currently, there is an NIH-wide effort to clarify guidelines for reviewing the traditional research project grant applications (R01s), which are reviewed through the NIH Center for Scientific Review rather than directly by the institutes. In contrast, grant applications submitted in response to Requests for Applications (RFAs) are reviewed through the Institute's Review Branch.]*

VII. ADJOURN FOR LUNCH

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

VIII. 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, May 27, 2004, from 8:00 to 9:30 a.m.

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

X. FOLLOW-UP FROM SUBCOMMITTEE DISCUSSIONS ON TRANSLATIONAL RESEARCH

Dr. Spiegel reconvened the open session of the full Council at approximately 10:00 a.m. on Thursday, May 27, 2004.

Council Subcommittee on Digestive Diseases and Nutrition: Dr. Eckel presented a summary of the Subcommmittee's discussion on translational research. The Subcommittee reviewed issues related to other ICs as well as to the NIDDK, including the definition of the translational model, training of young scientists, and surrogate markers. Key points included:

- The translational model needs to be modified (or redefined) to consider the bidirectional nature of translation research by including "bedside-to-bench," and "population-to-bedside," in addition to the current "bench-to-bedside" focus.

- It is also important to look at individuals who are engaged in translation efforts to see the types of research training they have had, and whether they have an M.D., Ph.D., or a combined degree. A research "team" approach has advantages in promoting translational research. However, there are uncertainties about how the NIH might make awards to teams rather than to individuals; how the team concept might affect the career advancement of young scientists striving for promotion and tenure; and how institutions might take into consideration the contributions that an individual makes as a team member of a research project.

- Recognizing that translational research is, in part, mechanistic, researchers need to search for opportunities to modify disease processes while they study underlying disease mechanisms. Development of surrogate markers is a critical component of translational research, and could provide beneficial short-term outcomes that can be used instead of hard endpoints for clinical research studies. Short-term studies using an intervention over a period of months to a year or two could be very effective in validating therapeutic approaches to disease entities. Modification of the incidence and/or progression of disease could be a surrogate endpoint.

- In discussing translation, two specific examples considered by the Subcommittee were liver disease and obesity research. In both cases, planning activities include the development of a matrix that juxtaposes short, intermediate and long-term goals with the degree of difficulty in achieving them (low, medium or high risk research). An Action Plan for Liver Disease

Research, currently in development, is identifying specific goals for topic areas--such as autoimmune liver diseases. These goals are measurable along the pathways of discovery and translation. Similarly, planned obesity research initiatives include identification of biomarkers, development of methodologies related to energy balance, and the application of genomics, metabolomics and proteomics to understanding the pathogenesis of obesity. Leanness is not a major focus of research, but that may be significant in discerning important aspects of obesity. Long-term, high-risk goals would include the development of effective methods for obesity prevention and treatment.

▪ It is important to note that translation research can be biotechnology-driven rather than hypothesis-driven (e.g., proteomics research). Whatever the impetus, the NIH peer review system needs to recognize the difficulties and payoffs of translation research and clinical research generally.

▪ The process of choosing important goals for strategic planning includes developing a portfolio analysis of important disease areas, examining the current gaps in knowledge, and ultimately, determining a series of priorities for translational research areas for the Institute as a whole.

Dr. Hammond noted that the NIH is looking to clarify the standard review criteria for clinical/translational research so that it is not disadvantaged. In response to a question, he also noted that the congressionally-established Loan Repayment Program continues to be well-subscribed, that an evaluation of its results is being planned, and that he will report on the program at the next Council meeting.

Council Subcommittee on Kidney, Urologic, and Hematologic Diseases: Dr. Vaughn reported on the Subcommittee's review of translation in six specific disease programs which represent about 30 percent of the Division's funds. The Subcommittee's key points were:

▪ Research needs to be bi-directional, with movement not only from the lab to the clinic, but also with feedback from clinical observations to the bench. For example, data and tissue samples from well-characterized clinical trial cohorts--such as those which participated in the NIDDK's Medical Therapy of Prostatic Symptoms (MTOPS) trial to assess different therapies for benign prostatic hyperplasia--can provide a wealth of information for laboratory studies.

▪ Basic biological definitions of diseases are required for translational research to move forward. As an example, although there are more effective approaches to prevent acute renal failure today than in the past, once the disease presents, it is heterogeneous and difficult to treat. Researchers are not certain that existing animal models really reflect the basic biology of the disease. Clearly, the most useful animal models will replicate what is seen clinically.

▪ Surrogate or intermediate markers of disease could be useful in many ways. For example, they could help provide insights into diseases that develop over long periods of time, such as end stage renal disease (ESRD) as a complication of diabetes. A marker for interstitial cystitis would not only help follow a patient's prognosis, but also help define the epidemiology of the disease.

However, markers developed in one laboratory need to be replicated in others, and some standard or reference laboratories may be needed.

▪ Advances in orphan diseases may encourage pharmaceutical companies to independently develop therapies based on NIH-supported research. The NIDDK has been successful with research on treatments for iron overload in thalassemia, and with treatment with therapeutic agents of dietary modification in oxalosis. Perhaps oxalosis treatment may lead to interventions that could be useful in stone disease, and this could then be picked up by the pharmaceutical industry.

Dr. Briggs and Dr. Spiegel noted that, in translational research, "one size does not fit all." The Institute will probably have to focus on different parts of the research pipeline for different diseases, and prioritizing the research will be challenging--with the guidance of the Council.

Council Subcommittee on Diabetes, Endocrinology and Metabolic Diseases: Dr. Porte noted that three areas were discussed in the Subcommittee meeting: insulin resistance, obesity, and beta cell replacement for the treatment of diabetes. Initially, the group looked for similarities and differences among the three areas to determine the issues, and the processes that could be encouraged using currently available resources. The Subcommittee noted the following:

▪ In the areas of basic biology and the development of pathways, the NIH has made substantial investments in increasing the knowledge base related to syndromes and diseases, has been successful in carrying out this research, and has made the results readily available.

▪ There exists a history of problems with the application of animal models to human diseases. The value of having animal models that replicate human diseases is particularly high, because researchers can then select from a wide variety of targets and move forward in developing and/or testing new therapeutic approaches.

▪ It is advisable for the NIH to invest in the development of better animal models. This is something the NIH can do, but that industry traditionally does not. Within industry, there is the belief that animal models are so limited that it is necessary to proceed quickly from model systems to short-term phase I human trials to see if there is a possibility of any proof-of-principle for the compound under development. This haste can lead to poor outcomes if the phase I data are not correctly interpreted or if the model is not representative of the disease.

▪ The NIH should focus on development of pathophysiological understanding of disease in human beings. This is particularly important for complex conditions such as the metabolic syndrome. To develop and test therapeutic agents successfully, researchers need to do studies in homogeneous groups of patients, whose conditions are well-characterized.

▪ The NIH has played a seminal role in the development of surrogate outcome measures, which are particularly useful in clinical research studies that must be of a limited duration. The NIH should build such surrogates into the clinical trials it funds.

▪ Productive interactions with industry need to be encouraged. For example, industry might become interested in investing in beta cell replacement research if—assuming that there are reductions in the need for immunotherapy—such research might apply to type 2 diabetes patients who take insulin--and not only to the more limited population of type 1 diabetes patients. The further along a product is in the pipeline, the risk of pursuing it is diminished, and it may become possible to pick up additional collaborators or investors.

In discussion, it was noted that there are different types of opportunities to interact with industry at different points in the translation pipeline. Moreover, there is an enormous amount of biological information obtained in industry-funded studies which would be useful to academic and government scientists, but to which they do not have access. With respect to training, it was suggested that the NIDDK and some of the professional societies explore whether new flexibilities in training now permitted by the American Board of Internal Medicine might be used for translational training. Dr. Spiegel also noted that the NIH intramural program is considering ways in which it can bolster translational research training. By the conclusion of the discussion period, it became clear that there were many common themes struck by the Council Subcommittees, many of which echoed Dr. Staten's presentation. They included recommendations to:

- Modify the current "bench-to-beside" model so that it is bi-directional.
- Develop biomarkers that can facilitate progress in translation research over a shorter timeframe.
- Develop more and better surrogate outcomes that can be used in clinical trials.
- Support specific research training programs and other incentives to attract talented individuals to clinical investigation.
- Garner industry support, particularly for orphan diseases.
- Promote public-private partnerships.
- Develop better animal models.
- Attain a better understanding of human disease.

XI. REPORT FROM THE NIDDK DIRECTOR
Dr. Allen Spiegel

Appropriations Update

Appropriations hearings focused on the FY 2005 President's budget request $28,757,000,000 in budget authority for the NIH, an increase of 2.6 percent NIH-wide over the FY2004 enacted funding level. The NIH Roadmap Initiative was featured in the written testimony of Dr. Zerhouni and the Institute and Center Directors.

On April 22, 2004, the Labor/HHS appropriations subcommittee with jurisdiction over the NIH held a hearing on NIH management--both corporate management and scientific portfolio management. The NIH Director, Dr. Elias Zerhouni, was the principal witness, with supporting testimony given by Dr. Story Landis, Director, National Institute of Neurological Disorders and Stroke, and by Dr. Spiegel. In his testimony, Dr. Spiegel noted that the NIH priority-setting process includes such considerations as the burden of disease, scientific opportunity, stakeholder

input, and scientific merit as determined by the NIH peer review system. He presented examples of NIDDK disease-specific portfolio management with respect to research on Crohn's disease and polycystic kidney disease. He also discussed portfolio management for research areas that traverse NIH Institutes and Centers, citing as an example the recent trans-NIH obesity research planning effort, which he leads along with Dr. Barbara Alving, Acting Director, National Heart, Lung, and Blood Institute. Dr. Spiegel's written testimony can be accessed at: http://www.niddk.nih.gov/federal/planning.htm.

Update on the NIH Roadmap

As discussed at previous Council meetings, the Roadmap provides a framework for research initiatives the NIH must do, but which no single Institute or Center can do alone. Through the Roadmap, the NIH as a whole can optimize its entire research portfolio by addressing important cross-cutting areas that are not specific to any single Institute or disease. Investments in such research can benefit the entire research community, as NIH components coalesce to promote progress. The three main themes of the Roadmap are: (1) New Pathways to Discovery, (2) Research Teams of the Future, and (3) Re-engineering the Clinical Research Enterprise. The extent of Roadmap funding was discussed at a recent meeting of experimental biologists, which Dr. Zerhouni addressed, along with Dr. Spiegel and others. With all NIH components contributing funding, Roadmap efforts now represent approximately 0.8 percent of the NIH annual budget. Currently, it is estimated that a total of $2.1 billion will be expended on Roadmap efforts through FY 2009, which will represent less than 1.0 percent of the NIH budget for that period.

The NIDDK is administrative lead on three Roadmap initiatives: metabolomics technology development, training for a new interdisciplinary research work force, and short programs for interdisciplinary research training. These initiatives will be brought to the Council for review. Council's input will also be sought on two initiatives specific to the major Roadmap theme of Re-engineering the Clinical Research Enterprise. One initiative involves creating regional centers that would provide resources to investigators beginning translational research and would potentially build on existing General Clinical Research Center networks. A workshop on this topic will be held on July 16, 2004, in Bethesda, MD. The other initiative involves making contract resources available to pilot pre-IND (Investigational New Drug) development. Dr. Briggs, the NIDDK liaison to the NIH Roadmap effort, urged Council members to visit the website for more information at: http://nihroadmap.nih.gov.

REPORT FROM THE NIDDK DEPUTY DIRECTOR

Dr. Griffin Rodgers

Update on NIH Conflict-of-Interest Policies

Dr. Rodgers presented an update on NIH conflict-of-interest (COI) policies, which have been a focus of both media and congressional attention. On December 8, 2003, an article in the *Los Angeles Times* suggested shortcomings in existing policies. In recent months, the Oversight and Investigations Subcommittee of the House Energy and Commerce Committee has conducted an investigation and hearings. Dr. Zerhouni created an NIH Ethics Advisory Committee (NEAC) to review ongoing and future external activities, and established a Blue Ribbon Panel to review

existing policies. The panel was chaired by Dr. Bruce Alberts, President, National Academy of Sciences; and Mr. Norman R. Augustine, Chairman, Executive Committee, Lockheed Martin Corporation. (http://www.nih.gov/about/ethics_COI_panelreport.pdf). (Note: Subsequently, on June 22, 2004, Dr. Zerhouni gave congressional testimony in which he announced that he would seek "a major reform of the Agency's ethics program by requesting restrictive rules and by seeking to increase the public availability of information related to outside activities with industry." http://www.nih.gov/about/director/062204zerhouni_COI.pdf)

XII. REPORT FROM THE NIDDK INTRAMURAL RESEARCH PROGRAM

Dr. James E. Balow
Clinical Director
NIDDK Division of Intramural Research

Dr. Balow announced the completion of the Mark O. Hatfield Clinical Research Center (CRC), the largest hospital in the world dedicated to clinical research. The CRC will also house the greatest number of patients with orphan and rare diseases and will serve as the Nation's major training center for clinical investigation. It will also offer an unparalleled confluence of basic and clinical researchers, thus providing an ideal venue for translational research. The CRC features four wings dedicated exclusively to inpatient care. One wing will be devoted to the NIH's intramural obesity research initiative, an initiative for which the NIDDK has primary responsibility. This initiative flows from the Strategic Plan of the NIH Obesity Research Task Force, which is co-chaired by Dr. Spiegel and by the Acting Director of the National Heart, Lung and Blood Institute, Dr. Barbara Alving. The goal of the intramural initiative is to advance knowledge on the causes, pathophysiology, prevention, and treatment of obesity and its multi-system comorbidities. Patient-oriented, bi-directional, translational research will be at the center of these efforts, which will span multiple institutes and disciplines. Likely topics for intramural obesity research at the CRC include genetic disorders, childhood obesity, obesity in minorities, and morbid obesity. The centerpiece of this research unit will be a specialized metabolic chamber for precise measurement of energy balance. A DEXA scan, a mass spectrometry isotope laboratory, a clinical physiology laboratory, and a behavioral unit will also be available through specialized core facilities. Exercise facilities, a computerized vending machine, and a metabolic kitchen are also available.

Obesity research and other components of the NIDDK intramural research program will undergo a Blue Ribbon Panel review led by Dr. Lee Lindberg, Chair of Pharmacology at Vanderbilt, beginning June 2, 2004. The anticipated scope of the review includes: Investigation of organization and management, balance within the portfolios of basic and clinical research projects, space and resource allocation decisions/prioritizations, research training and career development activities, and recruitment.

Discussion

Discussion topics included the importance of overcoming logistical barriers that hinder collaborations between intramural and extramural scientific communities; potential applications

of obesity research at the CRC, including applications to diabetes; and the availability of imaging technology with the capacity to isolate individuals weighing over 300 pounds. Council members also inquired about the requirements for acquiring laboratory space at the CRC and the availability of fellowship opportunities. Laboratory space at the CRC is allocated on the basis of the vitality of the proposed research, co-localization, and individual preferences.

XIII. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1410 grant applications, requesting support of $314,433,031 were reviewed for consideration at the May 26-27, 2004 meeting. Funding for these 1410 applications was recommended at a level of $314,433,031. Prior to the Advisory Council meeting, an additional 243 applications requesting $60,883,378 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the requested levels. The expedited concurrence actions were reported to the full Advisory Council at the May 27, 2004 meeting.

XIV. ADJOURNMENT

Dr. Spiegel thanked the Council members for their attendance and efforts. There being no other business, the 165th meeting of the NIDDK Advisory Council was adjourned at 12 Noon, May 27, 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