Meeting Minutes
Department of Health and Human Services
Public Health Service
National Diabetes and Digestive and Kidney Diseases
Advisory Council
September 18-19, 2002

I. CALL TO ORDER

The NIDDK Director, Dr. Allen M. Spiegel, called to order the 160th National Diabetes and Digestive and Kidney Diseases Advisory Council meeting on September 18, 2002, at 8:31 a.m. in Conference Room 6, Building 31C on the NIH campus in Bethesda, MD. Dr. Spiegel made several announcements. *Ex officio* Council member Dr. Daniel Porte, Jr., has been named the recipient of the 2002 Novartis Award for Diabetes Research. Council member Dr. C. Ronald Kahn has been awarded this year's J. Allyn Taylor International Prize in Medicine, along with two other NIDDK grantees, Dr. Graeme I. Bell of the University of Chicago and Dr. Ake Lernmark of the University of Washington.

Terms are expiring for five Council members whose service has been enormously helpful to the NIDDK: Dr. Jeffrey Gordon, Dr. C. Ronald Kahn, Dr. John McConnell, Dr. Robert Schrier, and Dr. Rena Wing. Dr. Spiegel announced that the nomination slate for the 2002 appointments to the Council had been approved; new members will begin their terms of service at the February 2003 meeting. He introduced the new Council members as follows:

Joining the Kidney, Urologic and Hematologic Diseases Subcommittee are: (1) Dr. Robert J. Alpern, Dean of the University of Texas Southwestern Medical School in Dallas and immediate past president of American Society of Nephrology; and (2) Dr. Edwin Darracott Vaughan, Jr., James J. Colt Professor of Urology at Joan and Sanford I. Weill Medical College of Cornell University. Dr. Vaughan also serves as Attending Urologist-in-Chief at the New York Presbyterian Hospital and Attending Surgeon to the Division of Urology at Memorial-Sloan Kettering Cancer Center in New York City.

Joining the Digestive Disease and Nutrition Subcommittee are: (1) Dr. Raymond N. DuBois, Jr., Director of Gastroenterology, Hepatology and Nutrition, and Associate Director of the Vanderbilt-Ingram Cancer Center, and Mina C. Wallace Professor of Medicine and Cell Biology at Vanderbilt University Medical Center in Nashville, Tennessee; and (2) Dr. Robert H. Eckel, Charles Boettcher Professor of Medicine and Professor of Physiology and Biophysics at the University of Colorado Health Sciences Center in Denver, Colorado, and Director of the University's General Clinical Research Center.

Joining the Diabetes, Endocrinology and Metabolism Subcommittee is Dr. Linda A. Sherman, Professor, Department of Immunology, Scripps Research Institute in La Jolla, California.

Dr. Spiegel reported the recent death of a former Council member, Dr. Walter Mertz.

Several new staff appointments have been made: Dr. Joyce Hunter, Deputy Director of the Division of Extramural Activities; Dr. Elizabeth Wilder, program director with the Division of Kidney, Urologic, and Hematologic Diseases; Dr. Paul Rushing, scientific review administrator in the Review Branch; and Dr. Neal Musto, Deputy Chief of the Review Branch.

Three new reports will help guide NIDDK program planning efforts: *Conquering Diabetes* -- a scientific progress report on program efforts, research advances and opportunities since issuance of the 1999 "Strategic Plan of the Diabetes Research Working Group;" a report of an ad hoc advisory panel on the Special Statutory Funding Program for Type 1 Diabetes Research; and a strategic plan of the Bladder Progress Review Group.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Mr. David Baldridge
Dr. Edward J. Benz, Jr.
Dr. Jose Caro
Ms. Mary E. Clark
Dr. Richard H. Goodman
Dr. Jeffrey I. Gordon
Hon. Levan Gordon
Dr. Edward W. Holmes
Dr. C. Ronald Kahn
Dr. Carolyn Kelly
Dr. James W. Kikendall (*Ex officio*)
Dr. Earl Harrison (*Ex Officio*)
Dr. Sum P. Lee
Dr. John McConnell
Dr. Daniel Porte, Jr. (*Ex Officio*)
Dr. Sandra Puczynski
Dr. Vicki Ratner
Dr. Robert W. Schrier
Dr. W. Allan Walker
Dr. Rena Wing

Council members absent:
Ms. Nancy Norton

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:

Karen Adams, NIDDK;
Linda Addison-Hardy, NIDDK;
Beena Alkolkar, NIDDK;
Syed Amir, CSR;
David Badman, NIDDK;
Michele Barnard, NIDDK;
Terry Bishop, NIDDK;
Rochelle Blaustein, NIDDK;
Sharon Bourque, NIDDK;
Josephine Briggs, NIDDK;
Gary Brittenham, Columbia U.;
Francisco Calvo, NIDDK;
Michelle Cissell, NIDDK;
Catherine Cowie, NIDDK;
Maria Davila-Bloom, NIDDK;
Florence Danshes, NIDDK;
Jane DeMouy, NIDDK;
Devon Drew, NIDDK;
Linda Edgeman, NIDDK;
Michael Edwards, NIDDK:
Thomas Eggerman, NIDDK;
Jody Evans, NIDDK;
Patricia Evans, Masimax;
James Everhart, NIDDK;

Richard Farishian, NIDDK;
Robert Fay, NIDDK;
Carol Feld, NIDDK;
Harold Feldman, Univ. of PA;
Teresa Fitzpatrick, NIDDK;
Olaf L. Fonville, NIDDK;
Judith Fradkin, NIDDK;
Joanne Gallivan, NIDDK;
Sanford Garfield, NIDDK;
Janet Gregory, NIDDK;
Frank Hamilton, NIDDK;
Mary Harris, NIDDK;
Trude Hilliard, NIDDK;
Gladys H. Hirschman, NIDDK;
Eleanor Hoff, NIDDK;
Jay Hoofnagle, NIDDK;
Thomas H. Hostetter, NIDDK;
Ann Karen Howard, NIDDK;
Stuart Howards, NIDDK;
Donna Huggins, NIDDK;
Joyce Hunter, NIDDK;
Donna James, NIDDK;
Stephen James, NIDDK;
Scott Jenkins, The Blue Sheet;
Ann Jerkins, CSR;
Robert Karp, NIDDK;
Mary Beth Kester, NIDDK;
M.A. Khan, CSR;
Sooja Kim, CSR;
Kathy Kranzfelder, NIDDK;
Krish Krishnan, CSR;
Maren Laughlin, NIDDK;
Kim Law, NIDDK;
Todd Le, NIDDK;
Maxine Lesniak, CSR;
Barbara Linder, NIDDK;
Helen Ling, NIDDK;
Billie Mackey, NIDDK;
Saul Malozowski, NIDDK;
Denise Manouelian, NIDDK;
Ronald Margolis, NIDDK;
Winnie Martinez, NIDDK;
Michael K. May, NIDDK;
Catherine McKeon, NIDDK;
Catherine Meyers, NIDDK;
Carolyn Miles, CSR;
David Miller, NIDDK;
Nancy Miller, OSP/OD;
David Mineo, NIDDK;
Teresa Mixon, NIDDK;
Marva Moxey-Mims, NIDDK;
Christopher Mullins, NIDDK;
Neal Musto, NIDDK;
Leroy Nyberg, NIDDK;
Diana O'Donovan, NIDDK;
Elizabeth Paterson, NIDDK;
Hazel Perez, NIDDK;
Peter Perrin, CSR;
Judith Podskalny, NIDDK;
Sharon Pope, NIDDK;
Rebekah Rasooly, NIDDK;
Patricia Robuck, NIDDK;
Lakshmanan Sankaran, NIDDK;
Sheryl M. Sato, NIDDK;
Jim Scherbenske, NIDDK;
Jose Serrano, NIDDK;
Kathleen Shino, NIDDK;
Jann Sidorov, Masimax;
Betsy Singer, NIDDK;
Philip Smith, NIDDK;
Margaret Snyder, OER;
Robert Star, NIDDK;
Paul Tibbits, ADA;
Mehrdad Tondravi, NIDDK;
George Tucker, NIDDK;
Renetta Turner, NIDDK;
Dorothy West, NIDDK;
Elizabeth Wilder, NIDDK;
Susan Yanovski, NIDDK;
Charles Zellers, NIDDK

II. CONSIDERATION OF SUMMARY MINUTES OF THE 159th COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to accept the summary minutes of the 159th Council as submitted.

III. FUTURE COUNCIL DATES

Dr. Spiegel announced the proposed dates for the future Council meetings as follows:

February 19-20, 2003
June 11-12, 2003
September 24-25, 2003
February 4-5, 2004
May 26-27, 2004
September 22-23, 2004

The NIH Director, Dr. Elias Zerhouni, will address the Council at its February 19, 2003 meeting.

IV. ANNOUNCEMENTS: CONFIDENTIALITY AND CONFLICT OF INTEREST STATEMENT
Dr. Hammond

Dr. Hammond called to the Council's attention the procedures to guarantee confidentiality and to avoid conflicts-of-interest. He discussed the scope and applicability of these procedures and requested Council compliance. Members were asked to sign and return a conflict-of-interest statement. The materials furnished to Council members are privileged and are to be used for the purpose of review and discussion only during the closed portion of the meeting. The outcome of the closed portions is considered privileged and can be disclosed only by staff and only under appropriate circumstances. Council members should not respond to any direct communications they receive from applicants; they should, in all such cases, refer applicants to NIDDK staff. Council members need to leave the room when individual applications from their institutions are discussed in order to avoid an actual or perceived conflict-of-interest. They do not need to do so for *en bloc* actions. Under new procedures, Council members from multi-site campuses do not need to leave the room when applications from sites separate from their own specific sites are discussed. An updated document regarding multi-campus institutions of higher education applies to both state and private institutions. If Council members have an appointment to only one of the campuses with a disqualifying financial interest on the other campuses, they would not have a conflict in reviewing the other sites.

V. REPORT FROM THE DIRECTOR
Dr. Spiegel

Dr. Spiegel mentioned that Dr. Elias Zerhouni had assumed his official duties as Director of the National Institutes of Health on June 1, 2002. He recently appointed Dr. Thomas R. Insel, formerly Director of the Center for Behavioral Neuroscience at Emory University, as the Director of the National Institute of Mental Health. He appointed Dr. Tim Kai Lee, formerly Director of the Alcohol Research Center at Indiana University, as the Director of the National Institute of Alcohol Abuse and Alcoholism.

Road Mapping Process: Dr. Zerhouni has initiated a leadership process (informally called a road map process) in consultation with Institute and Center Directors, along with expert representatives from the extramural and intramural communities. Through this process he is developing several cross-cutting themes that have great importance with respect to the ability of the NIH research enterprise to have the greatest positive effects on human health. Through a series of meetings, Dr. Zerhouni has identified promising, cross-cutting areas of need and opportunity, and the most significant roadblocks to progress, which the NIH will address over the next 3 to 5 years. Major themes include clinical research issues, research resources such as critical infrastructure issues, new directions for research, and interdisciplinary research. Major themes to emerge are the importance of studying our own species at a level of molecular specificity previously reserved only for model organisms, and the challenge of maintaining bi-directional communication channels between fundamental molecular discoveries and the application of these discoveries to the bedside and to patients. Although the blueprint of our own genome provides extraordinary opportunities, the research enterprise cannot simply continue as "business as usual." It will necessitate an unprecedentedly high level of institutional planning at universities in order to encourage greater

patient-oriented research and to foster the "bench-to-bedside" flow of research discoveries. The high level of planning required to promote these objectives offers an enormous perceived opportunity for energizing the research and planning communities, as well as a means for responding to the Congress regarding the ways in which the NIH has, and continues to, make productive research investments.

Stem Cell Task Force: Dr. Zerhouni has announced the formation of a National Institutes of Health Stem Cell Task Force to be headed by Dr. James Battey, Director of the National Institute of Deafness and Communication Disorders. The mission of this 14-member Task Force is to evaluate barriers and roadblocks to the conduct of stem cell research and to develop options for Dr. Zerhouni and the Institute Directors for the conduct of this research. The NIDDK has been proactive in this area, which traverses the various programmatic interests of the Institute. One example is a linked series of stem cell genome anatomy projects that derived from the recommendations of the trans-NIDDK planning groups on genetics, genomics, bioinformatics, and on stem cells and developmental biology.

RFAs for Stem Cell Research: Dr. Rebekah Rasooly, the Director of the Genetics and Genomics Program of the Division of Kidney, Urologic and Hematologic Diseases, reported on a new consortium created through two RFAs. These RFAs are based on one of the major recommendations of the Stem Cell Working Group: to establish genome anatomy projects that would create catalogs of the genes expressed in stem and progenitor cells. The first task facing the new internal trans-NIDDK genomics working group was to decide how to implement this recommendation. The result was initiation of two Requests for Applications (RFAs): the first aimed at hematopoietic stem cells, the second at other stem cells for other tissues of interest to NIDDK researchers. Applicants were asked to describe the tools and methods they would use to catalog gene expression, and how they would provide bioinformatics approaches that would ensure user-friendly outreach to, and access by, the research community. Through the peer review process, a total of seven outstanding projects were identified, one of which proposed to use human embryonic stem cells, in accordance with NIH criteria, to determine whether these cells could be induced to adopt the fate of the organ that was being studied. Other efforts will seek to determine the genes that are expressed in specific stem cell lineages under study, and to define the unique properties that constitute the essence of a stem cell. The funded investigators will work together as a consortium, with a steering committee to promote data collection and analysis in ways that will ensure interoperability.

Dr. Spiegel commented that the stem cell research is relevant to a wide spectrum of NIDDK interests, including research on hematopoiesis, bone formation and remodeling, the prostate and other parts of the urologic system, and the liver and general gastrointestinal system. The Beta Cell Biology Consortium--discussed at previous meetings--represents a parallel effort and includes work in the form of pilot and feasibility projects. Consortium goals will need to be balanced with requirements in academic institutions. There is a new and growing impetus for a high level of interaction and sharing between investigators at different institutions. These changes emphasize the importance, not only of interdisciplinary research within institutions, but also the necessity of cross-institutional collaboration and cooperation. A question was raised regarding whether political and social issues were keeping talented researchers away from this stem cell research. The general

view among the Council members is that a pool of talent is currently available, but that training initiatives would be helpful to propel this field of research.

The Council discussed the implications of immediate sharing of data. The fiscal 2003 budget may allow investigators who already have R01 grants to join various consortia where there will be increased opportunities for cross-fertilization and sharing of data. Dr. Spiegel mentioned the dynamic tension created by multi-authored papers and the effect that data sharing may have on opportunities for academic promotion. A comment was made that this was a problem of particular importance in bioinformatics. Dr. Spiegel agreed wholeheartedly and stated that the roadmapping initiative was considering this problem extensively. Clinical trial data in particular have differences in end points and other aspects of study that make interoperability difficult. Meaningful progress to address these problems will require substantial efforts. The process of achieving data standardization will likely be similar to completing a giant jigsaw puzzle, with the picture emerging gradually over time.

VI. REPORT FROM THE DEPUTY DIRECTOR
Dr. Rodgers

Dr. Rodgers reported that one of Dr. Zerhouni's first actions as NIH Director was to form a committee to report to him about the future of the K30 program. The purpose of K30 grants is to improve skill sets for new clinical investigators by giving them sound didactic training in research design, data collection methods, data analysis, and requirements for human subjects protection, and thus facilitate their success in obtaining funding for R01 grant applications. It had previously been observed that, owing largely to a perceived lack of these skills, these investigators were not faring as well with their R01 grant applications as their basic science colleagues. (The K12 program, by contrast, was largely directed either at particular disorders or disease topics.) The K30 program is an NIH-wide initiative, administered by the National Heart, Lung, and Blood Institute. The first year, 17 Institutes signed on, and a total of 35 awards were made. The success of the program led six additional Institutes to join the second year, during which 20 more awards were made. Dr. Zerhouni's committee recommended continuation of the existing program to permit completion by the original cohort, and then reissuance of the program solicitation, with funding for a new cohort estimated to start in FY 2005. Some discussion centered on the current failure of the K30 programs to pay stipends; other comments focused on the fact that many of the institutions receiving K30s are linked to NIH General Clinical Research Centers.

Dr. Rodgers reported briefly on an Institute of Medicine committee that, at the directive of the Congress, is examining the organizational structure of the NIH. With respect to organizational issues, a Council member asked how effectively NIH components are collaborating. Dr. Spiegel noted several examples of excellent coordination and collaboration. The July 2002 meeting of the statutory Diabetes Mellitus Interagency Coordinating Committee, which focused on macrovascular complications of diabetes, featured an opening address by Dr. Claude Lenfant, Director of the National Heart, Lung and Blood Institute. Other examples were given. During discussion, it was noted that multidisciplinary and trans-NIH collaborations can help to leverage research funding. A question was raised about the NIDDK's potential involvement with other NIH components in research on biodefense. Dr. Spiegel responded that Institute staff members have identified food-borne illness and food safety as NIDDK research areas that might be relevant to this topic.

Program staff has framed some tentative initiatives, now in preliminary draft form, which could be shared with Council members if they so wished.

VII. NIH EXTRAMURAL LOAN REPAYMENT PROGRAMS FY 2002 Results and FY 2003 Plan

Dr. Hammond

Dr. Hammond said that final figures on the Loan Repayment Program (LRP) for FY 2002 are now available. The focus of this statutory program is the recruitment and retention of highly qualified professionals, both in pediatric research and in clinical research. Because initially there was no way of forecasting the number of applications that would be submitted, there was no way to generate models of success rates. The NIH funding target for the first year of this program was established in relation to each Institute or Center's funding for clinical research, resulting in a target of $2 million for the NIDDK for both programs. The number of applications each Institute or Center received was not necessarily consistent with its funding target, and this resulted in the transfer of funds across Institutes. Of the 63 applications submitted to NIDDK, the Institute used the targeted $2 million of its own funds to make 22 awards for clinical research and 16 awards for pediatric research. However, with funds provided by other NIH components, the NIDDK was able to make an additional eight awards for the clinical program, and an additional nine for the pediatric program. The success rate of applications was 65 percent for clinical researchers and 55 percent for pediatric researchers. However, these rates were augmented by the financial contributions of other NIH components to become 88 percent for clinical researchers and 86 percent for pediatric researchers. All applications had to document NIH grant support. Award recipients ranged from junior to senior, holding T32, F32 or R01 grants, though few awardees held the latter. Importantly, applicants needed to have a "qualifying" amount of educational debt. Dr. Spiegel pointed out that a significant characteristic of the loan eligibility requirement was the ratio of eligible debt to current salary. The correlation between salary level and seniority contributed to the pipeline being front-loaded.

Looking ahead to FY 2003, Dr. Hammond reported that the overall funding target would be twice that for FY 2002, with some differences in eligibility requirements. In FY 2003, individuals with non-NIH research support will be eligible to apply. Clear review criteria will ensure that applicants who hold NIH grants compete on a level playing field with those funded by foundations, voluntary health organizations or other sources. The hope is that letters of recommendations will provide a solid indication that the applicants have a strong interest in a career in clinical or pediatric research. The last quarterly payment of the award may be the best opportunity to gain insights on each awardee's career plans.

VIII. SCIENTIFIC PRESENTATIONS - VISIONS OF FUTURE RESEARCH

At Dr. Spiegel's request, four Council Members--Drs. Gordon, Kahn, McConnell, and Schrier--whose terms are expiring this year presented their "visions" of future research in their respective fields. (Dr. Rena Wing, who is also departing from the Council, made a similar presentation at the May 2002 meeting; see previous minutes.) Summaries of each of their presentations are appended.

IX. ADJOURN FOR LUNCH

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

X. SUBCOMMITTEE MEETINGS

At approximately 1:15 p.m., separate meetings were convened of the Diabetes, Endocrinology and Metabolic Diseases; the Digestive Diseases and Nutrition; and the Kidney, Urologic and Hematologic Diseases.

Subcommittee meetings reconvened on September 19 at approximately 8:00 a.m. and continued until approximately 9:45 a.m.

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

At approximately 9:50 a.m. on Thursday, September 19, 2002, Dr. Spiegel reconvened the open session of the full Council.

XII. REPORTS FROM EXTRAMURAL DIVISIONS

A. Division of Kidney, Urologic, and Hematologic Diseases
Dr. Briggs

Dr. Briggs recognized this year's recipients of the Lasker Award for Clinical Medical Research, Dr. Willem J. Kolff of the University of Utah and Dr. Belding H. Scribner of the University of Washington. They received the award for the development of renal hemodialysis, an advance that revolutionized the treatment of acute and chronic kidney failure. Dr. Scribner is a former NIDDK grantee.

Update on the National Kidney Disease Education Program (NKDEP): Dr. Briggs turned to Dr. Thomas Hostetter, Director of the NKDEP, for an update. The NIDDK believes that a national education program aimed at reducing the burden of kidney disease is both timely and necessary, given that kidney disease is a large and growing health problem, that effective testing and therapies for this disease exist, and that these tests and therapies are inadequately applied. In 2000, for example, about 100,000 people developed kidney failure; 300,000 end-stage renal disease (ESRD) patients were undergoing dialysis; and an estimated 75,000 received kidney transplants. The economic cost estimates for treating ESRD with dialysis or transplantation in the year 2001 is about $20 billion--with most of those costs incurred by the Federal Government. It is projected that 170,000 individuals will develop kidney failure in 2010, and that approximately 600,000 people will be on dialysis.

A target audience of the pilot phase of the NKDEP is African Americans with hypertension, diabetes, and/or a family history of ESRD. Also targeted are primary care physicians, who are well placed to identify and treat kidney disease in its early stages. The formal launch of the program in March 2003 will involve four pilot sites: Jackson, Mississippi; Atlanta, Georgia; Baltimore,

Maryland; and Cleveland, Ohio. The NDKEP has launched a public education campaign and has opened a web site (<http://www.nkdep.nih.gov>). Advice on development of the NKDEP is provided to the Institute by a Steering Committee with representation from many parts of the kidney community, including primary care providers, nephrology groups, directors of other public education programs at the NIH (including those for diabetes and high blood pressure), and community groups. There are three working groups: (1) a group that evaluates planned actions prospectively; (2) a working group of individuals at risk for ESRD, which identifies appropriate educational materials for target audiences; and (3) a professional working group that helps reach primary care providers. The NIDDK is planning to evaluate the effectiveness of the pilot phase of this program.

Strategic Plan of the Bladder Progress Review Group (BPRG): Dr. Briggs noted that the BPRG evaluated the research portfolios of NIDDK and NIH, identified research opportunities, and defined unmet needs in bladder research. A major theme throughout the BPRG recommendations is the need for the expansion of both the scope of research and the number of investigators focusing on basic bladder research if translational and clinical studies are to have an impact. The report emphasized the importance of encouraging both basic and clinical investigators with a wide range of expertise to consider research questions relevant to bladder function and disease. Dr. Linda Shortliffe of Stanford University was the leader of the BPRG Steering Committee.

Examples of New Initiatives: Dr. Briggs described a clinical trial entitled "Complementary and Alternative Medical Therapies for Urological Symptoms (CAMUS)," which will test saw palmetto for the treatment of prostate symptoms and will be co-sponsored with the Center for Complementary and Alternative Medicine. The recently concluded MTOPS study will enter a follow-up phase during which the samples collected during the trial will be studied for molecular clues to the responsiveness of the patients to therapy. A network of investigators to study focal glomerulosclerosis in children has been established. A trans-NIH initiative is under way to develop full-length cDNAs from the model organism zebrafish.

Recent and Upcoming Meetings Sponsored by the Division: Dr. Terry Bishop, program director for careers and training, KUH, organized a 2-day meeting of K and F awardees. Dr. Robert Star led a series of similar meetings for young clinical investigators. With input from Dr. Stuart Howards and Dr. Robert Hammond, the Division is drafting a proposal for a new career award mechanism aimed at clinical investigators in procedure-intensive fields. Upcoming meetings include one on proteinuria as a surrogate marker for kidney disease, a workshop on urologic complications of diabetes, a trans-NIH workshop on recruitment of minorities into clinical trials, and a workshop co-sponsored with NHLBI on cardiovascular disease and renal disease.

B. Division of Diabetes, Endocrinology and Metabolic Diseases
Dr. Fradkin

Dr. Fradkin reported that this Council reviewed applications for Diabetes Endocrinology Research Centers and Diabetes Research and Training Centers, for which a total of eight competing continuation applications were received. The DEM SubCouncil recommended continued funding for six competing continuation applications and funding for four new centers. In addition,

Dr. Fradkin highlighted several of the RFAs made possible by the Special Statutory Funding Program for Type 1 Diabetes Research. These fostered bench to bedside and other clinically relevant research, and efforts to attract new talent into research on diabetes.

Pediatric Endocrinology Researchers: Dr. Fradkin reported on a new initiative designed to provide research training to pediatric endocrinologists and to foster their career development. This initiative arose from a meeting in June 2001, which was jointly sponsored by NIDDK, the Juvenile Diabetes Research Foundation International, and the American Diabetes Association. Because many leading pediatric endocrinologists are retiring from research, there is tremendous concern about training the next generation, particularly when there is an epidemic of type 2 diabetes in children. An RFA spearheaded by Dr. Jim Hyde called for a combination of T32 and K12 awards, institutional awards to support the transition to an independent research career. The response to this initiative was outstanding: 13 applications were received and seven applications will be funded at Baylor College of Medicine, University of Colorado, Joslin Diabetes Center, University of Pennsylvania, Yale University, Washington University, and Children's Hospital of Pittsburgh.

Functional Atlas of Orphan Nuclear Receptors: Dr. Ronald Margolis, Senior Advisor, Molecular Endocrinology Program, described this initiative to elucidate the functional complexes through which "orphan nuclear receptors" exert their effects. These receptors, for which the endogenous ligands are not fully known, play important roles in the regulation of lipid and carbohydrate metabolism and have been implicated in diabetes and obesity. They have a role in drug metabolism, and represent targets for therapeutic drug development. The functional atlas project is a consortium of five institutions led by Baylor College of Medicine, with investigators at the Salk Institute, Duke University, UT-Southwestern, and the University of Pennsylvania. The National Institute on Aging and the National Cancer Institute are also supporting this project.

Treatment and Prevention of Type 2 Diabetes in Children: Dr. Barbara Linder, the Division's program director for Clinical Endocrinology and Diabetes Complications, described two clinical trials the NIDDK has initiated to address the epidemic of type 2 diabetes in children. One study is investigating treatment options for those already diagnosed. The second trial will develop and test a school-based primary prevention program. Both the treatment and prevention trials will include major representation of minority populations--particularly African Americans, Hispanic Americans, and American Indians who are at disproportionately high risk of developing type 2 diabetes. The Council members discussed the protocol related to treatment of children with type 2 diabetes, and particularly the combination of two medications, metformin and thiazolidinedione treatment, noting that thiazolidinediones are not yet approved in children. Dr. Linder noted that such studies are underway with pharmaceutical support and that the protocol will be carefully reviewed and monitored by a newly-created Data Safety and Monitoring Board (DSMB). Dr. Fradkin will invite Dr. Francine Kaufman, Chair of the Steering Committee for the trial, to a future meeting of the Diabetes, Endocrinology and Metabolism Subcommittee of Council to discuss the protocol and DSMB deliberations. An update on the trial will also be presented to the full Council. The prevention trial will be a population-based 3-year intervention beginning with a cohort of sixth graders, who will then continue the intervention in seventh and eighth grades. The intervention will consist of enhanced physical education in the school; a change in food service and vending machines to offer more healthful choices; and a curriculum oriented toward enhancing physical activity both in physical education class and outside of school. A pilot study will examine the

feasibility of using as the primary outcome the percentage of eighth graders with pre-diabetes in the control schools compared to the intervention schools. This study will provide the first population-based prevalence information about both pre-diabetes and diabetes in middle-school children.

C. Division of Digestive Diseases and Nutrition
Dr. Hoofnagle

Among grants received by the Division for the September Council, 56 R01s were fundable within the current payline. Of these, 26 were renewals and 30 were new grants. About 50 percent of the funded R01s were revisions.

Use of R03s and R21 Grants: The Division has actively used the mechanisms of small research grants, R03s and R21s, which are 2-year awards of $50,000 to $100,000 each. There are two types of R03 grants: a clinical grant, usually a planning grant or pilot study, and a K awardee grant, that is awarded during the fourth or fifth year of K funding. The Division hopes to be able to fund several applications including, three in training: one dealing with hepatitis C and two on stem cells. The remaining four R03 grants are clinical studies, two in pediatrics, one in inflammatory bowel disease, and one in irritable bowel syndrome. Thus, funding using this special mechanism has captured many of the important areas in digestive disease and nutrition research. Among R21 grants to be funded were two on clinical topics: one on bariatric surgery; and another on hepatitis C looking at non-invasive markers for the disease. Nine other R21s were potentially fundable, covering a wide variety of basic science topics, including intestinal stem cell research, liver stem cells, signaling and intestinal development, use of non-vertebrate models of disease, inflammatory bowel disease, and hepatitis C.

New RFAs: Coming to this Council was an RFA on Barrett's esophagus, gastrointestinal reflux disease and adenocarcinoma of the esophagus. Barrett's esophagus refers to intestinal metaplasia that occurs in the esophagus due largely to a response to chronic reflux of acid. The importance of Barrett's esophagus is that it is a pre-malignant condition. The associated malignancy is adenocarcinoma of the esophagus, one of the fastest growing tumors in the United States. This relatively under-studied disease typically affects middle-aged white men with a long history of reflux disease. An RFA for R01s and R21s was issued jointly with NCI, and 48 applications were received, of which many will be funded. A second RFA that came to this Council focused upon environmental approaches to the prevention of obesity. Two types of grant proposals were requested: pilot studies for up to $150,000 per year for 3 years; and full-scale studies for up to $500,000 annually for up to 5 years. Some 80 applications were received in this new and promising area. Funding decisions await final commitments from other Institutes that have co-sponsored this RFA. [N.B.: 16 grants were funded, totaling $2.6 million. The NIDDK funded 12; the National Heart, Lung, and Blood Institute, 3; and the National Institute of Environmental Health Sciences, 1.]

Meetings: The Division, in collaboration with the CDC, has planned a meeting on the problem of hepatitis C in prisons. Directors of prison medicine from all 50 states will meet January 25-26, 2003, to discuss common approaches to dealing with hepatitis C, which affect approximately 30 percent of male inmates of prisons. The Division is also preparing a Consensus Development Conference on Celiac Disease, which is tentatively scheduled for Spring 2004. Two recent

meetings of importance to the Division were the June 10-12 Consensus Development Conference on "Management of Hepatitis C: 2002," and an investigators workshop on Innovative Approaches to Prevention of Obesity. Both meetings have been summarized and will be published. The Consensus Conference document and proceedings will also be available on the World Wide Web.

Dr. Hoofnagle applauded the work and accomplishments of outgoing Council Subcommittee members Drs. Rena Wing and Jeffrey Gordon.

D. Division of Extramural Activities
Dr. Hammond

Items for February 2003 Council Meeting: The February Council meeting will include a report on program projects, as well as Council review and approval of revisions in operating procedures. One issue involves *en bloc* early concurrences. The NIH is encouraging and expanding this practice to provide for an orderly pacing of award processes. Another innovation is the broadening of the merit extension from the old 3-year limit to a new period of up to 5 years, which may reduce overhead costs. A similar revision in operating procedures is the delegation to staff of some additional authority for making administrative supplements and restorations.

Expanded Use of Special Emphasis Funds for Selected Program Announcements: As has been discussed previously, the Divisions identify high-priority applications outside of the payline and recommend them for Special Emphasis funding, according to established criteria. In addition, the NIDDK plans to announce a subset of active program announcements (PAs) that are of sufficiently high priority to warrant a set-aside of NIDDK Special Emphasis funds. Responsive applications within the Institute's general payline will all be paid with regular research project grant (RPG) funds. In addition, special funds will be set aside to support applications that are responsive to these PAs, but have received scores beyond the general payline. These funds will be separate from those for Requests for Applications and other initiatives. In addition to the criterion for responsiveness, applications must be of sufficiently high merit and program relevance to warrant funding beyond the announced payline. Specific PAs on the Special Emphasis list will change over time, along with the NIDDK's funding priorities.

Dr. Hammond reported the recent death of Dr. Bill Elzinger, a scientific review administrator who served in the NIDDK Review Branch for over 20 years.

XIII. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1,434 grant applications, requesting support of $444,371,054 were reviewed for consideration at the September 18-19, 2002 meeting. Funding for those 1,434 applications was recommended at a level of $443,363,187.

XIV. ADJOURNMENT

Dr. Spiegel thanked the Council members for their attendance and advice. There being no other business, Dr. Spiegel adjourned the 160th meeting of the NIDDK National Advisory Council on September 19, at 11:35 a.m.

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

APPENDIX. SCIENTIFIC PRESENTATIONS - VISIONS OF FUTURE RESEARCH

Digestive Diseases Research - Dr. Jeffrey Gordon
Professor and Head, Department of Molecular Biology and Pharmacology
Washington University School of Medicine

Dr. Gordon's presentation focused on the remarkably complex and abundant consortium of microorganisms that normally colonize the intestine, and how these microbes influence postnatal development and adult physiology. An understanding of how microbial gene products affect our biology should provide new molecular targets and strategies for preventing or treating human diseases. Our interactions in our gut microbiota may play a role in predisposing susceptible individuals to a range of diseases, such as inflammatory bowel disease, irritable bowel syndrome, obesity, and diabetes. Dr. Gordon's laboratory has taken the experimental approach of raising mice under germ-free conditions, adding back defined microbial populations, and then evaluating the impact of colonization on host gene expression and physiology. *B. thetaiotaomicron* (*B. theta*) was selected as a model gut symbiont. These studies revealed that *B. theta* colonizes the gut without evoking pro-inflammatory responses and that it is able to fortify the intestine's mucosal barrier by regulating expression of a variety of host genes, including those that encode microbicidal compounds. In addition, this organism helps direct postnatal development of the intestine's microvasculature through a pathway that involves bacteria-sensing Paneth cells. *B. theta* up-regulates genes involved in fat and carbohydrate processing - suggesting that the microbiota may influence predisposition to obesity. Using molecular methods to enumerate components of the microbiota in healthy individuals and in those with various intestinal and extra-intestinal disorders is key for developing and testing hypotheses about the contributions of indigenous microbial communities to disease pathogenesis, and for designing and interpreting probiotic experiments. Dr. Gordon stressed that to complement the human genome sequencing efforts and to define the impact of key environmental factors on our patterns of gene expression, it is important to define the genomes of our resident microbiota (collectively termed the "microbiome"). This effort would constitute a 'microbiome genome anatomy project' whose scale and scope would be analogous to the human genome project. Dr. Gordon's laboratory has just completed sequencing the *B. theta* genome revealing some of the molecular mechanisms its deploys to establish a symbiotic relationship with its host. Dr. Gordon concluded with the statement that it is critical for universities, together with federal agencies such as the NIH, to promote research and career development at the interfaces between the biological, chemical, clinical, physical, and computational sciences to attack these types of interdisciplinary problems related to human health.

In subsequent discussion, Dr. Spiegel drew attention to a very recent report and accompanying editorial in *The New England Journal of Medicine* concerning the "hygiene hypothesis." This hypothesis holds that indigenous microbes are beneficial to health in that they help to induce tolerance to environmental and food antigens. Without such tolerance, we are more at risk for development of atopic diseases. There are case reports, for example, that children raised on farms and other rural settings--where they are exposed to endotoxins from animals--have considerably lower rates of asthma. The Council discussed this hypothesis, as well as other factors that have an impact on microbial ecology and infectious diseases, including vaccination policies, and the over-use of antibiotics.

Diabetes Research - Dr. C. Ronald Kahn
Director
Joslin Diabetes Center

Dr. Kahn framed his vision of the future of diabetes research around the five extraordinary opportunities highlighted in the original report of the Diabetes Research Working Group, which he chaired. These opportunities are: the genetics of diabetes and its complications; autoimmunity and the beta cell; cell signaling and regulation; obesity; and clinical research and clinical trials of critical importance. Real progress has been made in these areas. For example, major gene clusters have been identified in type 1 diabetes. In type 2 diabetes and obesity, six genes contributing to Maturity Onset Diabetes of the Young have been identified; six monogenic forms of insulin resistance and/or obesity have been identified; and two genes for lipoatrophic diabetes have been identified. The NIDDK should maintain this research momentum, especially with respect to type 2 diabetes and its serious risk factor, obesity. Tremendous progress has been made in the area of autoimmunity and the beta cell, especially in the prevention of islet transplant rejection; in the understanding of basic mechanisms of autoimmunity; and in beta cell development and regulation. Additional efforts are needed on the prevention of type 1 diabetes, particularly identification of both the environmental triggers that initiate and accelerate autoimmunity directed at the beta cell, and the protective factors that mitigate this autoimmune process. The mechanisms of beta cell development represent another compelling opportunity. With respect to cell signaling, two important advances have been made. First, knowledge of the mechanisms underlying insulin resistance has greatly increased. Researchers now know that insulin resistance produces a wide range of phenotypes, not only related to the tissue or organ that is resistant, but also to specific steps in the insulin signaling pathway. Second, research has shown that hormone action goes beyond the classic target tissues, and that different tissues and organs can actually "talk" with one another. This is a robust and growing field with future opportunities focusing on transcription factors and co-activators and co-repressors of cell signaling. The NIDDK should now strive to define the molecular basis underlying complications; the role of glucose in metabolic control and hormonal abnormalities; and fundamental mechanisms that can play a role in complications. We must identify and address the environmental factors that have led to the rapid emergence of obesity as a major threat to the nation's health. Clinical research and clinical trials remain critically important for evidence-based medicine. In addition, there is a desperate need for more clinical investigators and for additional research training programs to produce such investigators.

Urologic Research - Dr. John McConnell
Executive Vice President
University of Texas Southwestern Medical Center

Dr. John McConnell spoke on “The Future of Urology: Translational Research Opportunities and Challenges.” His perspective reflects his role as the lead investigator of the Medical Therapy of Prostatic Symptoms (MTOPS) clinical trial and his service on the Executive Committee of the NIDDK-sponsored Bladder Research Progress Review Group, which issued its final report and recommendations in August 2002. Dr. McConnell briefly reviewed major clinical advances in urology from the past 20 years that have transformed the field, such as diagnostic tests based on levels of prostate specific antigen (PSA), and laparoscopic surgical procedures for the kidney and

prostate. He then focused on the crucial need for improved progress in current basic urology research in order to supply the next generation of therapies and surgical interventions for benign urologic diseases. Using as an example the disease benign prostatic hyperplasia (BPH), he noted the tremendous wave of new clinical findings and treatment options over the past decade–progress which was fueled by basic research findings from 20 to 30 years ago. Dr. McConnell then offered two alternate "visions of the future." In one scenario, basic research in prostate biology stagnates such that fourth generation drugs and non-validated phytotherapy regimens provide the only "new" therapeutics for BPH. In the second scenario, basic research flourishes, new therapeutic targets emerge, and the advent of new techniques enhances diagnosis of BPH. The challenge is to ensure that the more optimistic vision prevails. To help address this challenge, a recent Bladder Progress Review Group has identified a number of research needs and priorities for basic and clinical research. Advanced imaging technologies are important in the detection of urological disorders, and the possibility of research collaboration with the new National Institute of Bioimaging and Bioengineering should be explored. The NIDDK and its advisors can influence the future of urologic research by continually assessing the state of research and research needs, setting goals, providing research tools and funding, adjusting the complex system of research relationships and research training in urology to obtain maximum productivity, and providing strong leadership.

Kidney Research - Dr. Robert Schrier
Professor and Chairman, Department of Medicine
University of Colorado School of Medicine

Dr. Schrier spoke of two overarching themes: first, the need for NIH to balance basic research and patient-oriented research; and second, the need for NIH and industry to work together, when appropriate, to perform clinical trials and other patient-oriented research. Dr. Schrier's perspective reflects his own extensive work on the pathogenesis of acute renal failure, genetic renal disorders, mechanisms of cell injury, diabetic nephropathy, and renal and hormonal control of body fluid volume in cirrhosis, cardiac failure, nephrotic syndrome and pregnancy. Dr. Schrier reviewed a number of clinical trials, including the United Kingdom Prospective Diabetes Study, the Hypertension Optimal Treatment trial, the Appropriate Blood Pressure Control in Diabetes study, and the Heart Outcomes Prevention Evaluation study. These trials examined the impact of hypertension on people with diabetes. In general, tight control of blood pressure in diabetes is the most effective way to prevent or ameliorate some of the most common complications of diabetes, including cardiovascular disease and kidney disease.

Dr. Schrier also reviewed the problem of hypertension in people with polycystic kidney disease (PKD). As in patients with diabetes, people with PKD are particularly at risk for complications and progression to ESRD if they also have high blood pressure. Recent clinical studies have suggested that more aggressive control of blood pressure in these patients may have a dramatic effect on slowing progression of patients with PKD to end-stage renal disease and cardiovascular death.

Dr. Schrier closed by reemphasizing the two related themes. The first was the need for NIH to balance basic research and patient-oriented research. He also stressed his belief that the NIH and industry needed to work together, when appropriate, to perform clinical trials and other patient-oriented research. He pointed out that some of the important trials he reviewed represented joint efforts of industry and the NIH.