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

I. CALL TO ORDER

Dr. Rodgers

Dr. Griffin Rodgers, Director, NIDDK, called to order the 210th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on May 8, 2019, in the Porter Neuroscience Research Center (Building 35), Conference Rooms 610-640, the NIH Campus, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Ms. Tracey Brown+
Dr. David D'Alessio*
Dr. Iain Drummond+
Dr. Joel Elmquist
Dr. Penny Gordon-Larsen+
Dr. Lisa Guay-Woodford
Dr. Caren Heller
Dr. Barbara Kahn
Mr. Richard Knight
Dr. Paul Lange
Dr. Jill Macoska+
Mr. Thomas Nealon
Dr. Richard Peek
Dr. Jeffrey Pessin
Dr. Michael Snyder+
Dr. Ronald Sokol
Dr. Ian Stewart*
Ms. Lorraine Stiehl
Dr. Beverly Torok-Storb
Dr. Gary Wu+

Also Present:

Dr. Griffin P. Rodgers, Director, NIDDK, and Chair of the NIDDK Advisory Council
Dr. Karl F. Malik, Executive Secretary, NIDDK Advisory Council
Dr. Stephen P. James, Director, Division of Digestive Diseases and Nutrition, NIDDK
Dr. Robert A. Star, Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK
Dr. Philip Smith, Acting Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK
Dr. Richard Hodes, Director, National Institute on Aging

* *Ex Officio* member
+ Served as an *ad hoc* member for this meeting

B. NIDDK STAFF AND GUESTS

Abbott, Kevin – NIDDK
Abraham, Kristin – NIDDK
Agodoa, Lawrence – NIDDK
Arreaza, Guillermo – NIDDK
Barthold, Julia – CSR
Bateman, Jessica – Amer. Urological Assoc.
Berti-Mattera, Liliana – CSR
Boerboom, Lawrence – CSR
Begum, Najma – NIDDK
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Burch, Henry – NIDDK
Burgess-Beusse, Bonnie – NIDDK
Camp, Dianne – NIDDK
Castle, Arthur – NIDDK
Cerio, Rebecca – NIDDK
Chan, Kevin – NIDDK
Chowdhury, Bratati – NIDDK
Connaughton, John – NIDDK
Curling, Mitchell – NIDDK
Curtis, Leslie – NIDDK
Dayal, Sandeep – NIDDK
Denny, Alexis – PKD Foundation
Doherty, Dee – NIDDK
Doo, Edward – NIDDK
Drew, Devon – NIDDK
Eggerman, Thomas – NIDDK
Evans, Mary – NIDDK
Fisher, Rachel – NIDDK
Fonville, Olaf – NIDDK
Gansheroff, Lisa – NIDDK
Gossett, Danny – NIDDK
Greenwel, Patricia – NIDDK
Haft, Carol – NIDDK

Hamilton, Frank – NIDDK
Hanlon-Tilghman, Mary – NIDDK
Herzog, Peter – Digestive Diseases Nat'l Coalition
Hoofnagle, Jay – NIDDK
Hoshizaki, Deborah – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jerkins, Ann – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kozel, Peter – CSR
Kuczmarski, Robert– NIDDK
Laakso, Joe – Endocrine society
Larkin, Jennie – NIDDK
Laughlin, Maren – NIDDK
Lee, Christine – NIDDK
Leschek, Ellen – NIDDK
Li, Yan – NIDDK
Linder, Barbara – NIDDK
Lynch, Christopher – NIDDK
Malozowski, Saul – NIDDK
Martey, Louis – NIDDK
Martinez, Winnie – NIDDK
Maruvada, Padma – NIDDK
Mendley, Susan – NIDDK
Mullins, Christopher – NIDDK
Murray, Ryan – Am. Society of Nephrology
Osganian, Voula – NIDDK
Otradovec, Heidi – NIDDK
Parsa, Afshin – NIDDK
Pawlyk, Aaron – NIDDK
Perrin, Peter – NIDDK
Perry Jones, Aretina – NIDDK
Rankin, Tracy – NIDDK
Roberts, Tibor – NIDDK
Rooker, Ceciel– NIDDK
Rosenberg, Mary Kay – NIDDK
Rojas, Raul – CSR
Roy, Cindy – NIDDK
Sanovich, Elena – NIDDK
Saslowsky, David – NIDDK
Sato, Sheryl – NIDDK
Sechi, Salvatore – NIDDK
Serrano, Jose – NIDDK
Shea-Donohue, Terez – NIDDK
Shepherd, Aliecia – NIDDK
Sherker, Averell – NIDDK
Sierra-Rivera, Elaine – CSR
Silva, Corinne – NIDDK
Singh, Megan – NIDDK
Smith, Jaime – NIDDK
Smith, Philip – NIDDK
Smith, Thomas – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Stoeckel, Luke – NIDDK
Tatham, Thomas – NIDDK
Teff, Karen – NIDDK
Thornton, Pamela – NIDDK
Tilghman, Robert – NIDDK
Unalp-Arida, Aynur – NIDDK
Van Raaphorst, Rebekah – NIDDK
Vij, Vibha - Westat
Wang, Xujing – NIDDK
White, Vanessa – NIDDK
Wilkins, Kenneth – NIDDK
Wright, Elizabeth – NIDDK
Yang, Jian – NIDDK
Yanovski, Susan – NIDDK

C. ANNOUNCEMENTS

Dr. Rodgers

Council Member News

Dr. Rodgers opened the meeting by welcoming **Dr. Jill Macoska**, the Alton J. Brann Endowed Distinguished Professor in Science, Mathematics and Cancer Biology at the University of Massachusetts, Boston. She is also the director of the Center for Personalized Cancer Therapy, a joint program between the University of Massachusetts, Boston, and the Dana-Farber Cancer Institute. Her research career focuses on exploring the molecular genetic alterations in dysfunctional inter- and intracellular signaling mechanisms that promote prostate pathobiology. Dr. Macoska attended the meeting as an *ad hoc* member and served on the Subcommittee on Kidney, Urologic, and Hematologic Diseases.

Dr. Rodgers also noted a change in the usual order for the Council meeting. A working group from the NIH Advisory Committee to the Director has recommended measures to ensure that NIH institutes and centers follow a uniform process for vetting concepts for possible Funding Opportunity Announcements (FOAs). Henceforth, new concepts must receive clearance from an advisory committee constituted under the Federal Advisory Committee Act (FACA). At this meeting, NIDDK is piloting a "concept clearance" process that will include an in-depth discussion of new and renewed concepts in subcommittee, followed by a brief summary of each concept in an open session of the full Council.

Dr. Rodgers also noted the absence of **Dr. Greg Germino, NIDDK Deputy Director**, who was in Boston attending the 2019 spring clinical meeting of the National Kidney Foundation (NKF). At this meeting, Dr. Germino received the Dr. Shaul Massry Distinguished Lecturer Award, established in honor of Dr. Massry, for his scientific achievements and contribution to the kidney health care community and NKF. In announcing the award, Holly Kramer, NKF president, noted that "Dr. Germino's research has significantly improved our understanding of polycystic kidney disease and molecular basis of how kidneys develop tubules." Dr. Germino's lecture will focus on the state of research on polycystic kidney disease.

Ex officio member **Dr. David Klurfeld**, who represents the Department of Agriculture on the Council, was awarded the Ralph Holman Lifetime Achievement Award from the American Oil Chemist Society, which focuses on research into edible fats and oils.

Dr. Jeffrey Friedman, a long-time NIDDK grantee, of Rockefeller University was awarded the prestigious Wolf Prize in Medicine by the Wolf Foundation in Israel for his seminal work that identified leptin as a key hormone in regulating body weight and metabolism. This discovery revolutionized the field of obesity research by opening new avenues of investigations into the role of leptin, its receptors, and the related neural and hormonal factors that affect energy balance. A Howard Hughes Investigator, Dr. Friedman has received numerous awards and honors, including the Lasker Prize and the Shaw Prize. Dr. Friedman's current research includes a delineation of the neuronal effects of leptin and the mechanisms by which it reduces food intake, as well as the mechanisms responsible for leptin's antidiabetic effects.

Dr. Ronald Kahn, a former NIDDK Council member, of the Harvard Medical School and the Joslin Diabetes Center received the George Kober Medal from the Association of American Physicians (AAP). The award is given to an AAP member whose lifetime efforts have had an enormous impact on the field of internal medicine through their scientific contributions. Dr. Kahn, best known for his work on the mechanism of insulin action and insulin resistance in type 2 diabetes and obesity, has received NIDDK support for over 30 years.

NIDDK Staff News

Dr. Rodgers reported several staffing changes within NIDDK:

Dr. Terry Bishop, who has administered the hematology program within the Division of Kidney, Urologic, and Hematologic Diseases for nearly 20 years, is retiring. She has overseen a portfolio that includes developmental hematopoiesis, erythropoiesis, globin gene regulation, heme biosynthesis and cell differentiation. She has also led the Cooperative Centers of Excellence in Molecular Hematology program and the Stimulating Hematologic Investigations: New Endeavors (SHINE) program. Dr. Bishop started her career at the National Heart, Lung, and Blood Institute as a scientific review officer. Previously, she was on the faculty at The Johns Hopkins University where she was a principal investigator focused on erythropoiesis research. Dr. Rodgers praised her energy and enthusiasm for hematology and her dedication to the hematology program, as well as her devotion to recruiting and training the next generation of young researchers in hematology.

Dr. Anna Sadusky has joined the Division of Kidney, Urologic, and Hematologic Diseases as a program director. Prior to joining KUH, she worked for the American Association for Cancer Research as a director of regulatory science and policy within the Office of Science Policy and Government Affairs. She was a senior scientist at Omeros Corporation, a Seattle-based commercial-stage biopharmaceutical company. Dr. Sadusky earned her Ph.D. in interdisciplinary biological sciences from Northwestern University in 2005. She then completed post-doctoral work with Dr. Jurrien Dean in NIDDK's Division of Intramural Research.

NIDDK Strategic Planning Process

Dr. Rodgers informed the Council that the 21st Century Cure Act requires all NIH institutes and centers (ICs) to prepare a strategic plan. NIDDK has historically focused on disease- and organ-specific strategic plans. NIDDK will now take this opportunity to develop an overarching plan for the entire Institute. Planning will begin in 2019 and continue through 2020, which also happens to be NIDDK's 70th anniversary.

NIDDK will soon solicit advice on research planning from the Council. Additionally, the Institute also will reach out to the broader research and patient communities and others during this planning process. Dr. Rodgers hopes to use the results of the strategic planning process to augment and complement other planning efforts, as well as to inform Congress and other stakeholders of the critical research NIDDK supports and opportunities for the future.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 209th COUNCIL MEETING

Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 209th Council meeting, which had been sent to them in advance for review.

III. FUTURE COUNCIL DATES

2019

September 11 (Wednesday)
Natcher Conference Center, Building 45

2020

January 29-30 (Wednesday and Thursday)
Location to Be Announced

May 20-21 (Wednesday and Thursday)
Location to Be Announced

September 9-10 (Wednesday and Thursday)
Location to Be Announced

Most meetings are expected to be a single day. However, the NIDDK asks Council members to reserve two days for each meeting should a situation arise where a longer meeting is required.

Dr. Rodgers announced that the location planned for the 2020 meetings, Building 31 on the NIH campus, may be unavailable due to construction delays for asbestos abatement. Updated location information will be shared as it becomes available.

IV. ANNOUNCEMENTS

Dr. Karl Malik

Confidentiality

Dr. Malik reminded the Council Members that material furnished for review purposes and discussion during the closed portion of the meeting is considered confidential. The content of discussions taking place during the closed session may be disclosed only by the staff and only under appropriate circumstances. Any communication from investigators to Council Members regarding actions on an application must be referred to the Institute. Any attempts by Council Members to handle questions from applicants could create difficult or embarrassing situations for the Members, the Institute, and/or the investigators.

Conflict of Interest

Dr. Malik reminded the Council Members that advisors and consultants serving as Members

of public advisory committees, such as the NIDDK Advisory Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist Council Members to help ensure that a Member does not participate in, and is not present during, the review of applications or projects in which, to the Member's knowledge, any of the following has a financial interest: the Member, or his or her spouse, minor child, or partner (including close professional associates), or an organization with which the Member is connected.

To ensure that a Member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the Member, and this statement becomes a part of the meeting record. Dr. Malik directed each Council Member to a statement in his/her meeting folder regarding the conflict of interest in review of applications. He asked each Council Member to read it carefully, sign it, and return it to NIDDK before leaving the meeting.

Dr. Malik noted that when the Council reviews applications in groups without discussion--also called "*en bloc*" actions--all Members may be present and may participate. The vote of an individual Member in such instances does not apply to applications for which the Member might be in conflict.

Regarding multi-campus institutions of higher education, Dr. Malik said that an employee at one campus may participate in any particular matter affecting another campus, if the employee's financial interest is solely at one campus and the employee has no multi-campus responsibilities.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Rodgers

Budget Update

Dr. Rodgers updated the Council on the status of NIH's appropriation for Fiscal Year (FY) 2020. The President's Budget Request for 2020 was released in March. The Request for NIH is just under $34 billion, which represents an overall 13.3 percent drop from the FY 2019 level, and approximates the FY 2017 level.

Funding for the 21st Century Cures Act initiatives will be provided at authorized levels, and funding for some programs, like the HEAL Initiative, will remain flat. But across NIH, the proposed decrease in funding would result in the number of research grants falling from approximately 11,600 to about 7,900. For NIDDK specifically, the Request would represent a 14 percent decline of approximately $283 million less than the FY 2019 level, excluding the separate mandatory funding for the Special Diabetes Program.

As was the case in both FY 2018 and FY 2019, the President proposes moving the free-standing Agency for Healthcare Research and Quality (AHRQ) to a new institute within NIH. The proposed National Institute for Research on Safety and Quality would receive $256 million, a 24 percent cut from AHRQ's 2019 funding level.

As part of the appropriations process, the House Appropriations Subcommittee for Labor-HHS-Education held a hearing on NIH in April. NIH Director Dr. Francis Collins and several IC

directors testified. When asked what the NIH would prioritize if it could exceed the proposed budget constraints, Dr. Collins replied that the NIH would fund more grants. Instead of the current funding rate of one in five grant applications, he would like to fund one in three.

Dr. Collins also testified that since 2013, NIH has more than doubled the number of early career investigators receiving grants from about 600 to nearly 1,300. Chairwoman Rosa DeLauro said that the lawmakers are united in boosting NIH funds and are focusing their attention on putting funds into research areas that haven't seen big increases in recent years. Representative DeLauro said she intends to hold additional hearings with other NIH institute directors who have not appeared before the Subcommittee in the recent past.

The Senate Appropriations Subcommittee for Labor-HHS-Education also held its hearing for NIH in April. Dr. Rodgers joined Dr. Collins and other IC directors at the hearing. Asked to describe some of the latest progress in diabetes research, Dr. Rodgers spoke of the development of the first hybrid artificial pancreas and the next generation of continuous glucose monitors, noting that much of the progress in this area was made possible by NIDDK's Special Diabetes Program.

Moving forward, the appropriations subcommittees and the full appropriations committees in each chamber review and revise their draft bills, a process known as markup. The House subcommittee started by marking up its bill, which provides NIH with an increase of $2 billion, or 5.1 percent over 2019. Of this amount, NIDDK would receive about $100 million, a 4.9 percent increase over 2019. As in recent years, the difference between the percent increase in NIH overall and an IC average increase of 4.9 percent reflects additional funding targeted to specific programs. The Senate Subcommittee markup is scheduled to be completed by the end of June.

Dr. Rodgers noted that while the appropriations committees are writing and marking up their bills for 2020, the overall spending caps for defense and non-defense discretionary programs for 2020 have not yet been finalized. He said that the caps for 2020, currently defined by the Budget Control Act of 2011, are substantially lower than the actual 2019 funding levels provided by a previous amendment to the law. These caps are important even though they don't actually appropriate money, and bipartisan legislation is required to change the caps. In April, the House Budget Committee approved H.R. 2021, the Investing for People Act legislation, to raise both the defense and non-defense discretionary spending caps for 2020 and 2021. The proposed new caps potentially would increase NIH funding. In fact, the House appropriations subcommittee for NIH based its recommended FY 2020 funding level on a presumptive increase in the non-defense discretionary spending cap.

Apart from the regular appropriations process, Dr. Rodgers mentioned that the Special Diabetes Program's current authority will expire September 30, but that he believes it is prudent to plan as if the program will be renewed, as it has been since its inception in 1998. Therefore, NIDDK will hold meetings with diabetes experts to provide input about pressing needs and opportunities in diabetes research. This information will be used to plan for new and expanded initiatives that could be pursued with renewed funding.

Dr. Rodgers ended his report by noting that Congress is on a faster track than usual in dealing with the appropriations bill this year, leaving him hopeful that the 2020 budget will be approved by the end of September, as was the case last year.

VI. UPDATE: NATIONAL CENTER FOR COMPLEMENTARY AND INTEGRATIVE HEALTH

Dr. Helene Langevin

Dr. Rodgers introduced Dr. Helene Langevin, Director of the National Center for Complementary and Integrative Health (NCCIH). Dr. Langevin was sworn in as Director of NCCIH on November 26, 2018. Prior to leading NCCIH, Dr. Langevin worked at the Osher Center for Integrative Medicine, jointly based at the Brigham and Women's Hospital and Harvard Medical School. She served as a director of Osher Center and professor in residence of medicine at Harvard Medical School. As a principal investigator of several NIH-funded studies, Dr. Langevin's research has centered on the role of connective tissue in chronic musculoskeletal pain and the mechanisms of acupuncture, and manual- and movement-based therapies. She has authored more than 70 scientific papers and is a fellow of the American College of Physicians.

Dr. Langevin began by explaining that the term "integrative health" includes concepts like treating the whole person, applying conventional and complementary approaches together in a coordinated way, and emphasizing practices that improve or even restore health in addition to preventing disease. She contrasted this integrative approach with the predominant disease model in modern medicine which is, of course, organized around and focused on the etiology and dysfunction of individual organ systems.

Dr. Langevin introduced the concept of "unhealth," noting that it is an actual word although rarely used, unlike the more familiar term "unhealthy." Even though the state of unhealth is rarely considered in medicine, she finds it to be a useful concept in bridging the gap between health and disease because it implies that the transition between health and unhealth is dynamic and reversible, whereas actual disease may be harder to reverse. Disease prevention and health promotion inhabit a broader spectrum that includes a full range of transitions between health, unhealth, and disease, so she prefers to broaden the concept to include primary, secondary, and tertiary prevention.

Dr. Langevin defined primary prevention as what happens when people make improvements to their environment, nutrition, and lifestyle in an attempt to preserve health (and prevent disease). At the other end of the prevention spectrum is tertiary prevention, which occurs when people make efforts to either limit disability or preserve function in the presence of established disease. Between the two is secondary prevention, which focuses on arresting disease progression by means of early detection but also includes interventions to restore health. The latter—restoration of health—needs more research attention, she said.

In examining disease states, Dr. Langevin believes in what she calls a behavioral dysfunction phase, in which healthy behavior is deteriorating and corresponding physical abnormalities are beginning to develop. One example of this phenomenon is how pre-diabetes precedes the full-blown disease state of diabetes. In this instance, defining the difference between pre-disease and disease is important because it determines when behavioral interventions alone are sufficient or

when medical interventions should be added.

Going forward, NCCIH will increasingly prioritize investigations into ways complementary and integrative healthcare can address the full spectrum of disease prevention and health restoration, Dr. Langevin said. This includes natural food or low-dose nutritional supplements for prevention. On the disease-control end of the spectrum, isolation of specific molecules from natural products can lead to the development of conventional pharmaceuticals. In the middle of the spectrum are different approaches to restoring health after disease—such as probiotics to restore a healthy gut environment.

Additionally, she sees untapped potential in investigating how to use behavioral interventions to restore health. Research shows cognitive behavior therapy, meditation, yoga, and tai chi can improve subjective sensations of emotional well-being and feelings of health. Dr. Langevin encourages researchers to explore how these interventions affect physiological processes such as repair, regeneration, restoration, regrowth, and resolution of disease.

While conventional medicine (and even NIH) is organized around different physiological systems, patients aren't just a collection of individual body parts—the systems interact and are connected by tissue, called fascia, the importance of which is only beginning to be understood. Dr. Langevin noted the need for investigations into these connections. For example, the nervous system and the cardiovascular system are connected via the autonomic nervous system, and we are gaining understanding of the connections among the nervous, immune, and endocrine systems. But, for example, we know much less about the connections between the respiratory system and the digestive system. She pointed out that the mechanical forces produced by the diaphragm during breathing can compress the abdominal organs, which may explain the connection some see between yoga and digestion, but a literature search on the terms "respiratory" combined with "gastrointestinal" yields few results. One area to investigate might be how the forces produced by breathing could have an effect on gastroesophageal reflux disorders, she said.

Dr. Langevin pointed out the need for more research into the fascia and how connective tissues affect nearby organs and structures. Although certain conditions that frequently occur together, such as chronic back pain and irritable bowel syndrome or chronic pelvic pain and interstitial cystitis, are usually thought of as being driven by central nervous system phenomena, Dr. Langevin suggested that direct physical and/or mechanical connections between the musculoskeletal system and the genitourinary or digestive systems also should be considered.

Emphasizing that mechanical forces influence biological processes at all levels of function from intracellular biochemistry to whole-organ physiology, Dr. Langevin described connective tissue as a scaffold that determines the shape of the entire body and remodels itself in response to mechanical forces such as gravity, posture, muscle contractions, and other events, such as surgery or injury. Gravity, inactivity, posture, scarring, and adhesions remodel and shorten connective tissue and muscle, which can lead to increasing atrophy, weakness, and inflammation. This in turn creates a predisposition to additional injuries, mostly commonly joint sprains.

Fortunately, connective tissue remodeling can also work in a positive way, Dr. Langevin said, noting that behavioral interventions can prevent injuries and restore function. In particular, yoga and tai chi provide gentle stretching and positive physical awareness of correct movement, which

can assist in the remodeling of connective tissue and correcting postural abnormalities and poor alignment.

At times, the muscles' mechanical forces may not be intense enough to remodel the connective tissue to regain healthy function. Hands-on, direct application of mechanical forces can then help break down adhesions, stretch the connective tissue to a proper length, and allow the muscles to be retrained at a more favorable length and may help modulate processes like inflammation.

Dr. Langevin then described several projects, including some from her own lab. In one, rats were trained to stretch their bodies as part of a model of inflammation of the thoracolumbar fascia in the back. Over the course of two weeks, the animals became less sensitive to pain and had a marked reduction in macrophage infiltration of the thoracolumbar fascia, a sign of reduced inflammation. In another, she collaborated with Dr. Charlie Sarhan of Brigham and Women's Hospital to describe the phenomenon of inflammation resolution in which the body produces molecules derived from dietary omega-3 fatty acids that are converted to specialized pro-resolving mediators. These molecules are up to 1,000 times more potent than the omega-3 fatty acids themselves in reducing and resolving—though not suppressing—inflammation.

Dr. Langevin also discussed a recently published study from Dr. Geoffrey Bove of the University of New England in which he and his colleagues developed a repetitive motion model in which rats were trained to pull a lever with increasing amounts of force to earn a reward. As the force increased over time, the rats developed repetitive motion injuries. However, rats that received gentle massage during training improved function and did not develop injuries. Function deteriorated in the rats that were not massaged. What's more, fibrous collagen in the connective tissues increased in the rats that did not receive massage, while levels remained close to normal in the massaged rats, preventing the development of fibrosis. Another small study from the same group indicated that abdominal massage following surgery may prevent adhesions.

Dr. Langevin also wants to see more research exploring systemic inflammation and its consequences. She believes that many of the same behavioral interventions that can help with musculoskeletal inflammation, pain, and connective tissue fibrosis can also help with chronic inflammatory disease processes. In general, she sees a need to better understand how behavior modifications can have profound physiological effects.

She sees some application of this research to investigations of the effects of sedentary lifestyle and poor diet on weight gain and the development of pre-diabetes and diabetes. In the debate over whether to treat pre-diabetes, she pointed out that many of the same behavioral interventions that can help with musculoskeletal inflammation, pain, and connective tissue fibrosis may also help with sleep, stress, and diet and help restore health and prevent chronic disease. The key is early intervention.

Dr. Langevin closed by summarizing NCCIH's role in exploring and promoting whole-person health and non-pharmacological approaches to restorative health practices. Since NCCIH is a small center, inter-center and inter-institute collaborations, including with NIDDK, are vital and very much welcomed. She then took questions from the audience.

Council Questions and Discussion

Do we need to reinterpret findings from clinical trials based on these new designations you described? For example, in microbiome research, studies include healthy controls, but maybe we're not controlling adequately for behavioral factors like insufficient sleep. In the future, perhaps we should incorporate some of the parameters you mentioned today.

Dr. Langevin agreed there is much to consider, especially because the concept of a healthy population has never been truly defined. She believes that the NIH Office of Behavioral Health and Disease Prevention would be an important partner in reaching a consensus.

Dr. Rodgers noted that this comment from Council hinges upon redefining what potential placebo effects are or could be. Dr. Langevin agreed that research into the placebo effect is important and needed, given that we already know that placebo effects are not just subjective but physiology-changing.

It seems the principles laid out would have equal application to the growing crisis of nonalcoholic fatty liver disease and NASH and the need for behavioral modifications in the absence of effective medical treatment.

Dr. Langevin agreed.

NCCIH's focus area may be well-suited to the techniques of "citizen science" and for bringing rigor and reproducibility to examinations of things like dietary supplements. Do you have plans to create and implement such initiatives, alone or in conjunction with other institutes?

Dr. Langevin mentioned the importance of NIH's *All of Us* program to NCCIH, noting that the scale and longitudinal nature of *All of Us* may yield insights into how people can grow old and remain healthy. Specifically relating to the issue of dietary supplements, she noted that this is a priority area for NCCIH, particularly with the emergence of cannabidiol and related products.

The NIDDK portfolio includes a number of diseases, such as polycystic kidney disease and sickle cell disease, that include chronic pain and major quality-of-life issues. We also know that these patients are not immune to getting caught up in the opioid crisis. What is NCCIH doing to learn about pain?

Dr. Langevin responded that pain is one of NCCIH's major focus areas, particularly in looking at pain in an integrative way. One center priority is to study how to measure pain sensitivity at baseline to learn to predict who will respond to specific types of treatment. The same principles of health restoration and whole-body and nonpharmacological treatments apply to pain as well as NCCIH's other research interests.

In looking at chronic kidney disease, when flow is arrested, the organ degenerates in a self-amplifying process. This raises the issue of whether imposing flow by peristaltic application of force to the ureter would actually preserve kidney function. What would be the equivalent of rat massage for the kidney?

Dr. Langevin found this to be an intriguing question. She focused on the relationship between

the kidney and psoas muscle, noting that the psoas, while poorly understood, appears to play an important role in back pain. So a massage of this area would both impart mechanical force onto the kidney and possibly relax the psoas, potentially relieving back pain as well. She also noted that some people are trying to develop manual techniques to promote lymphatic flow. Something comparable may be possible for urine flow, even within the kidney.

VII. SCIENTIFIC PRESENTATION: Autosomal Recessive Polycystic Kidney Disease: New Insights Reveal Provocative Complexities

Dr. Lisa Guay-Woodford

Dr. Rodgers introduced Dr. Lisa Guay-Woodford, Council member, internationally recognized pediatric nephrologist, and Richard L. Hudson professor of pediatrics at Children's National Health System at George Washington University School of Medicine and Health Sciences. Dr. Guay-Woodford's research interests include inherited renal disorders, especially autosomal recessive polycystic kidney disease.

References:

(1) The ciliary protein cystin forms a regulatory complex with necdin to modulate Myc expression. Wu M[1], Yang C, Tao B, Bu S, Guay-Woodford LM. PLoS One. 2013 Dec 11;8(12):e83062.
(2) Autosomal recessive polycystic kidney disease: the prototype of the hepato-renal fibrocystic diseases. Guay-Woodford LM. J Pediatr Genet. 2014;3(2):89-101
(3) Clinical and genetic characterization of a founder PKHD1 mutation in Afrikaners with ARPKD. Lambie L, Amin R, Essop F, Cnaan A, Krause A, Guay-Woodford LM. Pediatr Nephrol. 2015 Feb;30(2):273-9
(4) Cystic kidney disease: a primer. Cramer MT, Guay-Woodford LM. Adv Chronic Kidney Dis. 2015 Jul;22(4):297-305.

VIII. UPDATE: NATIONAL INSTITUTE ON AGING

Dr. Richard Hodes

Dr. Rodgers introduced Dr. Richard Hodes, Director of the National Institute on Aging (NIA), which leads the federal effort to support and conduct research on the biological, clinical, and behavioral and social aspects of aging. A leading researcher in the field of immunology, Dr. Hodes has served as Director since 1993, overseeing a strong, diverse, and balanced research program. NIA is the lead NIH institute for research into effective ways to treat and prevent Alzheimer's disease (AD), and cutting-edge research conducted and supported by NIA has helped revolutionize the way we think about Alzheimer's disease and related dementias (ADRD).

Dr. Hodes started by summarizing recent changes in NIA's budget, which has tripled from $1.045 billion in 2013 to $3.083 billion in 2019. Most of the additional funds stem from the Congressional appropriation targeted at Alzheimer's disease and related dementias, reflecting a strong national and global emphasis on this disease and these conditions. He pointed out that although the funds have come to NIA as the lead institute, success in this mission depends on bringing together talents across the biological and behavioral science disciplines supported by many other institutes within NIH.

NIA accomplishes this by awarding administrative supplements to grantees whose work is relevant to ADRD. Some 300 of these supplements were funded, 21 of which went to NIDDK grantees. Some examples of research supported at NIDDK include efforts to identify specific

associations between central nervous system impairments and complications of diabetes, the role of nitric oxide signaling in the development of dementia, an examination of cell biology and the role of peptide hormones in type 2 diabetes and AD, and a gene therapy method to investigate whether there is a connection between AD-related pathologies and inflammation in the gut. In all, about $200 million of research was funded at other NIH institutions in 2018, including $7 million to NIDDK.

Dr. Hodes pointed out that NIA is looking for ways to recruit leading and innovative researchers to the field. From 2015 to 2018, one-quarter of awards went to new or early-stage investigators and one-third were new to the field of AD and ADRD research.

Thus far, large clinical trials targeting AD have been disappointing. Many have aimed at addressing amyloid, a protein that builds up in the brain and has been implicated in the development of AD, especially the rare but tragic form of autosomal dominant AD, caused by gene mutation that runs in families. This mutation may also be relevant to other conditions, Dr. Hodes said. Despite the evidence of amyloid's involvement with AD, industry-supported trials targeting amyloid with antibodies have yielded negative results, especially in addressing AD once symptoms start. Brain scans show that by the time even early symptoms appear, amyloid accumulation has reached maximum levels. Continuing efforts are looking at very early stages of the disease, looking at individuals who inherit the autosomal dominant gene and who will, tragically, develop the disease, often in their 40s. The idea is to treat people decades before symptoms begin to prevent the appearance of amyloid lesions in the brain and prevent rather than reverse damage.

Additional funding for AD research has also enabled basic science discoveries that target multiple pathways and networks. Currently, NIA has 140 broadly defined interventions and treatment trials underway, including several that target caregivers and caregiver interventions. Of the 35 pharmaceutical trials currently underway, 12 target amyloid. The majority target other pathways, including neurotransmitters, growth factors, diseases that affect proteins, and inflammation. NIDDK and NIA are both active in a consortium looking at vascular aspects of hypertension and diabetes to see if there's any application to the development of ADRD. Until a cure is found, there is an enormous burden on those caring for loved ones with AD. Some of the most successful trials have looked at lifestyle interventions to improve quality-of-life, delay the need for institutionalization, and address the stress on caregivers and providers.

Dr. Hodes presented a list of genes that have been linked to AD either as risk factors or protective factors. The discoveries, which started in the 1990s, have accelerated in recent years. In 2018 there were more new genetic factors identified than all previous years.

He pointed out that both AD and type 2 diabetes are important topics for the Accelerating Medicines Partnership (AMP), a public-private partnership among the NIH, FDA, the pharmaceutical and life sciences industry, and nonprofit organizations. Launched in 2014, the partnership is working to develop new diagnostics and treatments by identifying and validating promising targets, with the goal of reducing the time and cost of developing new therapies. The consortium has released a list of more than 100 promising targets to accelerate the pace of this information into clinical trials.

Another important area of investigation is to gather and assess evidence to make health

recommendations for prevention of ADRD. In a two-phase process in cooperation with the Agency on Healthcare Research and Quality (AHRQ) and the National Academy of Medicine (formerly known as the Institute of Medicine), NIA found encouraging but inconclusive evidence for cognitive training, blood pressure management, and increased physical activity to prevent ADRD. Dr. Hodes pointed out that along with other reasons to increase physical activity and manage blood pressure, we don't have to wait for conclusive evidence for AD prevention to encourage these activities. He pointed to findings from the Systolic Blood Pressure Intervention Trial (SPRINT) study that looked at standard versus intensive treatment of hypertension in severe vascular disease. Although the trial was stopped prematurely because the intensively managed group was doing substantially better, the researchers continued to follow participants with brain imaging and cognitive testing to monitor different in cognitive function. Results published in January from the SPRINT-MIND (Memory and Cognition in Decreased Hypertension) trial found a 19 percent reduction in the rate of mild cognitive impairment (MCI), which is frequently a precursor to dementia, and a 15 percent reduction in the rate of MCI and dementia combined. He said this is probably the strongest evidence to date of the impact of a preventive intervention on age-related cognitive decline and risk of dementia.

Dr. Hodes pointed to other shared interests with NIDDK, including strategic planning for nutritional research. NIA is a co-sponsor of the Look AHEAD study, which collects data on the long-term effects of intentional weight loss on body composition and physical function. Look AHEAD Mind is a 4-year, $5.7 million ancillary study that will repeat cognitive assessments in the cohort to confirm findings and identify potential mechanisms for both benefits and harms from intentional weight loss. Another study, the CALERIE Biobank Analysis, found that participants in the caloric restriction arm had slower increase in biological aging compared to controls.

Dr. Hodes also briefed the group on the activities of the trans-NIH GeroScience Interest Group initiated by NIA and involving 21 institutes, including NIDDK. The purpose is to explore the role of age as a risk factor for disease and chronic disease. He discussed the components—or pillars—of GeroScience, focusing particularly on senolytics, or the breakdown of senescent cells, which do not have the ability to proliferate or divide. Senescent cells accumulate in all tissue as we age and secrete a number of factors that affect the function of non-senescent cells, including breaking down telomeres (associated with life span), damaging DNA, and reducing tumor suppression. These cells also increase oxidative stress, which reduces the body's ability to repair itself.

To explore the role of senescent cells in the development of disease, researchers are looking at ways to reduce or eliminate them. In recent studies, mice who were treated with a combination of two drugs that eliminate senescent cells lived longer than control mice and experienced less cognitive decline. Eliminating senescent cells has also improved obesity-induced metabolic function, including renal function, heart function, and hemoglobin A1c in animal models.

In a pilot study in humans, individuals with idiopathic pulmonary fibrosis treated with the same drug combination saw increases in function, including distance walked in six minutes, walking speed, and standing up from a chair. Dr. Hodes says more studies are underway into the association between senescent cells, aging, and development of disease.

He closed with the hope that NIA and NIDDK will continue to collaborate on joint interests. He

then opened the floor to questions.

Have you looked at the senolytics approach to diabetes? Is there data on blood sugar regulation?

Dr. Hodes said investigations of senolytics and senescent cells in diabetes are underway and such research presents an opportunity for collaboration between NIDDK and NIA, looking at hemoglobin A1c in people with diabetes or at risk for diabetes. Diabetes is a known risk factor for dementia, so remains an important target.

Is the lack of an animal model for AD a limiting factor in this line of research? Are investigators using CRISPR to develop better models?

Dr. Hodes agreed that there has been a lot of concern about the quality of animal models in AD. He explained that, to date, animal models for AD have involved mice with one or a combination of gene mutations associated with the risk of AD. But interventions that appeared to work in the mouse model have failed in human trials to reduce amyloid in the brain and improve cognitive performance. He said that NIA has established two new research centers committed to developing new animal models that will be more reflective of the disease in humans.

He said that CRISPR is being used on mouse models. He said there is also interest in non-transgenic natural models of AD, looking beyond mouse and rodent models to primates and marmosets.

You mentioned that the effect of senescent cells is evident even when few cells are detected. How do we know they are limited in number or if our detection methods are not adequate?

Dr. Hodes explained that detection has relied on reporter genes like p16 and admitted that not all senescent cells may be in that pathway. He said that methodologies for single cell exploration of gene expression may help here. The initial focus has been peripheral blood because that is easiest, but further explorations will look at other tissues.

Is there interest at NIA in nutritional research into alternative food utilization and the brain, specifically ketogenesis and some of the intriguing initial observations on cognitive function in elderly people?

Dr. Holes explained that both animal models and human studies are investigating the impact of administering ketones or ketogenic treatments on many aspects of aging, including cognition. A current clinical trial is looking at intranasal insulin delivery, which has been shown to achieve selective insulin increases in the brain without increasing systemic insulin levels , as a means of preventing AD. The idea is that relative insulin resistance in the brain may contribute to metabolic abnormalities in the dementia process.

Have there been many studies on families or individuals who live long and never get dementia?

In addition to looking at risk factors, studies have looked at protective factors and identifying genes that may protect. The numbers of super-centenarians—people who have escaped cognitive deterioration—are small but investigators might be able to find protective factors against ADRD. There might be opportunities for collaboration with researchers who are already looking at individuals in these populations.

Is the senescent cell a particular type of cell?

Dr. Hodes explained that most, if not all, cell types progress to senescence, although the signs of senescence appear to differ under different circumstances and by cell type. In some, such as lymphocytes, the process is less obvious than others. In addition to senescence, there's also exhaustion and other states in which cells don't proliferate any more (quiescence). Macrophages are among those cells in which, under certain conditions, senescence can be induced by DNA damage, radiation, and normal aging.

Can you comment on the idea that AD plaques are formed as a defensive response to infection? Would blood pressure data reflect a blood-brain barrier leakiness that might expose the brain?

A number of researchers are looking at the interrelationship between AD, amyloid, and infectious disease. Over the years, there have been several proposals for how infectious agents can contribute to AD. Rudolph Tanzi's group at Harvard has suggested that amyloid may protect against certain infections. Analysis of brains with AD and unaffected brains resulted in sequences that suggest human viruses and responses to those viruses. An ongoing trial is looking at the impact on cognition of antivirals on individuals with herpes infection. The question is whether the amyloid is a protective response to inflammation or infection or if infection is driving neurodegeneration through inflammatory intermediaries.

The CDC publishes "heat maps" that show the incidence of obesity and diabetes on a state-by-state basis. Does AD parallel that trend? Has the incidence of AD gone up as populations age and obesity becomes more common? Do you see similar generational trends in AD as we do in children or even grandchildren of obese and diabetic mothers are more likely to be obese and diabetic?

Dr. Hodes explained that reports from a number of countries, including the U.S., showed that the age-specific rate of AD was decreasing a few years ago. Associated variables were education level and cardiovascular risk factors. Although clinical trials on this are difficult to design and perform, natural experiments suggest that education can be protective, whether as an actual effect due to neural development or whether individuals simply have more cognitive reserve as a result of education and therefore don't show clinical signs of dementia as early. In recent years, the decline in dementia rates has leveled off and may be increasing again, along with the rate of obesity and cardiovascular disease.

Generational patterns have been of interest going back to the Barker hypothesis that correlated low birthweight and premature birth with the development of hypertension, heart disease, and type 2 diabetes. However, the link with cognitive decline has not been studied.

Can you comment on what the NIA is doing to explore the connection of diet and exercise with cognitive impairment?

In addition to looking at drugs and molecular targets, AD research is also looking at lifestyle factors. Currently, 13 clinical trials of exercise or diet and exercise are underway, mostly looking at preclinical or early stage disease. Investigations into cognitive training have shown that short-term, intensive cognitive training improves processing speed, memory, and executive function, with individuals maintaining those advantages for many years. There's a suggestion from these studies—although they were not designed to determine this—that the early training was associated with decreased risk of cognitive decline. NIA is planning studies with more power to look at that connection. Other studies are looking at blood pressure and blood pressure control and its connection to cognition.

IX. CONCEPT CLEARANCE

Dr. Rodgers explained again that, to comply with new recommendations from the NIH Advisory Committee to the Director, NIDDK is piloting a new process for clearing concept for Funding Opportunity Awards (FOA) prior to publication. After in-depth discussion in the subcommittees, NIDDK staff presented brief concept summaries to the full Council.

Diabetes, Endocrinology, and Metabolic Diseases Subcommittee

- **Accelerating Medicines Partnership for Type 2 Diabetes (AMP T2D)** focuses on disease-modifying therapies for type 2 diabetes. Five pharmaceutical companies and NIH form the partnership. The purpose of this pre-competitive collaboration is to aggregate and harmonize human genetic data to identify and validate therapeutic targets and biomarker candidates for clinical trials. The database includes more than 400 genomic risk variants and has identified 70 probable-causal therapeutic target/biomarker effector transcripts. It hosts automatic analytic methods so that non-geneticists can mine the data across a wide range of phenotypes. The concept proposes to continue this work to foster fundamental, translational and clinical research through the open dissemination of genetic and network analysis of T2D and its complications.
- **Catalyst Award in Diabetes, Endocrinology and Metabolic Diseases**, piloted a year ago, is patterned on the NIH Common Fund Pioneer Award Program to fund high-risk/high-reward projects proposed by creative investigators with a proven track record of innovation. The pilot elicited a robust response from many people outside the diabetes community, and the project funded a number of innovative proposals.
- **Support of Emerging Physician Scientists to Develop Research Careers in Diabetes, Endocrinology & Metabolic Diseases** helps overcome roadblocks for physicians to pursue research careers in NIDDK's submission areas. Physicians emerging from training programs don't have publications or research experience to compete effectively for K awards compared to Ph.Ds. This program links medical doctors with productive, funded researchers in the diabetes mission areas and provides significant support beyond the fellowship level to help them gain experience and productivity so that they can compete effectively for K awards.
- **Bioinformatics Training in DEM Research Areas** grows out of an increasing need to apply computational methods to compelling research problems in diabetes, endocrinology, and metabolic diseases. To increase the number of trained bioinformatics scientists in this area of research, the DEM division plans to support interdisciplinary

training in both bioinformatics and DEM disease with training awards for predoctoral students and postdoctoral fellows.

Digestive Diseases and Nutrition Subcommittee

- **Molecular Mechanism of Metabolic Adaptation to Weight Change** addresses the problem of regaining weight after weight loss. After weight loss, people have a new metabolic set point that requires fewer calories to maintain that weight loss. The goal of this program will be to take a deep look into the biology behind this process.
- **Chronic Pancreatitis, Diabetes, and Pancreatic Cancer** aims to support collaborative multidisciplinary research into pancreatic diseases, including acute, recurrent, and chronic pancreatitis as well as the development of pancreatic cancer.
- **Food Insecurity and HIV** addresses the issues of inadequate nutrition among people with HIV/AIDS, particularly those who remain untreated and continue to contribute to the epidemic.
- **Obesity and HIV** addresses the rise in obesity among people with HIV and the increasing evidence that indicates effects on adipose tissue physiology and other unique mechanisms associated with HIV may be at play. The purpose of the program is to determine the underlying mechanism and understand the relative contribution of HIV and/or anti-retroviral therapy to weight gain.

Kidney, Urologic, and Hematologic Diseases Subcommittee

- **Centers of Excellence in Hematology** program seeks renewal funding to continue support of multidisciplinary research, collaboration, and resources to support hematology research through a national consortium aimed at combatting nonmalignant hematologic disease. It includes a national pilot and feasibility program for enrichment of emerging scientists in this field and development of shared resources and data.
- **Prevention of Lower Urinary Tract Research Consortium** seeks renewal to continue work to establish the scientific basis for intervention studies to promote bladder health and prevent bladder conditions in adolescent and adult women. The program aims to expand understanding of risk and protective factors associated with urinary tract diseases and identify targets for future study. A collaborative and transdisciplinary group of investigators will look at risk factors across the lifespan.
- **United States Renal Data System (USRDS)** is a critical data resource on the incidence, prevalence, mortality, and cost of kidney disease in the United States that is mandated by Congress. Its annual data report is shared and used widely by other government agencies, and investigators also rely on the data and analysis files. The renewal will establish a special study section to look transitions of care in chronic kidney disease.
- **Supporting Descriptive Epidemiology of Non-Malignant Urological Disease (UDA)** tracks data on the incidence, prevalence, and costs of urological disease.
- **National Survey of Prevalence of Kidney Disease** is a population-based survey that has continued for more than 20 years to measure the prevalence of chronic kidney disease in the U.S. Information from this survey is used by other divisions of NIDDK as well as by the USRDS and UDA mentioned above.
- **Polycystic Kidney Disease Centers Program** funds four PDK research centers as well as a coordinating site. The research centers develop and validate resources and the coordinating center administers a common pilot and feasibility program.
- **(Re)Building a Kidney**, a project described at the January Council meeting, conducts a

variety of research projects aimed at stimulating regeneration, enhancing productive repair, or generating functioning kidney tissue that can then be integrated into structures that replicate human kidney function.

Trans-NIDDK

- **NIDDK's Therapeutics Discovery Translational Pipeline** promotes the translation of basic science discoveries into knowledge and development of tools to support later-phase drug discovery and development. It has resulted in 36 awards and brought in more than a dozen medicinal chemistry groups to NIDDK mission areas.
- **Pathways for Review and Release of Available NIDDK Repository Samples** maximizes benefit from data and samples collected from multicenter and large single-center trials, then makes them available to interested scientists by application and administrative review.
- **Optimization of NIDDK Investment in Large Research Programs** is a replacement for the Program Project Grants, which will be phased out to allow resources to be shifted to more flexible awards to support collaborative research.
- **Supporting Transition to Independence for NIDDK Career Training Awardees** provides support to currently funded K awardees to undertake short-term, limited-scope projects. These $75,000/year supplemental grants are designed to allow them to conduct small, independent feasibility or pilot studies. Usually, researchers apply in the latter years of their K experience to encourage them to accrue publications from their K work, particularly for clinically oriented projects.

All concepts presented to the council are available on the NIDDK website and are associated with the NIDDK Advisory Council section of the website. (See https://www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/national-diabetes-digestive-kidney-diseases-advisory-council/concept-clearances.)

IX. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS.

A total of 1,158 grant applications (369 primary and 789 dual), requesting support of $434,087,880 were reviewed for consideration at the meeting. An additional 1,292 Common Fund applications requesting $1,905,758,566 were presented to Council. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Council meeting, 1,139 applications requesting $376,875,076 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 Council at the meeting.

XI. ADJOURNMENT

Dr. Rodgers

Dr. Rodgers expressed appreciation on behalf of the NIDDK to the Council members, presenters, and other participants. He thanked the Council members for their valuable input. There being no other business, the 210th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m.

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

Griffin P. Rodgers, M.D., M.A.C.P.
Director, National Institute of Diabetes and Digestive and Kidney Diseases
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council