# DRAFT

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

**May 31, 2006**

## I. CALL TO ORDER

Dr. Griffin Rodgers, Acting Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called to order the 171st National Diabetes and Digestive and Kidney Diseases (NDDK) Advisory Council meeting at 8:35 a.m., Wednesday, May 31, 2006 in the Congressional Ballroom, Bethesda Marriott Hotel, Bethesda, Maryland.

### A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Janis Abkowitz
Dr. Robert Alpern
Dr. Janice Arnold
Ms. Janet Brown
Dr. Roberto Coquis
Dr. Raymond DuBois
Dr. Robert Eckel
Dr. Jeffrey Flier
Dr. William Henrich
Dr. David Klurfeld (Ex Officio)
Dr. Mitchell Lazar
Dr. Rudolph Leibel
Dr. Juanita Merchant
Dr. Brian Monahan (Ex Officio)
Dr. David Perlmutter
Dr. Jerry Palmer (Ex Officio)
Ms. Margery Perry
Dr. Linda Sherman
Dr. Darracott Vaughan

Also present:

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

### B. NIDDK STAFF AND GUESTS

In addition to Council members, others in attendance included NIDDK staff members, representatives of the National Institutes of Health (NIH) Office of the Director (OD), Center for Scientific Review (CSR) Scientific Review Administrators, and other NIH staff members. Guests were present during the open sessions of the meeting. Attendees included the following:

Abraham, Kristin, NIDDK
Agodoa, Lawrence, NIDDK
Amir, Syed, CSR
Appel, Michael, NIDDK
Arreaza-Rubin, Guillermo, NIDDK
Barnard, Michele, NIDDK
Beckley, Carey, NIDDK
Bishop, Terry, NIDDK
Blondel, Oliver, NIDDK
Briggs, Josephine, NIDDK
Brown, Clarice, Social Science Systems
Castle, Arthur, NIDDK
Chamberlain, Joan, NIDDK
Chianchiano, Dolph, National Kidney Foundation
Connaughton, John, NIDDK
Cowie, Catherine, NIDDK
Curtis, Leslie, NIDDK
Donohue, Patrick, NIDDK
Doo, Edward, NIDDK
Eggers, Paul, NIDDK
Elder Leak, Gayla, NIDDK
Everhart, James, NIDDK
Farishian, Richard, NIDDK
Feder, Ned, NIDDK
Feld, Carol, NIDDK
Ferguson, Frances, NIDDK
Fradkin, Judith, NIDDK
Gansheroff, Lisa, NIDDK
Garfield, Sanford, NIDDK
Gordon, Shefa , NIDDK
Goter-Robinson, Carol, NIDDK
Guo, Xiaodu, NIDDK
Haft, Carol, NIDDK
Hamilton, Frank, NIDDK
Hanlon, Mary, NIDDK
Harrison, Barbara, NIDDK
Hilliard, Trude, NIDDK
Hoff, Eleanor, NIDDK
Horlick, Mary, NIDDK
Howards, Stuart, NIDDK
James, Stephen, NIDDK
Jeffress, Suellen, NIDDK
Jerkins, Ann, CSR
Jones, Teresa, NIDDK
Karp, Robert, NIDDK
Ketchem, Christian, NIDDK
Kim, Sooja, CSR
Kostolansky, Edward, NIDDK
Krishnan, Krish, CSR
Kuczmarski, Robert, NIDDK
Kusek, John, NIDDK
Laughlin, Maren, NIDDK
Leschek, Ellen, NIDDK
Linder, Barbara, NIDDK
Malik, Karl, NIDDK
Malozowski, Saul, NIDDK
Manouelian, Denise, NIDDK
Margolis, Ronald, NIDDK
May, Michael (Ken), NIDDK
McDermott, Julie, NIDDK
McGeehan, Gene, NIDDK
McKeon, Catherine, NIDDK
Merchant, Barbara, NIDDK
Meyers, Catherine, NIDDK
Miles, Carolyn, NIDDK
Miller, David, NIDDK
Miller, Megan, NIDDK
Mineo, David, NIDDK
Moen, Laura, NIDDK
Moxey-Mims, Marva, NIDDK
Mullins, Christopher, NIDDK
Musto, Neal, NIDDK
Nyberg, Leroy, NIDDK
Owens, Crystal, NIDDK
Patel, D.G., NIDDK
Perry-Jones, Aretina, NIDDK
Peterson, Elizabeth, NIDDK
Pope, Sharon, NIDDK
Rasooly, Rebekah, NIDDK
Robuck, Patricia, NIDDK
Rosenberg, Mary Kay, NIDDK
Rushing, Paul, NIDDK
Sahai, Atul, NIDDK
Salomon, Karen, NIDDK
Sankaran, Lakshmanan, NIDDK
Sato, Sheryl , NIDDK
Serrano, Jose, NIDDK
Sheard, Nancy, CSR
Singer, Elizabeth, NIDDK
Smith, Phillip, NIDDK
Snyder, Margaret, OER

Star, Robert, NIDDK
Staten, Myrlene, NIDDK
Tietz, Dietmar, NIDDK
Torrance, Rebecca, NIDDK
Walker, Karen, NIDDK
Wellner, Robert, NIDDK
Wilder, Elizabeth, NIDDK
Williams, Garman, NIDDK
Woynarowska, Barbara, NIDDK
Wright, Daniel, NIDDK
Wright, Elizabeth, NIDDK
Wysong, Chad, NIDDK
Yanovski, Susan, NIDDK
Yining, Xie, NIDDK

## C. ANNOUNCEMENTS

***Dr. Griffin Rodgers, Acting Director NIDDK***

*Deaths:* Dr. Rodgers announced with sadness the recent deaths of two prominent NIDDK grantees:

- *Dr. Bruce Merrifield*, was an NIDDK grantee for nearly 30 years. Working at Rockefeller University in the early 1960s Dr. Merrifield, developed a rapid, automated system for making peptides. This system contributed significantly to research on and development of treatments such as blood pressure medicines, insulin and other hormone medications, and is widely used in genetic research today. For his work Dr. Merrifield won a number of prestigious awards including the Nobel Prize in Chemistry in 1984 and the Lasker Award for Basic Biomedical Research in 1969.
- *Dr. Norman Siegel,* was a leading pediatric nephrologists and long-time NIDDK grantee. He was Chair of Pediatrics at Yale University and Chair of the Steering Committee for NIDDK's ongoing Focal Segmental Glomerulosclerosis in Children and Young Adults Interventional Study. Dr. Siegel made substantive contributions to the classification of renal transplant rejections and the mechanisms of acute renal failure, and was esteemed as an outstanding teacher and mentor.

*NIDDK Staff Promotions:* Dr. Rodgers announced the promotion of Dr. Van S. Hubbard to rank of Rear Admiral in the United States Public Health Service.

- Dr. Hubbard is one of only 8 individuals currently at the level of Flag Officer at the NIH – there are only 41 total in the entire Public Health Service. Throughout Dr. Hubbard's career, he has consistently progressed to positions of increased responsibility and leadership within NIH and has provided primary leadership for numerous activities and initiatives within DHHS, other federal agencies, World Health Organization, and other professional organizations. Dr. Rodgers commented that NIDDK is proud to have Dr. Hubbard serve as NIDDK's Director of the Division of Nutrition Research Coordination and congratulated Dr. Hubbard on this fitting recognition.

*NIDDK Staff Recognition:* Dr. Rodgers announced honors garnered by two members of the NIDDK Intramural Research Division.

*Dr. William A. Eaton*, Chief of the Laboratory of Chemical Physics within NIDDK's Division of Intramural Research was elected to the National Academy of Sciences.
Dr. David M. Harlan, Chief of the Diabetes Branch within the NIDDK Division of Intramural Research, was given the Public Health Service, Physicians Professional Advisory Committee "Physician Researcher of the Year" Award.

*New NIDDK Staff:* Dr. Rodgers introduced two new NIDDK staff members:

- *Dr. Daniel G. Wright* recently assumed the position of Program Director for Hematology Research within the Division of Kidney, Urologic and Hematologic Diseases, succeeding David Badman, Ph.D. who built this Program to prominence over three decades. In this position Dr. Wright will be working alongside Terry Bishop, Ph.D., who has been Hematology Genomics and Training Program Director at NIDDK. Dr. Rodgers explained that this is a professional homecoming for Dr. Wright who, after receiving his M.D. and immediate post-graduate training at Yale, came to the NIH as a Clinical Associate at the NIAID in the mid-1970's and was subsequently a junior staff investigator at NCI. Dr. Wright left NIH in 1980 to become Chief of Hematology at the Walter Reed Army Institute of Research and, after 12 years there, moved to Boston University Medical Center where he was Professor of Medicine and Pathology and Chief of Hematology-Oncology prior to his recent return to the NIH. He has authored over 130 basic and clinical research publications relating to blood cell biology and blood disorders, and he is an elected member of the American Society of Clinical Investigation, as well as a member of the American Society of Hematology and American Society for Cell Biology.
- *Ms. Suellen Jeffress* has been selected as Director, Office of Acquisitions, NIDDK. In her role as Director, Ms. Jeffress will be responsible for overall management of R & D contract and procurement activities for the NIDDK, NICHD, FIC and NIAAA, supervising the branch chiefs in those branches. She comes to NIH from the U.S. Army Contracting Agency, where she managed the Army Contracting Agency's Small Business Program. She has an M.B.A. in Procurement and Contracting from George Washington University. Dr. Rodgers noted that Ms. Jeffress extensive and diverse contracting experiences and her skills in leading people make her an ideal choice.

*Awards to NIDDK Grantees*: Dr. Rodgers announced that a NIDDK grantee has received the Albany Medical Center Prize in Medicine and Biomedical Research:

- Dr. Seymour Benzer, the James Griffin Boswell Professor of Neuroscience, Emeritus (Active) at the California Institute of Technology, has been awarded the $500,000 prize, in recognition of more than 50 years of pioneering research in molecular biology, behavior, and neuroscience. The Albany Medical Center Prize, established in 2000, is the largest US prize for biomedical research, and is second in size worldwide only to the Nobel Prize. In the 1950s, Dr. Benzer's research on the mechanism of genetic

recombination made him one of the founding figures of molecular biology. Beginning in the 1960s, he laid the foundations of neurogenetics with his use of fruit flies to study genetic control of behavior and development of the nervous system. This work has made important contributions to our modern understanding of mechanisms of circadian rhythms, learning, and memory. His recent and current work is expanding our understanding of mechanisms of neurodegeneration associated with aging and specific neurodegenerative diseases. NIDDK supports Dr. Benzer's genetic analysis work on the control of feeding behavior, physical activity, and metabolic rate in fruit flies. Dr. Rodgers explained that most of the genetic pathways worked out in fruit flies by Dr. Benzer have subsequently been shown to operate in humans as well.

## II. CONSIDERATION OF SUMMARY MINUTES OF THE 170th COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 170th NDDK Advisory Council (February, 2006) as submitted.

## III. FUTURE COUNCIL DATES

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

September 20-21, 2006
February 21, 2007
May 30-31, 2007
September 19-20, 2007

## IV. ANNOUNCEMENTS

### A. CONFIDENTIALITY AND CONFLICT OF INTEREST

***Dr. Brent Stanfield, Director, Division of Extramural Activities***

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

Furthermore, Council members should recuse themselves when individual applications from their institutions are discussed in order to avoid an actual or perceived conflict of

interest. This is unnecessary with *en bloc* votes, for which all members may be present and may participate. Council members from multi-campus institutions of higher education may participate in discussions of any particular matter affecting one campus of that multi-campus institution if their disqualifying financial interest is employment at a separate campus of the same multi-campus institution and is in a position with no multi-campus responsibilities.

## V. REPORT FROM THE NIDDK ACTING DIRECTOR

***Dr. Griffin Rodgers, Acting Director, NIDDK***

Fiscal Year (FY) 2007 Appropriations Process

Dr. Rodgers reported that he and the directors of six other NIH institutes were invited to accompany Dr. Zerhouni to the House Appropriations Subcommittee for Labor/HHS hearing on April 6th, 2006. Dr. Rodgers noted that Dr. Zerhouni answered most of the questions at the hearing and the members were generally very supportive of NIH.

At the hearing Dr. Zerhouni highlighted several accomplishments of the NIH and their impact on health, including the fact that life expectancy continues to rise, now to an unprecedented 78 years for the total U.S. population. He also pointed out that Americans are not only living longer, they are also living healthier. For instance, Dr. Zerhouni cited that the disability rate for American senior citizens has dropped by almost 30- percent in the last 20 years, owing largely to a range of scientific advances. As an example, the death rate from cardiovascular disease has declined by 63- percent and the death rate from stroke has been decreased by 70- percent. Both of these achievements are directly attributable to advances made possible by NIH research investment.

Dr. Rodgers also related Dr. Zerhouni's fiscal arguments for NIH research returns on investment dollars. Dr. Zerhouni estimated that the total cumulative investment in cardiovascular disease research at NIH per American over the past 30 years, including the period of the NIH budget doubling, amounted to approximately $110 or about $4 for each year over this entire period. Dr. Zerhouni also cited advances in cancer research, detection and treatments and pointed out that for the first time since records have been kept, the absolute cancer death rate is declining. Dr. Zerhouni pointed out that these accomplishments are in large part due to our investment in the National Cancer Institute. Overall, Dr. Zerhouni pointed-out in his testimony that the average NIH investment of Americans over the last 30 years, including the doubling period, was $258, or about $9 per American per year.

Focusing on disease prevention Dr. Rodgers mentioned that Dr. Zerhouni cited NIDDK's Diabetes Prevention Program (DPP) as an example of a large prospective trial made possible by the doubling of the NIH budget. The fact that the trial demonstrated that lifestyle modifications reduced the risk of developing Type II diabetes by 58- percent resonated with the prevention component of Dr. Zerhouni's overarching "three Ps" motif: Prevention, Preemption, and Personalized medicine. Dr. Zerhouni also noted that

through the 1980s and 1990s the incidence of end stage renal disease nearly doubled each decade, but in the last five years the overall rates have stabilized and even declined in certain populations. This improvement is not only driven by improvements in the treatment of diabetes and hypertension and better blood pressure control, but also in monitoring for protein in the urine to prevent kidney disease or detect it in its early stages. Dr. Zerhouni estimated that the savings in federal health care expenditures are now approximately $1 billion per year by preventing patients with chronic kidney diseases to progress into end stage renal disease and require some type of renal replacement therapy—either dialysis or renal transplantation. A transcript of Dr. Zerhouni's House Appropriations Hearing testimony, including his slide set can be found on the NIH website (www.nih.gov) under the listing "2007 Budget Request Statement" (http://www.nih.gov/about/director/budgetrequest/fy2007directorsbudgetrequest.htm).

Dr. Rodgers also reported that the Senate hearings were held on May 19th, 2006. Dr. Zerhouni was accompanied to the Senate hearings by the directors of the National Cancer Institute, National Institute of Allergy and Infectious Diseases, and the National Human Genome Research Institute. He offered that Senators Specter and Harkin, who co-chair the Senate subcommittee overseeing NIH's budget are and always have been strongly supportive of the NIH.

Dr. Rodgers reported that there is a currently an effort underway within the Senate to effect an appropriation for NIH that is higher than the President's budget proposal. The President's proposed budget for FY 2007 is $28.6 billion. This is the same amount as the FY 2006 appropriation, however, the 2007 proposal includes an increase of $110 million for development of projects related to biodefense and so the institutes are slated to receive decreases of between 0.5- and 0.8- percent.

Historic Budget Trends and Payline

Dr. Rodgers then focused the budgets for both NIH and NIDDK over the past 30 years and considered the impacts of budget on paylines and success rates.

Dr. Rodgers first noted that NIDDK's appropriation has generally increased since 1970 and passed the $1 billion mark in Fiscal Year 2000. Between FY 2000 and 2006 NIDDK's budget increased to approximately $1.7 billion. There were three times in the 1970's and 1980's (1970, 1974 and 1987) when the percentage change of the budget from the previous year fell below zero (was negative). There was also a negative percentage change in FY 2006. In FY 2007 NIDDK is again expecting to observe a slight decrease in its budget compared with FY 2006 levels. Dr. Rodgers also pointed out that between 1999 and 2003 there was a period of quite substantial budget gains—the NIH budget "doubling" period.

Dr. Rodgers then discussed the effects of adjusting actual budget dollars for inflation using the Biomedical Research and Development Price Index (BRDPI). Looking at dollars held constant to 1970 purchasing power levels Dr. Rodgers pointed out that there were several instances in which there were negative budget cycles. Dr. Rodgers

explained that his central point is that there have been ebbs and flows in NIDDK's budget since 1970, with substantial gains made especially during the NIH doubling period, but in the post-doubling period NIDDK's budget has clearly declined.

Dr. Rodgers then focused his discussion on success rates of applicants. He pointed out that it would be reasonable to think that the decline in NIDDK's appropriation would be the largest contributing factor driving the decline in success rates of applicants. However, looking at the data, the key contributing factor to declining success rates is the sharp increase in numbers of applications that started in 2003. Dr. Rodgers pointed out that during the past two years we have received approximately the same number of applications (8,300) as over the entire five-year period of the doubling (from 1999 to 2003).

Dr. Rodgers concluded that success rate is largely driven, at least in the short term, by the increase in demand reflected by increasing numbers of applications. Payline is driven by the dynamics between demand trends (applications) and the supply (funds) NIDDK has available. How success rates and payline play out in the future depend on NIDDK's appropriation and demand. If the current trends of declining budget and increasing applications continue then there will continue to be tension on success rates and paylines.

Council Questions and Discussion

*How much of the increase in the numbers of applications is related to concerns about funding leading investigators to submit more applications and how much of it is due to more investigators?* Dr. Rodgers indicated that NIH's Office of Extramural Research is currently investigating this question. The suspicion is that there is an interaction between more applicants getting funded and more applicants being introduced into the system. After some lag period there was an intersection that contributed to the increase in applications that we are seeing. However, the data are not yet in hand and so this is largely speculation.

*If you were to look at the proportional allocation of NIDDK's budget among different spending categories rolling backward in 5-year chunks, would there be any major changes in the apportioning of the budget to various components?* Dr. Rodgers indicated that the answer is by and large, no. In fact, Dr. Rodgers recalled presenting budget data at the end of the NIH doubling period and showing that there was decrease for NIDDK's intramural research apportionment. There was also a slight decrease in NIDDK's contracts line, but by and large the bulk of the funds are in the Research Project Grants line, in Career and in Centers. This didn't change appreciably during the doubling or subsequently.

Update on Multiple Principle Investigator (PI) Applications

Dr. Rodgers introduced Dr. Betsy Wilder, Renal and Urogenital Development Program Director and also Basic Kidney SBIR Program Director, within NIDDK's Division of Kidney, Urologic and Hematologic Diseases to report on NIH's plans for multiple PI applications.

Dr. Wilder informed the Council members that NIH is now accepting applications with multiple PIs on a limited basis. NIDDK has taken a leading role in developing the multiple PI policy and one of NIDDK's RFAs is one of the first to test the new policy. NIDDK's Council will be the first to review multiple PI applications at its September 2006 meeting.

Dr. Wilder conveyed that there were several principles that guided development of the Multiple PI policy. The most fundamental of all the guiding principles was that all PIs on a Multiple PI application are equal. When considering applications these applications Councils will be asked to consider all the PIs equal. To facilitate communication between the group of PIs and the NIH a "contact PI" will be designated. Because all PIs are equal the contact PI may rotate amongst the PIs on an annual basis. A leadership plan, required for all multiple PI applications, outlines how the team will function. The leadership plan is a new section of the application that describes the roles of all of the PIs, the process for resolving conflict, allocation of resources, and details such as publication plans and intellectual property rights.

The review criteria are not substantially changed for multiple PI applications, but a new phrase has been added to the review of the review criterion "Approach". This new phrase reads: *"For applications designating multiple PIs, does the leadership plan ensure that there will be sufficient coordination and communication among the PIs? Are the administrative plans for the management of the research project appropriate, including plans for conflicts?"* In other words, the review committee must consider how the applicants on a multiple PI application will work together as a group.

Dr. Wilder mentioned that the multiple PI application is in a pilot phase, and input is being gathered on the process. All Council members across the NIH will be asked to provide input on the process in the coming weeks and months by NIH's Office of Extramural Research.

Council Questions and Discussion

*When investigators leave one institution to take a job at another how will splitting a grant be adjudicated?* Dr. Wilder first established that there are two situations and several management strategies for multiple PI grants outlined in the NIH Guide notice. One situation is when all PIs are at one institution. In the other situation the multiple PIs are at different institutions and for this situation there are two management strategies—linked awards (awards to multiple institutions for a singe project) or a subcontract model where one PI and one institution would hold the award but would subcontract out to the

other PIs. So, if a PI moves from one institution to another institution, creating a two-institution situation, this can be resolved either by generating a new award to the second institution or subcontracting. Dr. Wilder pointed out that there is the caveat that NIH's computer systems cannot handle a high volume of linked awards and increasing capacity to accommodate these situations will be an ongoing implementation step.

*Currently multiple PI applications may only be submitted to a limited number of program announcements. When is it expected that these applications will be accepted on a broader scale?* Dr. Wilder indicated that for R01 applications the intent is to have full-scale implementation for February 2007 receipt. NIH anticipates including the ability to submit multiple PI applications for other grant mechanisms as the mechanisms are transitioned to electronic submission. Dr. Wilder did however point out that the caveat to this is linked awards, where two PIs at different institutions get their own grants while collaborating. It is anticipated that linked awards will not be available for full-scale implementation until 2008.

*Does NIH expect to receive many multiple PI applications in the long-term and what is the anticipated budget that will be connected to multiple PI awards? How will linked awards be counted?* Dr. Wilder stated that the number of multiple PI applications is difficult to predict. Dr. Wilder also indicated that the size of budgets for multiple PI grants is difficult to predict. Once could envision where a regular-sized R01 could be jointly led by two or three people and would not have a substantially increased budget. One could also envision where people coming together as teams would put together larger projects. Regarding counting projects, Dr. Wilder indicated that counting projects is what is more pertinent than counting grants per se. Counting projects will require from a systems development standpoint a way to identify projects—a project identifier—and this is what NIH needs to develop before linked awards can be fully rolled out. In other words, NIH needs to develop the capability to count linked grants to different institutions as a single project.

## VI. ADVISORY COUNCIL FORUM—PART 1

**Analysis & Discussion of NIDDK's Use of R21 Grants**

***Dr. Christian Ketchum, Basic Renal Biology Program Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK***

Background

Dr. Ketchum began his presentation by reviewing the original NIH language that defined the intent of the R21 program. He quoted, "*the primary intent of this mechanism is to foster development of high-risk pilot and feasibility research by both newly independent and established investigators*," and then mentioned that language goes on to say that the R21 should develop new ideas sufficiently to allow for the subsequent submission of an R01 application.

Dr. Ketchum then pointed out some of the general characteristics of the R21 mechanism. For example, the R21 has a budget cap of $275,000 in direct costs that can be spread over two years. The 15-page research plan for an R21 is slightly abbreviated compared to an R01 application. An R21 application does not technically require any preliminary data, though R21 applications go through the peer review process and in this context preliminary data is often advantageous. R21 applications are generally allowed two revisions or amendments if the original application is not funded, although those R21 applications received in response to a solicitation such as an RFA may be restricted from revision and resubmission to the same RFA. Finally, R21 grants cannot be competitively renewed. If the applicant would like the science to continue they need to seek support via another NIH mechanism such as an R01.

Dr. Ketchum then explained that not all Institutes and Centers (ICs) that comprise the NIH accept investigator initiated R21 applications—eighteen do and six do not. NIDDK is among the six ICs that do not accept investigator initiated R21 applications. R21 applications submitted to NIDDK must come in response to a specific NIDDK solicitation. Dr. Ketchum then explained that there are two primary ways that NIDDK solicits R21 applications. One way is via a Program Announcement (PA). PAs can be either broad or focused in scope but most are generally broad in scope, they are reviewed centrally at NIH by the Center for Scientific Review, and there are no set-aside funds for a PA. PAs are issued for three years and then they expire and currently NIDDK has 31 active PAs that allow submission of R21 applications. The other major way that NIDDK solicits R21 applications is through a Request for Applications (RFA). Again, RFAs can either be broad or focused but RFAs, as a group, are typically more focused than PAs. RFAs are reviewed in-house by NIDDK staff and they have a set-aside amount of money associated with them. Oftentimes RFAs expire after a single receipt date, so applications coming in under an RFA typically cannot be revised and resubmitted under the same RFA if the application is not funded. NIDDK had a maximum of eight RFAs for R21 applications at the end of the NIH budget doubling period in 2002 and 2003 and the number dropped and has remained low in FYs 2004, 2005, and 2006.

Dr. Ketchum then explained that his presentation would focus on three questions. First, how many R21s does NIDDK fund? Second, who receives NIDDK R21 grants? The focus of this second question is looking at the proportion of new versus established investigators who are awarded R21 grants. Third, how many NIDDK R21 awardees convert their research program into an R01 project. Dr. Ketchum noted that conversion of an R21 to an R01 was a questionable metric of success and that if it is indeed a good metric it is only one of several.

Before presenting his analyses Dr. Ketchum noted that in situations where he compared data on R21 applications and awards to R01 applications and awards he focused only on new or Type 1 R01 applications and awards. This is because R21 grants cannot be continued past the initial award period or in other words converted to a Type 2 award. Type 2 R01 applications, as would be expected, tend to do better in review than Type 1 R01 applications. Therefore, in the interest of appropriate comparisons, only Type 1 R01

applications and award data were included in comparisons with data on R21 applications and awards.

How Many R21 Grants Does NIDDK Fund?

Dr. Ketchum presented data showing that the number of new (Type1) R01 applications submitted to NIDDK rose from 1,566 in FY 2000 to 2,006 in FY 2006, a 1.3-fold increase. During the same time period the number of R21 applications rose from 162 to 1,100, nearly a 7-fold increase. Regarding awards, in FY 2000 NIDDK paid 340 Type 1 R01 grants, while in FY 2006 NIDDK expects to make 346 Type 1 R01 awards, which is essentially flat growth. In contrast, during the same time-period the number of R21 awards NIDDK made rose from 40 to an expected 151 in 2006, representing four-fold growth. In terms of percentages of Type 1 R01 and R21 applications being awarded, up through FY 2004 a slightly higher percentage of new R21 applications was awarded than the percent of new Type 1 R01 applications awarded. However, this trend reversed in FY 2005 and the difference became even more pronounced in FY 2006 when NIDDK expects to pay approximately 17 percent of Type 1 R01 applications and 14 percent of R21 applications.

Regarding cost of each application and growth over time Dr. Ketchum showed that Type 1 R01 awards averaged $197,000 per year in direct costs in FY 2000 and this increased to a current price tag of $225,000 per year in FY 2006, representing approximately 10 percent inflation over a 7-year span. In comparison, the average cost of R21 grants increased from $98,000 per year in FY 2000 to $133,000 per year in FY 2006, which is approximately a 40 percent increase. The primary driver behind this increase in direct costs for R21s was a decision by NIH to raise the direct cost budget cap for R21 grants from $200,000 over two years to $275,000 over two years. Overall the budget for new Type 1 R01 grants grew from approximately $100 million in FY 2000 to approximately $116 million in FY 2006, a growth rate of approximately 1.2 fold during the 7-year span. In contrast, the budget for new R21s during the same period grew from just below $6 million to slightly more than $30 million, representing an approximate five-fold growth rate. At this time R21s account for approximately 11 percent of NIDDK's competing Research Project Grant (RPG) portfolio. The competing RPG portfolio includes both new projects (Type 1) and competitive renewals (Type 2).

Compared to NIH overall from FY 2000 to FY 2005 while NIDDK observed 5-fold growth in total costs associated with new R21s, NIH-overall observed only 3-fold growth. Dr. Ketchum then pointed out that NIDDK's relatively high R21 budget growth rate is largely attributable to comparatively high growth rate in the numbers of R21 applications that NIDDK has received. For NIH overall, R21 applications have increased five-fold over the past seven years, while R21 applications submitted to NIDDK have increased seven-fold during the same time period.

Dr. Ketchum then showed that most of NIDDK's R21 applications come in under PAs, to the point where 99 percent of R21 applications received by NIDDK in FY 2006 came in response to a PA. Breaking down the data even further he demonstrated that since FY

2000, while the numbers of NIDDK-assigned R21 applications coming in to fairly narrowly focused solicitations (e.g. Erythroid Linage Molecular Tool Box) grew at a fairly fast four-fold rate, the numbers coming in response to broader solicitations (e.g., Innovative and Exploratory Research in Digestive Diseases and Nutrition) grew nearly seven-fold.

Who Receives NIDDK R21 Grants?

Dr. Ketchum reported that in FY 2005 approximately 40 percent of NIDDK-assigned R21 applications were received from New Investigators (NIs). However, New PIs lagged somewhat behind experienced investigators in their success rate in receiving R21 awards. For example, in FY 2005 17 percent of experienced investigator and 13 percent of NI applications were funded. Looking at final pay numbers, 97 of the 150 or 65 percent of R21 awards made in FY 2005 went to experienced investigators. These differential success rates and the proportional balance of R21 awardees for NIDDK are very similar to the R21 application and award data for NIH overall in terms of NI R21 success rates (14 percent of NI applications funded) and percentage of R21 awards to experienced investigators (63 percent of awards). Dr. Ketchum then compared these data to the NIDDK R01 portfolio and showed that in FY 2005 NIs submitted slightly less than 30 percent of all Type 1 R01 applications and competed well with experienced investigators in getting their applications funded (16 percent vs. 17 percent), though proportionally experienced investigators hold 72 percent of NIDDK Type 1 R01 awards. Dr. Ketchum stated his point in showing these data is that at least relative to the R01 portfolio, NIs make up a larger portion of the R21 portfolio and this raises the issue of whether the R21 is an appropriate mechanism for NIs.

R21 to R01 Conversion

Dr. Ketchum reported that there were 177 NIDDK R21 grants made between FY 2000 to 2002. He then presented an analysis where he followed the science within those applications forward to see if the science from any given R21 was converted into an R01 by the same investigator. Among the 177 NIDDK R21 grants funded between FY 2000 and 2002, the Principle Investigators (PI) of 103 of those grants did not go forward and submit a subsequent R01 on a similar scientific topic. For this exercise the line of research was considered "inactive" in these cases. There were 42 instances where the PI was pursuing R01 funding for a scientific topic but had not been successful yet. These cases were considered "active". Finally, PIs of 22 of the 177 (12 percent) NIDDK funded R21 grants were successful in obtaining NIDDK R01 funding on a similar topic and another 10 (6 percent) were successful in obtaining R01 funding on a similar topic from another NIH IC. Thus, the overall rate of converting NIDDK R21 grants into an R01 (funded by NIDDK or another component of NIH) is approximately 18 percent.

Dr. Ketchum then considered if there were any consistencies among those R21 grants that were converted to R01s versus those that were not successfully converted. No differences were identified among factors including solicitation type (RFA vs. PA), PI status (NI vs. experienced investigator), type of research (basic vs. clinical), or priority

score of the R21. The only factor that did appear consistent was that all 32 R21 grants that were converted to an R21 were funded as an initial application or after only one revision.

Discussion Points

Dr. Ketchum concluded his presentation with the following discussion points:

- There has been five-fold growth in NIDDK's new R21 budget since FY 2000 and this raises a question about the dollar amount and percent of NIDDK's Research Project Grant budget that the R21 portfolio has become.
- Compared to the R01 portfolio, proportionally more R21s are going to NIs. Is the R21 a good mechanism for NIs?
- Eighteen percent of R21s are converted into R01s. Is the conversion of an R21 into an R01 a good metric of success?

Comments by Assigned Discussants

*Dr. Abkowitz* commented that $30 million is too much of NIDDK's budget to be spending "without a real understanding of where it's going to and why." Dr. Abkowitz then indicated that she is not convinced that the R21 program is targeting or recruiting high risk pilot and feasibility studies that the program originally intended. She wondered if there has not been some mission creep where the program supports at least some investigators who are simply collecting preliminary data to submit an R01. Dr. Abkowitz indicated that whether or not mission creep is desirable is not clear, but it has to be considered critically. Use of the R21 should be focused to ensure that there is an appropriate return on the dollars invested. Dr. Abkowitz indicated that "at least to me, included in that focus should be high-risk science". New investigators, Dr. Abkowitz argued should be included in the general concept of high risk and what else should be included in terms of scope of the program needs to be explored. Dr. Abkowitz concluded that perhaps applicants can be asked specifically to identify how they fit criteria that are established as a way to help evaluate the applications.

*Dr. Leibel* indicated that he generally agreed with Dr. Abkowitz's comments and registered his surprise at the dollar amount being distributed under the R21 program. He commented that his interpretation regarding the growth in the program—and what is troubling the research community generally—is that the R21 is largely regarded as a way "to try to get in under the R01 threshold by submitting grants that are less well backed and formulated." Dr. Leibel went on to suggest that perhaps both young investigators and more experienced investigators look at the R21 as an opportunity to get around the strictures surrounding the R01 both in terms of resource availability and a systemic fondness of increasingly conservative applications. Dr. Leibel felt this behavior may be a symptom of something wrong with the system, both in terms of pressure on the mode of funding and how the scientific community regards the R01. Dr. Leibel went on to say that he felt the R21 is an important vehicle to have in place, but it needs to be deployed in a more thoughtful and appropriate way, and perhaps the financial commitment to the R21 program should be decelerated. Dr. Leibel summarized that he was surprised by the

dollar commitment to the R21, which he feels is an important mechanism that has been somehow partially derailed into some other kinds of use that was not its original intent.

*Dr. Sherman*, commented that she considers the best use of the R21 to be for NIs because the mechanism does not require substantial preliminary data. Dr. Sherman suggested that it might be helpful to shift the emphasis in the R21s program to focus primarily on new investigators rather than established investigators who are more likely to have access to resources that enable preliminary experiments. Dr. Sherman also commented on the escalation in numbers of R21 applications. She felt that the numbers of R21 applications requiring review and burden placed on the review system is not justified. She suggested that perhaps the R21 program should be more focused and solicitations should trend towards RFAs rather than more general PAs.

*Dr. Perlmutter,* indicated that he agreed with much of what had been said, but felt that more radical steps were needed in tough financial times and that perhaps the R21 program should be discontinued and the savings focused on R01 funding. This, he suggested, might fulfill many of the objectives that had been discussed. For example, if the R01 pool were expanded perhaps there would be retrenchment from conservative grant-writing and support of more NIs. Dr. Perlmutter argued that from an institutional point of view it is hard to support the R21. Two-years are rarely enough time for a good scientific project to evolve.

Council Questions and Discussion

Dr. Eckel argued that if the R21 mechanism is supposed to be focused on developing high-risk science with a limited period of funding and that focusing on junior people is not appropriate. Dr. Eckel commented that he felt that it may be necessary to return to a "First Award" type of concept, with a budget that is a bit more than the original "First Award," to transition junior investigators to R01 support. Dr. Eckel also suggested that the R21 program should be reduced in size and targeted towards established investigators who are experienced and who could take a new idea and "make something out of it in two years."

Dr. Flier indicated his support for Dr. Eckel's position and stated that he did not think the R21 a particularly good route for NIs. Dr. Flier suggested the emphasis should be on the high-risk aspect and most often experienced investigators will be better able to effectively make something of limited time and resources. He further suggested that NIDDK should address NIs in a different way. Dr. Flier indicated that he felt that overall what is needed is a rebalancing of the R21 program—where it is made leaner and more focused. He suggested that the program had drifted and is now being perceived an easier first step for NIs, which may be unfortunate because an R21 award does not provide much of a foundation for an NI.

Dr. Leibel agreed and indicated that he thought the R21 has come to be perceived as a way of getting a foot in the door of the NIH granting system and now the program has become "something of an unguided missile." Dr. Leibel continued that he felt it was the

sense of the entire Committee that appropriately supporting junior investigators is a critical issues and if that is so, then the junior investigator issue should be addressed as such and not as a pilot and feasibility or high-risk research issue. Dr. Leibel concluded that he felt it was the sense of the Committee that some portion of the funds currently directed towards the R21 program should be redirected in a way that specifically supports promising young investigators.

## VII. SCIENTIFIC PRESENTATION

***Dr. Barbara Kahn, Chief, Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, and Professor of Medicine, Harvard Medical School*—"Insulin Resistance in Obesity & Type 2 Diabetes: From Clinical Observations to Mouse Models to DNA Arrays and Beck to the Bedside"**

See attached presentation.

NIDDK_Kahn_0506.pdf

## VIII. ADVISIORY COUNCIL FORUM – PART 2

**NIH Obesity Research Update**
***NIDDK Staff***

Overview

Dr. Sue Yanovski, Co-Director of the NIDDK Office of Obesity Research gave an orientation and overview of the problem of obesity in the United States.

Looking at trends from 1976 through 2004, Dr. Yanovski showed that in the 1970s and 1980s slightly less than half the adult population was considered overweight with a body mass index greater than 25. Today more than 65 percent of the adult population has a body mass index above 25. Furthermore, obesity rates have increased from approximately 15 percent in the 1970's to approximately one-third of the adult population today. The numbers of overweight adolescents and children have more than tripled from 5 percent in the 1970s to 17 percent today and the momentum does not appear to be subsiding. Overall, these trends present a tremendous public health problem.

Dr. Yanovski explained that in recognition of this problem, in 2003 Dr. Elias Zerhouni, Director, NIH, established an NIH Obesity Research Taskforce to bring together different NIH institutes and help coordinate obesity research across NIH. The taskforce is co-chaired by the directors of the National Heart Lung and Blood Institute (NHLBI) and NIDDK, currently Dr. Nabel from NHLBI and Dr. Rodgers from NIDDK. Among its charges the taskforce was responsible for developing a strategic plan for obesity research, which has been done with input from the public and professional organizations. This strategic plan has four overarching goals:

1. Research towards preventing and treating obesity through behavioral and environmental approaches to modify lifestyle
2. Research towards preventing and treating obesity through pharmacological, surgical, or other medical approaches
3. Research towards understanding the relationship between obesity and its associated health conditions
4. Cross cutting topics: technology development, multidisciplinary research teams, translational research, and training, education and outreach

Dr. Yanovski mentioned that while they are listed separately, all of the themes are interdependent. The taskforce is focused on an interdisciplinary approach in which lifestyle interventions together with an understanding of some of the basic biological and genetic factors that cause obesity are combined. The strategic plan can be found online at http://obesityresearch.nih.gov.

NIDDK's Role

Dr. Phil Smith, Co-Director of the NIDDK Office of Obesity Research then explained that NIDDK has a very comprehensive view of what needs to be done in obesity research to try to quell the rising tide of obesity. This view spans a large spectrum of science from the molecular level to the societal level and NIDDK participates in a number of initiatives across that span.

Dr. Smith mentioned some examples of what NIDDK is doing to enhance its obesity portfolio including:

- At the very basic molecular biology level, NIDDK has twice solicited research using an RFA on the use of model organisms to better understand feeding behavior and activity. Dr. Seymour Benzer, winner of the Albany Award, who is studying feeding behavior in drosophila, is one such grantee. The notion behind these types of studies is that they will uncover novel pathways and novel molecules involved in energy balance that will hopefully lead to new research that facilitates development of new therapies.
- NIDDK is encouraging partnerships between basic and clinical investigators through initiatives that also leverage NIDDK's clinical investigations. The hope is these initiatives will facilitate rapid translation of findings, through NIDDK's translation initiative, into education and outreach efforts.
- NIDDK is working to stimulate research on effects of obesity and diabetes in the mother on the risk of offspring to develop metabolic diseases. This initiative spans a broad spectrum of work from molecular epigenetics to clinical interventions.
- NIDDK is also working to stimulate research on the neurobiology of human behavior to understand the mechanisms of human eating behavior. This is an initiative designed to bring behavioral scientists together with biologists to better understand controls of feeding behavior in humans within different contexts and environments
- At the very "societal" end NIDDK is participating in an NCI-led initiative to encourage studies of the economics of diet, energy balance, and obesity so that we

can understand not just the health impact of obesity but also the impact to society in terms of health care costs and also to understand the potential impact of interventions in terms of costs and savings.

- NIDDK is working to foster outreach and education through programs such as "We Can" a partnership among a number of institutes, spearheaded by NILBI, to give parents the tools they need to educate their children regarding healthy diet and activity.

Dr. Smith then explained that several program staff would next give updates about upcoming initiatives and workshops focused on different areas of obesity research and this would be followed by some examples of ongoing programs in the area of obesity.

Workshops and Initiatives (NIDDK Led)

- Dr. Maren Laughlin introduced a trans-NIH workshop planned for 2007 that will be led by NIDDK and the National Institute on Drug Abuse (NIDA), along with several other NIH institutes including the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The overall goal is to elucidate areas of the brain involved in the regulation of eating behavior and energy balance in humans and the interrelated roles of physiological, societal and environmental signals. The focus of the workshop is to define those questions that might be asked and answered using in vivo imaging of people.

- Dr. Carol Haft described an initiative focused on enhancing our understanding of determinants of fat and pancreatic beta cell number throughout the human lifespan and in response to particular stressors. The goal of these studies is to learn more about the origins of obesity and the susceptibility to diabetes and also discover novel ways to modulate lipid and glucose homeostasis in vivo. As a first step, a workshop is planned in to 2007 to assess the state of the science and consider the tools that are currently available. The hope is then to follow up the workshop with a pilot program supporting partnerships in tool development since this is considered key in getting the field stimulated. The longer term plan is then to continue stimulating the area with a directed program announcement or multiple-receipt RFA, depending on the availability of funds.

- Dr. Sanford Garfield presented an initiative on health disparities focused on diabetes and obesity. The crux of the initiative is to identify the variables including pathobiology, genetics and behaviors that lead to disparate clinical outcomes in terms of risk for developing obesity and diabetes and also the risk for subsequent complications. Dr. Garfield described a plan to first conduct a workshop that brings together experts in the area to provide advice regarding gaps that need to be addressed. Then, informed by this workshop an RFA or program announcement could be generated to stimulate appropriate research.

  Dr. Garfield also described an initiative to study second generation antipsychotic drugs. Dr. Garfield reported that these drugs lead to an extremely high risk for

development of obesity and fifty percent of individuals taking these drugs develop Type 2 diabetes. Since at least 6 million individuals take these drugs the problem is a true public health issue. Working with the National Institute of Mental Health NIDDK is planning a workshop in 2007 to bring in experts on pharmacology, diabetes and obesity, and metabolism to consider directions to begin to understanding the metabolic targets affected by antipsychotic drugs. Then, informed by this workshop, subsequent RFAs or program announcements might be planned.

- Dr. Mary Horlick introduced a workshop planned for 2007. Dr. Horlick commented that there are major research gaps in pediatric clinical obesity and small rigorous studies are needed to address basic questions. If uniform definitions are used across these studies there will be a unifying effect and each study will make a greater contribution. The proposed workshop will bring together investigators in pediatric obesity to develop consensus on a minimum set of definitions that will allow comparisons across studies. Research related-elements that would be defined include population characteristics across multiple domains, outcome measures, and uniform definitions of short, intermediate and long-term outcomes.

Initiatives and Workshops (Led by Other Institutes)

- Dr. Laughlin explained that NHLBI led an RFA on bioengineering approaches to energy balance and obesity last year that resulted in a small number of applications of which three were funded. The institutes participating in the RFA (including NIDDK) agreed that more time was required to work with the community to stimulate more thought on approaches to developing new technologies for measuring eating behavior, energy balance and physical activity. While the RFA will be reissued later in 2006, there will also be a workshop prior to reissuing the RFA. The workshop will be spearheaded by NSF and will include a number of young engineers to who will be presented with the problem, consider how measurements are made today, and what the research and clinical needs are for the future. The hope is that these young engineers can be energized and grow to become resources for this area in the future.

- Dr. Robert Kuczmarski described the Obesity Academic Award Program which NHLBI will be spearheading. The program is designed to enhance competencies in clinical care of overweight and obese persons. The basis for the program is that obesity is under-diagnosed and under-treated by physicians and this problem needs to be addressed. The program will have three phases. The first phase is program development by multidisciplinary health teams in conjunction with medical school administrators. The second phase would be development and evaluation of training topics and materials that will be integrated into various courses at the undergraduate level, in residency programs and in clinical conferences. The final phase would then be dissemination of educational materials in collaboration with organizations such as the American Association of Medical Colleges, as well as others.

- Dr. Horlick described an initiative established by the National Cancer Institute (NCI) that includes participation by a number of other institutes including NIDDK. The

initiative is a survey to obtain baseline national data on primary care physician's knowledge, attitudes, and practices related to diet, physical activity and weight. The survey is currently in development phase and it is hoped that it will be out in the field by spring of 2007.

NIDDK Clinical Obesity Programs

- Dr. Barbara Linder described the HEALTHY Trial, a large multi-site trial of diabetes prevention. The study is slated to begin in the fall of 2006 and is a school-based program designed to decrease risk factors for Type 2 diabetes in middle school children. The trial is a response to increases in rates of overweight and Type 2 diabetes in youth. It was spurred by the results of adult trials, including NIDDK's Diabetes Prevention Program, which showed that modifying eating habits and activity habits could delay or prevent the onset of Type 2 diabetes among at-risk adults. HEALTHY is a population-based study. Schools are the units of randomization. The intervention is started in the sixth grade and the sixth grade cohort is followed for three years. There are seven HEALTHY sites across the United States. Each site will recruit six schools and therefore there will be a total of 42 schools. Half of the schools at each site will be randomized to intervention and half will be randomized to control. To be eligible for the HEALTHY study, all schools must have at least 50 percent minority youth in the school or low socioeconomic students defined by eligibility for free school lunch.

  The overall intervention goal is to reduce the risk factors for Type 2 diabetes. The study is designed to decrease the percentage of children within the intervention schools who are overweight, have pre-diabetes, or have insulin resistance as evidence by increased serum insulin. The schools have already been recruited. Student recruitment and baseline data collection will begin in the fall of 2006, during the first semester of sixth grade. The intervention will begin in the second semester of sixth grade and continue through the end of the eighth grade. At the end of the eighth grade there will be an end of study data collection.

  The intervention will be multi-level. Physical education (PE) teachers will be included in an extensive training program that will not only teach curriculum but also help with class management skills to reduce inactive time in PE classes. Comprehensive food service changes are planned and these changes target the school breakfast and lunch programs, a la carte lines in the cafeteria, and also vending machines. The overall goals of the food service intervention are to lower the fat content of the items served, to increase fresh fruits and vegetables served, cut down on snack foods available, eliminate added sugar beverages (including juice and sports drinks), and increase whole grain foods served. In addition there will be a host of behavior change activities planned that are designed to motivate kids to change their behavior. Part of this is establishment of Fun Learning Activities for Student Health (FLASH), which will take place in the classroom for 20-30 minutes per week. These activities are designed to make the children aware why they are being asked to make

changes and teach them decision making skills. Along with this, children in intervention schools will participate in individual goal-setting activities and activities that will reward goal achievement. The program will also use students as peer communicators to help promote messages and model behaviors. There will also be outreach to parents including newsletters and other school-wide events to tie individual components together.
Dr. Linder concluded that she felt the study will establish a very valuable resource. It is anticipated that the study will include 6,000 consented children. The baseline outcomes collection will provide a wealth of cross-sectional data. The cohort will provide longitudinal data over three years related to obesity, diabetes, and many other health issues in general.

- Dr. Kuczmarski provided an overview of his Obesity Prevention and Treatment Program, a portfolio that is composed primarily of human clinical intervention trials. Dr. Kuczmarski explained that the portfolio includes several board categories of research including prevention (typically focused on energy intake and energy expenditure), treatment (focused on reducing dietary intake, increasing physical activity and also surgical and pharmacologic interventions), maintenance (long-term maintenance of weight loss and lifestyle changes once they are established), and translation. Various RFAs and program announcement have helped the portfolio grow and the research within the portfolio is now quite diverse. For example, research conducted within the portfolio takes place in a number of settings including schools, the community, the home, and at worksites. Some examples of ongoing studies include:
  - A study of reducing sugar-sweetened beverage consumption in overweight adolescents by Dr. David Ludwig. The study is a home based intervention for adolescents consuming at least one 12-ounce sugar-sweetened beverage per day. The intervention was home delivery of non-caloric beverages for a period of six months and the primary endpoint was a change in body mass index. In a pilot study the intervention effect was significant for the heaviest children (above the $85^{th}$ percentile in body mass index for age). Children in the intervention group lost almost four pounds while children in the control group continued to gain weight (approximately a pound). This study has implications for evidence based recommendations (reduce sugar-sweetened beverage consumption among children) and also policy implications (major beverage companies have already in some cases volunteered to take sugar sweetened beverages out of school vending machines). A follow-up study is now ongoing in five Boston area high schools and the intervention will move from a six-month to one-year intervention and will include after school peer reinforcement of behaviors and counseling of parents by study investigators.
  - A study of long-term exercise maintenance via Internet support by Dr. Paul Williams. The question in this study is what can be done to motivate historically active runners and walkers to continue to stay active? The study provides a model to examine innovative ways of maintaining healthy behaviors by integrating new technologies that can be applied to at-risk populations. The test group will receive Internet based support including delivery of information

and interactive tools to promote running and walking. Participants will have a choice of selecting from three virtual transcontinental routes that are traversed as participants accumulate mileage. Participants can communicate with partners to provide support and there will be team competitions and recognition. There are also reminders and encouragement when self-reported activity levels begin to decrease.

- Dr. Horlick described the new Pediatric Clinical Obesity Program. The hope it that the new program will be populated with clinical research projects relating to aspects of pediatric obesity including impact of fetal and neonatal environment, evaluation of feeding behavior, energy expenditure and body composition, studies of the impact of obesity or its treatment on body composition, metabolic and psychosocial factors or co-morbidity, and interventions in a clinical setting with a primary goal of weight loss or prevention of inappropriate weight gain.

  As an example of studies in the program Dr. Horlick described a study "Adolescent Bariatrics: Assessing Health Benefits and Risks" representing an intensive option for treatment of severe pediatric obesity. The principle investigator of the study is Dr. Tom Inge, a pediatric surgeon at Cincinnati Children's Hospital. Preliminary data and literature on changes in co-morbidities after bariatric surgery suggest that early intervention, that is bariatric surgery in adolescence, leads to resolution or major improvement in co-morbidities whereas later intervention (bariatric surgery in adults) leads to only mild improvement. The hypothesis is that surgery performed during the adolescent period is a more effective treatment for juvenile onset extreme obesity compared to surgery delayed until adulthood and that the nutritional and surgical risks will be acceptable. Adults and adolescents are recruited for the study after they have been approved and scheduled for bariatric surgery. The plan is to enroll 200 adolescents aged 14 to 18 who are approved for bariatric surgery and therefore have extreme obesity, and enroll a BMI and sex-matched group of young adults enrolled in the Longitudinal Assessment of Bariatric Surgery (LABS) who have been shown by a validated questionnaire to have had onset of extreme obesity by age 18 years. A comparison between adolescent and young adult cohorts will lead to a better understanding of the plasticity of medical and psychosocial co-morbidities in the life course of those with extreme obesity and will also provide valuable data for scientifically informed decision making regarding appropriate time of bariatric surgery in young people with extreme obesity.

Council Questions and Discussion

*Regarding the HEALTHY Study, it seems that the consent process must be extraordinary since the experiment involves whole schools. How is consent obtained?* Dr. Linder explained that the consent process has been piloted because it is potentially very daunting. The pilot, performed at three sites with four schools at each site (total of 12 schools) was successful in consenting over 1,700 children to have blood drawn in the schools. Dr. Linder commented that it took substantial work on the part of the staff but the pilot resulted in consenting in the range of 50- percent of the grade and in some of the

bigger schools recruitment had to be cut off because the budgeting process had not anticipated such success. Dr. Linder continued that the process does require substantial personnel time to participate in assemblies and Back to School nights with parents, to send out consents and follow-up with parents. Based on the pilots Dr. Linder indicated that she was confident that at least 50 percent of the sixth grade could be recruited.

*In HEALTHY Study, everyone in selected schools gets the intervention. Is this a problem from an IRB standpoint?* Dr. Linder indicated that it is not. The intervention is a program that the school board or district have agreed to. For example, the PE class will use the HEALTHY curriculum. There were no IRB problems.

*Regarding the obesity epidemic, what is your level of optimism of reducing current trends?* Dr. Smith indicated that the bottom line is that it is imperative to come up with clever ways to get people to exercise. Short of that, there are some positive trends. Already, for example, the beverage industry is recognizing that there is a problem and is considering ways to address it (e.g., by creating alternatively sweetened beverages and voluntarily removing sugar-sweetened beverages from schools). There are also potential new drugs coming down the pipeline and it appears promising that the genetics community will bring some new ideas for additional drug targets in the next several years. A huge problem right now is preventing people who loose weight from becoming discouraged and falling back into bad habits. Once someone loses weight they often must struggle to keep the weight off. Hopefully, new drugs will be developed that will help people maintain weight loss. The Diabetes Prevention Trial showed that it does not take much weight loss to improve health. Advances in our understanding of the multiple causes underlying obesity and potential prevention and treatment options provide cause for optimism.

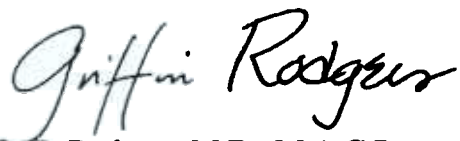
## IX. CONSIDERATION OF REVIEW OF GRANT APPLICTIONS

A total of 710 grant applications, requesting support of $192,216,745 were reviewed for consideration at the May 31, 2006 meeting. Funding for these 710 applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 852 applications requesting $206,350,099 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the May 31, 2006 meeting.

## X. ADJOURNMENT

Dr. Rodgers thanked the Council members for their attendance and efforts. There being no other business, the 171st meeting of the NIDDK Advisory Council was adjourned at 4:50 p.m., May 31st, 2006.

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



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