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 206th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on January 24, 2018, in Conference Room E1/E2, Natcher Conference Center, Building 45, the NIH Campus, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Joseph Bonventre
Dr. Eugene Chang
Dr. David D'Alessio
Dr. Mark Donowitz
Dr. Joel Elmquist
Dr. Lisa Guay-Woodford
Dr. Caren Heller
Ms. Ellen Leake
Dr. Lee Kaplan
Dr. David Klurfeld
Mr. Richard Knight
Dr. Paul H. Lange
Mr. Thomas Nealon
Dr. Jeffrey Pessin
Dr. Craig Peters
Dr. Alan Saltiel
Dr. Jean Schaffer
Ms. Pamela Taylor
Dr. Beverly Torok-Storb+

+Participated in KUH Sub-Council by phone

Also Present:
Dr. Griffin Rodgers, Director, NIDDK and Chair of the NIDDK Advisory Council
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Karl Malik, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

Abbott, Kevin – NIDDK
Abraham, Kristin – NIDDK
Agodoa, Lawrence – NIDDK
Akolkar, Beena – NIDDK
Ananthanarayanan, Meena – CSR
Arreaza-Rubin, Guillermo – NIDDK
Barnard, Michele – NIDDK
Begum, Najma – NIDDK
Berti-Mattera, Liliana – CSR
Best, Caroline – Am. Urol. Assoc.
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Boerboom, Lawrence – CSR
Bourque, Sharon – NIDDK
Bremer, Andrew – NIDDK
Buchanan, Susan – NIDDK
Buckler Gretchen – NIDDK
Burch, Henry – NIDDK
Burgess-Beusse, Bonnie – NIDDK
Castle, Arthur – NIDDK
Cerio, Rebecca – NIDDK
Chen, Hui – CSR
Chowdhury, Bratati – NIDDK
Connaughton, John – NIDDK
Copeland, Randy – NIDDK
Crews, Donna – NIDDK
Curling, Michell – NIDDK
Curtis, Leslie – NIDDK
Davila-Bloom, Maria – NIDDK
Dayal, Sandeep – NIDDK

Densmore, Christine – NIDDK
Dirks, Dale – Health & Med. Counsel of Washington
Doherty, Dee – NIDDK
Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Drew, Devon – NIDDK
Eggerman, Thomas – NIDDK
Evans, Mary – NIDDK
Farishian Richard – NIDDK
Fisher, Rachel – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gansheroff, Lisa – NIDDK
Goglas II, Philip – Health & Med. Counsel of Washington
Greenwel, Patricia – NIDDK
Guo, Xiaodu – NIDDK
Haft, Carol – NIDDK
Hall, Sherry – NIDDK
Hanlon-Tilghman, Mary – NIDDK
Hansen, Dani – NIDDK
Hoff, Eleanor – NIDDK
Hoffert, Jason – NIDDK
Hoofnagle, Jay – NIDDK
Hoshizaki, Deborah – NIDDK
Hu, Jianxin – CSR
Hyde, James – NIDDK
Ivins, Jonathan – CSR
James, Stephen – NIDDK
Jerkins, Ann – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kranzfelder, Kathy – NIDDK
Laakso, Joseph – Endocrine Society
Larkin, Jennie – NIDDK
Laughlin, Maren – NIDDK
Lawlor, Sharon – NIDDK
Li, Yan – NIDDK
Linder, Barbara – NIDDK
Lynch, Christopher – NIDDK
Malozowski, Saul – NIDDK
Martey, Louis – NIDDK
Martinez, Winnie – NIDDK
Mendley, Susan – NIDDK
Morris, Ryan – NIDDK
Mullins, Christopher – NIDDK
O'Hare, Elizabeth – Lewis-Burke Associates
Olumi, Aria – AUA/Mass General Hospital
Otradovec, Heidi – NIDDK
Parsa, Afshin – NIDDK
Payne, January – NIDDK
Perrin, Peter – NIDDK
Pike, Robert – NIDDK
Raja, Maidah – NIDDK
Rankin, Tracy – NIDDK
Regan, Karen – NIDDK
Reiter, Amy – NIDDK
Roberts, Tibor – NIDDK
Rojas, Raul – CSR
Rooker, Ceciel – Int. Found. for Func. Gastrointestinal Disorders
Rosenberg, Mary Kay – NIDDK
Roy, Cindy – NIDDK
Rymaruk, Jennifer – NIDDK
Sanovich, Elena – NIDDK
Saslowsky, David – NIDDK
Sato, Sheryl – NIDDK
Sechi, Salvatore – NIDDK
Sherker, Averell – NIDDK
Shepherd, Aliecia – NIDDK
Sierra-Rivera, Elaine – CSR
Silva, Corinne – NIDDK
Singh, Megan – NIDDK
Smith, Jaime – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Stoeckel, Luke – NIDDK
Tatham, Thomas – NIDDK
Teff, Karen – NIDDK
Tenuto, Michael – NIDDK
Thornton, Pamela – NIDDK
Tilghman, Robert – NIDDK
Tuncer, Diane – NIDDK
Turner, Linda – NIDDK
Unalp-Arida, Aynur – NIDDK
Utama, Herman – NIDDK
Wallace, Julie – NIDDK
Wang, Xujing – NIDDK
Weiner, Jeff – NIDDK
Woynarowska, Barbara – NIDDK
Xie, Yining – NIDDK
Yanovski, Susan – NIDDK
Zhao, Aiping – CSR

C. ANNOUNCEMENTS
Dr. Rodgers

Council Member News

Dr. Rodgers noted that five Council members will complete their extended terms of service after this meeting: ***Dr. David Brenner***, ***Dr. Eugene Chang***, ***Dr. Craig Peters***, ***Dr. Jean Schaffer***, and ***Ms. Ellen Leake***. Dr. Rodgers congratulated them and expressed gratitude for their exemplary service during their appointed terms and their extended service.

NIDDK Staff News, and Annual Report

Dr. Rodgers welcomed two new staff members:

Dr. Afshin Parsa joined the Division of Kidney, Urology, and Hematologic Diseases (KUH) in September as senior scientific officer focusing on clinical kidney genomics, chronic kidney disease progression, and glomerulonephritis. Dr. Parsa received his M.D. from the Robert Wood Johnson Medical School in 1996 and completed his postgraduate training in internal medicine at Brown University and his fellowship in nephrology (which included training in genetic epidemiology) at the University of California, San Francisco. He also received a master's degree in public health from the University of California, Berkeley. Prior to accepting the position at KUH, Dr. Parsa was an associate professor in the department of medicine, division of nephrology at the University of Maryland School of Medicine and served as an attending physician at the Baltimore Veterans Affairs Medical Center. He has been involved and held leadership roles in large national and multinational consortia-based projects, which have resulted in many high-profile publications.

Dr. Susan Mendley also joined KUH as a program official focusing on pediatric nephrology. Dr. Mendley was the division head of pediatric nephrology at the University of Maryland Medical Center and served as an associate professor for pediatrics, medicine, and surgery at the University of Maryland School of Medicine. Dr. Mendley received her M.D. from Boston University and completed her postgraduate training in internal medicine and nephrology at the University of Chicago as well as a fellowship in pediatric nephrology at Northwestern University. She is recognized for her development of a robust clinical research portfolio at the University of Maryland and leadership roles in several pediatric studies. For 25 years, she has provided outstanding clinical care to children with kidney disease.

NIDDK 2017 Annual Report. Dr. Rodgers announced the newly published *NIDDK Recent Advances and Emerging Opportunities, 2017*, a report issued annually to highlight examples of NIDDK-supported research progress. He brought attention to the cover, which features the discovery of how pathogenic *E. coli* establishes a chronic urinary tract infection (UTI) by deploying one type of adhesion molecule to attach to receptors in healthy tissue and another to attach to already-infected tissue. This discovery could lead to new targets to fight UTIs.

The report also includes personal stories of patients who have participated in NIDDK-funded research, research stories of discovery, information on funding trends, and other special features. Dr. Rodgers acknowledged the work of NIDDK's Office of Scientific Program and Policy Analysis in developing the content and managing this project, and NIDDK's extramural and intramural research divisions for providing input and guidance.

The publication is available online at https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/niddk-recent-advances-emerging-opportunities-2018.aspx.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 205th COUNCIL MEETING
Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 205th Council meeting, which had been sent in advance for review.

III. FUTURE COUNCIL DATES

2018

May 16-17 (Wednesday and Thursday)
Natcher Conference Center (Building 45)
Conference Rooms E1/E2, D and F1/F2

September 7 (Friday)
Clinical Research Center (Building 10)
Conference Rooms FAES B1C205, B1C207, B1C209, B1C211, B1C204, B1C206, B1C208

2019

January 16-17 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6, and 7

May 8-9 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6, and 7

September 11-12 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6, and 7

Note that the September meeting will be held on a Friday, rather than the typical Wednesday-Thursday schedule, in the NIH Clinical Research Center (Building 10). The meeting will return to Building 31 for the January 2019 meeting.

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 for which a longer meeting is required.

IV. ANNOUNCEMENTS

Dr. Malik

Confidentiality

Dr. Karl 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 file. Dr. Malik directed each Council Member to a statement in his or 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 pointed out that at Council meetings when applications are reviewed in groups without discussion, also called "*en bloc*" action, all Council 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.

Dr. Malik also asked the Council to vote to approve the Council operating procedures that were included for Council review in the pre-meeting materials. He noted that he reorganized the document to include subheadings, and made a revision to give Dr. Rodgers some flexibility to make exceptions to the operating procedure guidelines under exceptional circumstances. He explained that he made these changes given the current uncertainties associated with the Special Diabetes Program authorization and the potential impact if there were an interruption getting materials to Council. The motion to approve was made and seconded and the Council members voted to approve the operating procedures.

V. REPORT FROM THE NIDDK DIRECTOR
Dr. Rodgers

Budget Update

Dr. Rodgers reported that just after the Council's September meeting the Senate bill for the Department of Health and Human Services passed the full appropriations committee, and the House passed all its appropriations bills on September 14, 2017. However, this did not complete the funding process, and Congress subsequently passed four continuing resolutions. There was a lapse of funding for one work day before the President signed the latest (fourth) continuing resolution, which runs through February 8, 2018.

Without a final budget for FY 2018, NIH and NIDDK continue to work at the FY 2017 funding level. Dr. Rodgers explained that the House and Senate bills for HHS propose increases in appropriations for NIH and NIDDK.

He also noted that the President's 2018 Budget Request includes moving the Agency for Healthcare Research and Quality under the NIH. The Senate bill rejects this proposal, but the House bill calls for a study to determine the best way to conduct the agency's research and reduce overlap with other agencies. The President's Budget Request also called for the dissolution of the Fogarty International Center, and caps indirect costs at 10%. The Senate and House bills did not contain those provisions, and specifically stated that indirect costs are not to be capped. The Senate and House bills both included increases of about $500 million for specific programs, including Alzheimer's disease, the BRAIN initiative, the All of Us Initiative, and several others.

Dr. Rodgers added that the Special Statutory Funding Program for Type 1 Diabetes Research has been continuously funded since 1997, and its expiration on October 1 is a major concern to NIDDK. The December 22, 2017, continuing resolution contained appropriation for one quarter of the usual $150 million annual funding, or $37.5 million. NIDDK hopes ultimately to get the remaining $112.5 million for the rest of FY 2018, but the funds have not yet been authorized. The Program issued two funding opportunity announcements in December 2017, and has others ready to go once the appropriation is made. Dr. Rodgers noted the Program has been extraordinarily successful over its nearly 20 years.

VI. UPDATE FROM THE DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE
Dr. Volkow

Dr. Rodgers introduced Nora D. Volkow, M.D., Director of the National Institute on Drug Abuse (NIDA). NIDA's mission is to advance science on the causes and consequences of drug use and addiction, and to apply that knowledge to improve individual and public health. With the current opioid crisis in the United States, this is a timely presentation.

Dr. Volkow has served as director of NIDA since 2003. Born in Mexico, Dr. Volkow earned her medical degree from the National University of Mexico in Mexico City and did her psychiatric residency at New York University. She spent most of her professional career at the Department of Energy at the Brookhaven National Laboratory in Upton, NY, where she held several leadership positions, including director of nuclear medicine, chairman of the medical

department, and associate director for life sciences. Dr. Volkow was also professor in the department of psychiatry and associate dean of the medical school at the State University of New York at Stony Brook.

As a research psychiatrist and scientist, Dr. Volkow has pioneered the use of brain imaging to investigate the effects of drug abuse on the brain, and her work has been instrumental in documenting drug addiction as a disease of the human brain. Her studies have documented changes in the dopamine system and effects on brain regions involved with motivation, drive, pleasure, and addiction. Her work has also contributed to our knowledge of the neurobiology of obesity, ADHD, and aging.

Dr. Volkow has received multiple honors and awards, including election to the National Academy of Medicine; the International Prize from the French Institute of Health; and the Carnegie Prize in Mind and Brain Sciences from Carnegie Mellon University. She has been named among Time Magazine's top 100 people who shape our world, Newsweek Magazine's 20 people to watch, Fortune Magazine's 34 leaders who are changing healthcare, and U.S. News and World Report's Innovator of the Year.

Dr. Volkow's presentation focused on NIDA's work on the science of opioid addiction and the devastating opioid crisis that is affecting the country. She showed graphics illustrating the rate of death from overdose in different parts of the country. In 1999, only two areas of the country had more than 26 overdose fatalities per 100,000 individuals—New Mexico and the center of the Appalachia region. Sixteen years later, those rates can be seen in many more areas of the country and some areas are experiencing 40 or more deaths per 100,000. She said that new numbers are due out soon from the Centers for Disease Control and Prevention, and she expects they will show very high rates in the Northeast as well.

She explained that the current crisis appears to be driven in part by well-intentioned efforts in the late 1990s to treat patients who are in pain more effectively. The number of opioid prescriptions increased substantially around 1999-2000, about the same time as the Joint Accreditation Commission made effective pain treatment part of their accreditation process—but without the process of evaluating the consequences.

She explained that multiple areas of the brain are dense with opioid receptors, especially in the networks involved in regulating pain, respiration, and reward. Drugs like morphine, Vicodin, and Oxycontin bind to these receptors and inhibit signaling, which is why they are effective at eliminating severe pain almost immediately. The problem is the brain becomes quickly tolerant to the analgesic effects of the drugs, and requires progressively higher doses to produce the same effect. The increasing dosage needed for pain relief can lead to adaptations in the brain linked with addiction. The need for higher and higher doses also increases sensitivity to overdose and respiratory depression.

Dr. Volkow pointed out that the opioid crisis comes at a time when more and more patients are suffering from chronic pain—120 million people, the National Academy of Medicine estimates. Part of the increase can be traced to people living longer and therefore having a greater likelihood of developing a disorder associated with pain. However, there may also be links with the increases in obesity and the associated musculoskeletal pain associates with that as well as pain linked with the inflammatory process, which is also more common with obesity.

Science and research can help lead to solutions that can be delivered immediately to help treat addiction and reverse overdoses, as well as long-term efforts to build our understanding of basic science and lead to safer, more effective strategies for pain management. Dr. Volkow pointed out that these different areas need to be addressed simultaneously in order to both reduce the need for opioids in pain management and help those who are already addicted to opioids. Currently, five Americans die every hour from opioid overdose.

She reported that NIDA is directing attention towards understanding the intersection between pain and reward to further understanding of why patients who become addicted to drugs are at higher risk of chronic pain disorders, and why patients with pain are at higher risk of substance-use disorders. Pharmaceutical companies have tried very hard to develop an opioid medication without side effects and risk of overdose or addiction—so far without success.

Dr. Volkow said that over the past three to four years there have been significant advances in understanding the three-dimensional structure of the mu-opioid receptor and the pathways involved in analgesia, respiratory and gastrointestinal depression, and tolerance. This knowledge may lead to a new class of drugs called "biased mu-opioid receptor ligands" that may be able to produce increased analgesia without slowing down respiratory or gastrointestinal function. She pointed out that more cohesive efforts across different institutes in the NIH may facilitate the development of alternative pain medications.

Dr. Volkow then shifted to discussion of treatment of opioid addiction. She reported that effective treatments exist but currently are underutilized. Three different classes of medications can be used in the treatment of opioid addiction.

- **Methadone** is the oldest, having been in use for more than 50 years. It is a full agonist, giving maximum potency when it binds to the receptor. However, it does not block all receptors. It requires daily dosing and is available only at methadone clinics.

- **Buprenophine** is a partial agonist, and was approved for use in opioid addiction in 2002. It blocks all opioid receptors so that if a person takes heroin, there are no receptors free to which the heroin can bind. Buprenophine must be administered by a trained clinician three to four times a week. It is not always effective in severe cases of addiction.

- The last medication is **naltrexone**, which occupies the receptor and blocks heroin or other opioid agonists from binding to it. Although some have felt it is not as effective as buprenorphine, recent clinical trials do not show that. Naltrexone is available as a monthly injection.

These medications have been shown to decrease opioid use, prevent overdose, decrease criminal activity, and decrease the transmission of hepatitis C, HIV, and other diseases. They are also associated with increased social functioning and retention in treatment, and can be effective in treating neonatal abstinence syndrome, which effects babies who were exposed to opioids *in utero*. While 50 percent of patients on these medications relapse within six months, nearly all patients who do not receive these medications will relapse. Dr. Volkow pointed out that different people respond better to different treatments. Therefore, having a variety of treatments available increases the chances of successful treatment.

Unfortunately, she said, the overwhelming majority of addicts do not receive medication-assisted treatment. Conservative estimates put the number of people addicted to opioids at 2.5 million. Of those, less than 500,000 receive medication to treat their addiction and, of those, 250,000 stay in treatment for more than six months. She said this "cascade of care" points out both the need for alternative medications, and the need to expand availability of current medications to more people.

NIDA is pursuing research on several fronts:

- **New medications for addiction treatment.** Dr. Volkow explained that NIDA's strategy has been to develop compounds, and then engage pharmaceutical companies to take them to clinical trials. The medications currently available were developed this way. Current interest is in extended-release formulations of naltrexone and buprenophine that help reduce the likelihood of relapse within the first six months.

- **Role of neurocircuitry in addictive disorders.** An example of long-term research is the study of the neurocircuitry that is disrupted by drugs. She pointed out that there is some overlap with patients with morbid obesity and compulsive overeating patterns that result from the disruption of the circuits involved in self-regulation and lead to enhanced reactivity to stress and an inability to control urges. This understanding may lead to interventions that target that neurocircuitry, but because of the complexity of disruption to neural circuits, it likely will take longer to bring to market.

- **Vaccines and passive immunization.** Another area of research is the development of vaccines for fentanyl and heroin. Fentanyl is an extremely potent opioid that is responsible for a significant increase in death from overdose in the last two years. In some cases, Narcan—the form of naloxone used for reversing overdoses—is insufficient to reverse fentanyl overdoses. Researchers at Scripps Institute have developed a vaccine for fentanyl in rodents. Dr. Volkow pointed out that the same team is working on a vaccine for leptin in the treatment of obesity. Unfortunately, the vaccine is not yet sufficiently antigenically effective in humans.

- **Making treatment more accessible.** NIDA is also investigating ways to increase availability of medication-assisted treatment for opioid addiction. One method may be to train physicians in proper screening and management of patients with opioid-use disorders. An example is a program at Yale University in which buprenorphine was initiated in the emergency department rather than referring the patient to treatment, leading to decreased drug use and emergency room utilization. NIDA is currently conducting a multi-site study based on this model.

- **Personalized treatment.** NIDA is also looking into how personalization of treatment plans both for pain and for addiction can increase effectiveness. She pointed to research that indicates that certain gene variants maybe associated with a higher risk for opioid-use disorder, and alcoholism and may also predict response to medication treatment with naltrexone. Sensitivity to opioid analgesics may also be associated with vulnerability to respiratory depression.

Dr. Volkow said that NIH Director Dr. Francis Collins has embraced the urgency of the situation. He co-authored an article with her calling for a public-private partnership to address

the opioid crisis. This partnership has two focuses: 1) to enhance the range of medication options to treat opioid use disorder and prevent/reverse overdoses, and 2) to develop new approaches to treating pain. This includes accelerating the development and introduction of new formations or combinations of medications to treat opioid use disorder and reverse overdoses. Developing alternative endpoints—reduced overdoses or fatalities rather than abstinence—may also be necessary to address the current crisis.

The partnership also hopes to spark interest in identifying biomarkers that might lead to an objective measurement for pain and help predict response to treatment and lead to the development of new medications. Data-sharing collaboratives and a clinical trial network to rapidly recruit pain patients might help accelerate these areas of research, she said.

Council Questions and Discussion

Are there resources being allocated into using technology to increase the frequency and effectiveness of communications between caregiver and patients?

Communication is a vital component of implementation science, Dr. Volkow said. This crisis is affecting some very remote, rural areas where access to health services and especially methadone clinics is very limited. NIDA is funding research into different models, such as one in which physicians work with nurses or behavioral care professionals that provide supervision of patients being treated for opioid use disorders. Telehealth can also be used to monitor patients in rural communities. The agency funds other areas of research, such as expanding access to naloxone and engaging citizens in addressing the problem. One possibility may be a cell phone app that can predict when overdose may occur, or that people can use to obtain naloxone if they witness an overdose.

What percentage of patients who overdose or die begin their path of addiction from recreational use or from pain management?

Dr. Volkow reported that there are not good numbers on this, but it appears that most people who became addicted to heroin started on prescription or "diverted" opioids. She explained that at one point, many believed that if you had pain and were given an opioid, you were protected from addiction. This unfortunate misconception was often taught in medical schools. It is now clear that patients can become addicted to their pain medications. Surveys vary from 3 percent to 35 to 40 percent—differences that reflect our own misunderstanding and confusion between physical dependence to an opioid and addiction.

Physical dependence is different from addiction, she explained. Physical dependence happens whenever there is repeated exposure to an opioid drug. It leads to tolerance of the drug. When the drug is interrupted, withdrawal symptoms develop, including increased heart rate, cramps, sweating, and extreme anxiety. The greater the exposure, the more intense the withdrawal. These symptoms dissipate after a few days or weeks. There is evidence that physical dependency can develop within just 24 hours of opioid exposure.

Addiction, on the other hand, takes longer to develop and doesn't develop in most patients—a conservative estimate is 10 percent. Addiction is much harder to treat, and is longer lasting. The confusion between addiction and physical dependence arises when people go into withdrawal when they stop taking the drug. To stop the withdrawal symptoms, they want more drug. If the

physician doesn't understand the dynamic of withdrawal, they may think that the patient is addicted. Slowly tapering the drug may alleviate the physical withdrawal symptoms.

The opioid crisis has led to a significant increase in the number of hepatitis C cases, often in parts of the country and in populations that were not previously seen as at risk. When someone is treated for overdose, is there any attempt to determine whether they are infected with hepatitis C before they are released back into the community?

Dr. Volkow acknowledged that this is an ongoing problem and concern. Hepatitis C treatment, which can effectively cure the disease, is very expensive, and Medicaid requires evidence of inflammation of the liver before approving treatment. Those with new infections may well be infecting others in the meantime. NIDA is partnering with NCI and the pharmaceutical company Gilead for a demonstration project to target an area in Kentucky where all people with hepatitis C will receive treatment. They will then compare outcomes with a community where people do not receive treatment. Although it is currently costly to do this, the expectation is that early treatment will save money in the long run.

Reimbursement and costs of treatment also play into pain management. Dr. Volkow explained that the CDC released new comprehensive guidelines in 2017 for pain management, specifying that opioids should not be a first-line treatment for chronic pain and that opioids should only be used as part of a comprehensive pain management plan. However, the current reimbursement system (Medicare, Medicaid, and private insurance) does not reinforce these guidelines since many adjunct treatments—including sedatives that are beneficial for chronic pain—are often more expensive than opioid medication.

There's a stigma associated with both opioid addiction and obesity. How do you think that stigma differs between the two conditions, and how could it be reduced so that we can focus on these as medical problems?

Dr. Volkow pointed out that drug addiction may be more easily hidden while obesity shows all the time. However, there is still an enormous amount of stigma associated with addiction and it can be seen even in the treatment of patients—some clinicians do not want to treat patients with opioid-use disorder. The healthcare system is starting to recognize the opportunity and obligation physicians have to address the situation. Family members, celebrities, and political leaders have also started to speak up. What will ultimately change the stigma, she said, is what changed for HIV—the community got together and advocated for itself.

Dr. Volkow noted that one of the easiest ways we can get rid of the stigma is by providing indications about how these conditions can be treated and to recognize the vulnerability of the individual. This is similar to obesity, with the availability of surgical procedures, medications, and other interventions for this complex medical condition.

She pointed to other possible connecting points between obesity and opioid addiction, such as recent clinical reports that people who have had bariatric surgery are at greater risk for alcohol-use disorder and perhaps also opioid-use disorder.

Dr. Volkow explained that she is also interested in another possible connection between obesity and addiction. She has been trying to identify factors that increase vulnerability to respiratory depression and overdose when taking opioids. Dose is one factor. She wondered, since obesity is associated with sleep apnea, whether obesity also a factor in overdose risk.

What do you think about the intersection between rapid weight loss with CB-1 antagonists or bariatric surgery and the brain circuits associated with addiction? Are there grants being funded related to that?

Dr. Volkow said that this is an area of interest for NIDA. Food behaviors, obesity, and what drives one to eat may be more complex than what drives one to take a drug, but in both cases the signals that spur the action are mediated by dopamine systems. Drugs go directly to the dopamine system; with food, it is indirect, but the dopamine pathway is still very relevant. The dopamine pathway is modulated by endogenous cannabinoids and glutamatergic pathways, which is another target that NIDA is exploring. One idea is that these peripheral regulators of appetite and food behaviors may also regulate response to drugs. In the case of alcohol, preclinical studies and some pilot human studies show that both ghrelin and leptin may modulate the effects of alcohol. Some of the targets identified in obesity research may have some potential in the treatment of drug addiction, and some of the medications currently used for diabetes are currently being evaluated for use in addictive disorders.

With the current opioid crisis, there's a danger of swinging too far and undertreating patients for surgical pain. Patients have varied responses to analgesics used for surgical pain. Without a biomarker for addiction, is there any tool that we can use to screen and identify patients at higher risk for addiction?

Dr. Volkow acknowledged the risk of undertreating pain in an effort to prevent addiction. One line of inquiry is the idea that improper treatment of acute pain may lead to chronic pain, and that chronic pain may increase the risk down the line of opioid use. She said that the NIH Common Fund is considering a trans-NIH project to research the factors that increase the risk of transitioning from acute to chronic pain.

She brought up that there are many questions about how best to treat pain. Some patients complain that with extended release formulations they are actually on opioids all the time rather than just taking a short-acting dose as needed.

She pointed out that teenagers are at greater risk for addiction. A teenager may be exposed to the drug—perhaps needed for a tooth extraction—and find the experience to be pleasurable, which may lead them to experiment with drugs. She urged caution when prescribing pain management for teens and called for additional study. She pointed out that dentists have been very proactive in retraining and educating clinicians on proper prescribing, resulting in decreases in use of opioids for dental surgery.

VII. COFFEE BREAK

VIII. COUNCIL FORUM: REGENERATIVE MEDICINE

Regenerative Medicine at NIH and NIDDK
Dr. Germino

Dr. Rodgers introduced Gregory G. Germino, M.D., Deputy Director of NIDDK. Dr. Rodgers reminded Council members that regenerative medicine seeks to develop functional cells, tissues, and organ substitutes to repair, replace, or enhance a biological function that's been lost as a result of congenital anomalies, injury, disease, or the aging process. He also explained that this meeting marked the debut of a new year-long initiative, the Council Forum, which will consist of special presentations on regenerative medicine today and at each of this year's subsequent Council meetings. Each of NIDDK's three divisions will have a chance to present on the status and progress of research into regenerative medicine within their program area. The plan is to seek input from the Council at the September 2018 meeting regarding where NIDDK and NIH should focus resources within the broad area of regenerative medicine.

Dr. Germino began by defining regenerative medicine and placing it in the context of NIH's and NIDDK's missions. According to NIH Research, Condition, and Disease Categorization (RCDC), regenerative medicine/tissue engineering is "A multidisciplinary field involving the life, physical, and engineering sciences that seeks to develop functional cell, tissue, and organ substitutes to repair, replace, or enhance biological function that has been lost...."

The list of tissues for which adult stem cells have been identified is diverse and includes brain, teeth, lung, bone marrow, testicles, hair follicles, GI tract, adipose cells, and muscle. In conjunction with these stem cells, a variety of technologies make regenerative medicine possible, including integrated technologies, gene editing, induced pluripotent stem cells (iPS), and biomaterials like scaffolding substances. Additionally, the list of organs for which we can currently grow organoids includes many of particular interest to NIDDK, including the esophagus, stomach, liver, pancreas, gallbladder, bile duct, small intestine, colon, prostate, and kidney.

Dr. Germino noted that this progress would not have been possible without parallel fundamental insights into developmental biology that have guided the reprogramming steps necessary to generate differentiated cell types. Organoids derived from the cells of individual patients can be used to identify beneficial personalized treatments, serve as autologous material for self-replacement therapies, or even future organ transplants, either with or without gene editing to correct underlying genetic defects. Organoids grown from groups of patients can also be used to model disease. These methods can be used to understand the mechanism by which specific mutations cause disease, and to develop cell screening assays that can be used to identify potential therapies in broad drug screening. Finally, organoids can be used to test for kidney- and liver-related drug toxicities.

This topic is attracting attention. The National Academies have established a forum on regenerative medicine that has brought together leaders from across the research, policy, and healthcare spectrum to discuss the opportunities and challenges of this emerging field. Congress has also expressed interest in regenerative medicine, Dr. Germino said. The *21st Century Cures*

Act contains language directing the NIH, in coordination with the FDA, to establish a regenerative medicine innovation project, with the goal of translating basic and preclinical science discoveries into clinical therapies. Congress has committed a total of $30 million over four years, with the requirement that there be an equal contribution from non-federal sources.

Dr. Germino said that, in fiscal year 2017, NIH awarded $2.7 million, divided among eight competitive supplements for projects on six different tissues and cell types. Of these, two awards were made to NIDDK investigators. Dr. Leif Oxburgh of Maine Medical Center in Portland is seeking to generate hypoxia-responsive erythropoietin-producing cells from iPS cells that one day may be used to treat the anemia associated with chronic- and end-stage kidney disease. Dr. Douglas Melton of Harvard University is focused on generating clinical-grade, patient-specific iPS cell lines derived from individuals having undergone pancreatectomies. The ultimate goal is to create a structure to produce insulin-producing cells suitable for autologous cell transplants.

For fiscal year 2018 and beyond, assuming appropriate resources, Dr. Germino foresees a focus on investigator-initiated projects that are directed towards developing clinical therapies and an emphasis on phased, milestone-driven approaches that are focused on regenerative medicine areas well-positioned for clinical application. Another focus will be on developing core resources and infrastructure critical for innovation in this field.

In FY 2017, NIDDK allocated approximately $95 million for research in regenerative medicine, and has the second largest portfolio on regenerative medicine at NIH, behind NHLBI.

Dr. Germino presented research highlights from each of NIDDK's three extramural programmatic divisions.

Division of Diabetes, Endocrinology, and Metabolic Diseases. Regenerative medicine strategies focused on treating type 1 diabetes include the production of glucose-regulated and insulin-responsive iPS cells and in vivo reprogramming of other differentiated cell types. Additionally, the Division is funding efforts to induce adipose tissue browning, with the objectives of controlling weight and addressing the obesity epidemic. For example, a patch might be placed over fat deposits that delivers nanoparticles containing browning agents, like rosiglitazone, to help induce the transition. At the other end of the spectrum, patients who suffer from lipodystrophy might benefit from genome editing of iPS cells that can then differentiate into fat cells for transplantation.

Regenerative medicine may also help develop more effective treatments for diabetic wounds, which currently result in more than 100,000 lower extremity amputations per year. Current efforts focus on delivery systems that use innovative biomaterials to slowly release the proteins that protect stem cells. Researchers are also developing nonbiologic and biologic therapies, such as modified progenitor cells.

Another major advance includes the development of robust cell differentiation protocols to produce large quantities of clinical-grade and highly functional human beta cells from pluripotent stem cells that can be used as cell replacement therapy (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4617632; https://doi.org/10.1038/nbt.3033). This progress builds in large part on 15 years of NIDDK investments in the Beta Cell Biology Consortium, supported by the Special Diabetes Program. Next steps towards clinical use for

these cells include building public-private partnerships for the development of a final product, and efforts to combine clinical-grade beta cell products with the next generation of cell encapsulation technologies. This would enable these cells to be introduced back into patients and protect them immunologically from attack and destruction.

NIDDK also continues to look beyond cell replacement therapy, supporting strategies to promote beta cell regeneration in vivo, particularly through investments in the Human Islet Research Network, which started in 2014, Dr. Germino said. Strategies include the manipulation of cell fate changes in the pancreatic islet, such as converting alpha cells to beta cells (https://doi.org/10.1016/j.cmet.2017.01.009), and reprogramming of non-pancreatic adult cells into functional beta-like cells (https://doi.org/10.1016/j.stem.2016.01.003). These nonpancreatic cells have the advantage that they may be less susceptible to the autoimmune destruction associated with type 1 diabetes.

In the area of obesity, investigators are poised to capitalize on more than 20 years of NIDDK-supported research in the development and differentiation of adipocytes, with the objectives of finding factors that can drive the "beiging" of white adipose tissue in vivo, or transplanting functional beige adipose tissue generated in vitro, to enhance metabolic profiles in obese, insulin-resistant individuals. A paper from Dr. Silvia Corvera at the University of Massachusetts describes how to generate in vitro beige adipocytes from progenitor cells associated with the capillary beds removed from surgically dissected fat. Activated beige fat cells were implanted into obese, glucose-intolerant mice that then displayed a lower fasting glucose and a more rapid glucose disposal rate than controls (https://doi.org/10.1038/nm.4031).

Dr. Germino referred to a second notable study, which features NIDDK investigators who generated beige fat pads in vitro using rodent white tissue to derive multi-potent stem cells. They transplanted these cells into severely obese mice with the result that the stem cells partially rescued their phenotype. (https://doi.org/10.2337/db15-0728).

Division of Digestive Diseases and Nutrition. The Division of Digestive Diseases and Nutrition manages a diverse portfolio of conditions. Three priorities include research into repairing gene defects, replacing organs, and supporting artificial organs.

Repairing gene defects may lead to the correction of severe epithelial cell failure syndromes. These syndromes, which include tufting enteropathy, or intestinal epithelial dysplasia, may be amenable to treatment using gene-corrected stem cells isolated from patients with intestinal failure. The idea would be to biopsy intestinal cells, isolate stem cells, and use CRISPR technology to correct the defect and introduce the cells back into the patient so that the stem cells would repopulate the intestinal lining.

Another area of interest is short gut syndrome caused by necrotizing enterocolitis, an important cause of morbidity and mortality in children. Current treatment requires intestinal transplantation, which does not have a good success rate. Production of tissue-engineered small intestine from the patient's own cells might one day restore normal intestinal function via autologous transplantation. Pilot studies in rats have shown some success.

Dr. Germino noted that organ transplantation is currently the only definitive treatment available for liver failure. With long waiting times and a shortage of available organs, many patients die before they are able to receive a transplant. Regenerative technologies may be helpful in

providing a therapeutic bridge, providing sufficient clearance and synthetic function to support individuals suffering failure either until their own liver function recovers or a replacement organ can be found.

Two interdisciplinary team efforts illustrate recent work of the NIDDK Intestinal Stem Cell Consortium.

- A team led by Dr. Kelley Yan identified the functional roles of Wnt and RSPO ligands in the intestinal crypt stem-cell niche, with broad implications for precise control of tissue regeneration. Dr. Yan received an NIDDK K08 award for this work. (https://doi.org/10.1038/nature22313).

- A team led by Dr. Michael Workman used a tissue engineering approach with embryonic and iPS cells to generate human intestinal tissue containing a functional enteric nervous system to develop human intestinal organoids. They used this system to investigate the cellular and molecular basis for Hirschsprung's disease, caused by a mutation in the gene PHOX2B. This is the first demonstration of human-pluripotent stem cell-derived intestinal tissue with a functional enteric nervous system, and shows how this system can be used to study motility disorders of the human gastrointestinal tract. (https://doi.org/10.1038/nm.4233).

Division of Kidney, Urologic, and Hematologic Diseases. The Division has several regenerative medicine priorities, including producing kidney components from stem and iPS cells for disease modeling, toxicology, drug screening, and cell production. Other priorities are the creation of a functioning clinical-grade bioartificial wearable or implantable kidney (in cooperation with the National Institute of Biomedical Imaging and Bioengineering), and the production of gene-edited autologous human stem cells for transplantation to correct cystinosis, a lysosomal storage disease characterized by the abnormal accumulation of the amino acid cystine.

Dr. Germino noted that, while hemodialysis therapy is life-saving, it is not optimal. There has been interest over many years in developing a bioartificial system that could provide better treatment. Longstanding investments by NIDDK in the GenitoUrinary Development Molecular Anatomy Project (GUDMAP; ***www.gudmap.org***), the Rebuild a Kidney (RBK, ***www.rebuildingakidney.org***) project, and other projects have led to greater understanding of how the kidney develops.

Dr. Germino also discussed investigations into the cellular molecular basis of normal kidney development which, together with major advances in stem cell biology, are now delivering options in regenerative medicine for the kidney not possible as recently as a decade ago. Investigators are now developing kidney organoids on a “chip” suitable for modeling organ development and human disease, evaluating toxicology, screening for therapies, and producing functional renal epithelial cells.

The Division also supports research on a number of genetic metabolic disorders, including cystinosis. Many affected individuals develop abnormalities in kidney function, due to cystine crystal formation, which often progresses to end-stage kidney disease. Pilot studies in a genetically faithful model of cystinosis have shown that transplantation of gene-modified hematopoietic stem cells prevented progression of renal dysfunction, and reduced crystal deposits.

Dr. Germino recounted several advances, including work from the laboratory of Dr. Joseph Bonventre (NIDDK Council Member) exploring the use of kidney cells and tissues derived from human pluripotent stem cells for disease modeling, drug screening, and organ regeneration. Noting that this organoid culture system can be used to study mechanisms of human kidney development and toxicity, Dr. Germino described this work as being of landmark importance. (https://www.ncbi.nlm.nih.gov/pubmed/26458176).

He also featured work from the laboratory of Dr. Jennifer Lewis in Boston on a bioprinting method for creating 3D human renal proximal tubules *in vitro* that can be maintained for longer than two months, providing a new route for fabricating advanced human kidney tissue models on demand. (https://www.ncbi.nlm.nih.gov/pubmed/27725720).

Dr. Germino noted the difficulty of studying toxicological mechanisms in human subjects due to ethical concerns, and pointed to work from Dr. Jonathan Himmelfarb's lab using human cells to create microphysiological organs on chips, which provide an alternate approach to examining toxicological effects of pharmaceutical and environmental chemicals. The researchers linked a kidney-on-a-chip with a liver-on-a-chip to determine the mechanisms of bioactivation and transport of aristolochic acid, an established nephrotoxin and human carcinogen. This integrated microphysiological system provides an *ex vivo* approach for investigating organ-organ interactions, in which the metabolism of a drug or other xenobiotic by one tissue may influence its toxicity toward another. (https://www.ncbi.nlm.nih.gov/pubmed/29202460).

Finally, Dr. Germino summarized work out of the lab of Drs. George Daley and Leonard Zon focusing on Diamond-Blackfan anemia, a congenital disorder characterized by the failure of erythroid progenitor differentiation, severely curtailing red blood cell production. Many Diamond-Blackfan anemia patients fail to respond to corticosteroid therapy, and there is considerable need for new therapeutics. The researchers adopted a reprogramming strategy to generate expandable hematopoietic progenitor cells from iPS cells from patients and used this to screen for drugs that promote red blood cell production. This method led to the identification of an agent that partially corrected the anemia phenotype. (https://www.ncbi.nlm.nih.gov/pubmed/28179501).

Dr. Germino closed by reminding the Council that each 2018 meeting will include a scientific seminar on regenerative medicine led by a leading expert from one of NIDDK's divisions. The goal is to engage in a discussion with the Council to seek guidance on priority-setting related to NIDDK's involvement with regenerative medicine. Relevant questions include the relative importance of:

- Basic versus preclinical explorations,
- Investigator-led versus consortia-led research, and
- Focusing on common conditions like obesity and diabetes versus using rare disease exploration as a paradigm for solving common problems.

Stem Cells and Intestinal Regeneration: Needs, Opportunities, and Challenges
Dr. Shivdasani

Dr. David Saslowsky, program director, Division of Digestive Diseases and Nutrition, introduced Dr. Ramesh Shivdasani, professor of medicine at Harvard Medical School and a distinguished physician at the Dana-Farber Cancer Institute. After earning an A.B. at Cornell

University and an M.D./Ph.D. at the University of Michigan, Dr. Shivdasani moved to Boston, where he completed internal medicine residency training at Brigham and Women's and a fellowship in medical oncology at the Dana-Farber Cancer Institute. He then moved to Boston Children's Hospital, where his post-doctoral fellowship focused on transcriptional regulation of hematopoiesis.

Dr. Shivdasani began his faculty career at Dana-Farber, where he has been conducting innovative research to elucidate gastrointestinal development, differentiation, and tumorigenesis for the past 20 years. Dr. Shivdasani is a principal member of the Harvard Stem Cell Institute, and is co-director of the Cancer Program there. He is a principal investigator on both an NIDDK and an NCI R01 grant, and serves as principal investigator on one of the ten U01 awards that are part of the NIDDK-funded Intestinal Stem Cell Consortium.

Dr. Shivdasani opened his remarks with a review of the fundamentals of intestinal biology, emphasizing the organ's functional complexity and its dual functions of absorption and secretion. He also discussed the most important features of a stem cell: it must provide long-term self-renewal of a tissue, and it must contribute to the entire intestinal cell lineage, or at least to more than one cell type. Much scientific work has been devoted to determining the source and precise location of intestinal stem cells. We now know they originate at the very bottom of intestinal crypts, in the crypt base columnar cells. Two vital discoveries have been the discovery of LGR5 (a G-protein coupled receptor) as a marker of adult intestinal stem cells, and the ability to trace the intestinal cell lineage *in vivo*. Additionally, it is now understood that, in addition to active intestinal stem cells, scarcer and more protected quiescent stem cells also exist within the intestinal crypt. Regenerative medicine has begun to understand the relationship between the two types of stem cells. The current thinking is how stem cells differentiate has to do with their progress along the crypt-villus axis to become either absorptive or secretory.

Dr. Shivdasani also discussed scientists' ability to create intestinal organoids based on understanding of the importance of Wnt R-spondin, the BMP antagonists, and notch inhibitors. The result is that a single cell can experience the outgrowth of sub-compartments that both look and function like intestinal crypts. We also now have the ability to generate human induced pluripotent stem cells (iPS). Despite the capabilities of complex tissue engineering, obstacles remain; the process is still extremely expensive and currently not scalable for clinical application.

Dr. Shivdasani sees great potential for harnessing the gut to help common problems in endocrinology and metabolic disorders like diabetes, ulcerative colitis, and Crohn's disease. Recent work has shown the existence of a significant immune compartment in the GI tract, but its biology is just beginning to be understood. He believes that gene therapy, together with gene editing that CRISPR Cas 9 promises, may result in the eradication of certain monogenic disorders within our lifetimes.

The session concluded with an invitation from Dr. Germino to Council members to weigh in on what type of information NIDDK staff can gather to help inform the planned September discussion about agency priorities.

Council Questions and Discussion

Council members posed several questions and comments about the process and objectives for the Council Forum and research priority setting. One council member asked for information about training opportunities and training pathways for young investigators, and another asked about whether NIDDK will seek input from patients or coordinate with other Institutes and Centers on research priorities. Council members also brought up the question of when to move from basic science to clinical applications and when to move to translational work.

Dr. Germino clarified that the intent of the Council Forum is to use regenerative medicine as a case study for how NIDDK and the larger research community prioritize investments in different areas of research, including how to balance the importance of regenerative medicine with existing and future commitments and opportunities. The hope is that the conversation will focus specifically on regenerative medicine but also more broadly on how to deal with research challenges and opportunities. Part of the goal of the forum is to promote communication across the Institutes and promote thinking about how to establish partnerships, share best practices, and support broad team development. Dr. Germino noted that industry connects to the process at the translation stage, given that most academic communities lack the necessary financial resources and are unfamiliar with or don't have access to the necessary corporate and regulatory infrastructure to do so.

Dr. Germino thanked Committee members for their comments and questions, as well as Dr. Shivdasani for launching the 2018 scientific seminars on regenerative medicine.

IX. SUBCOMMITTEE MEETINGS

X. REPORTS OF SUBCOMMITTEES

CONSIDERATION OF REVIEW OF GRANT APPLICATIONS.

A total of 1,055 grant applications (162 primary and 893 dual), requesting support of $372,111,433 were reviewed for consideration at the January 24, 2018, meeting. An additional 60 Common Fund applications requesting $114,293,063 were presented to Council. Funding for these applications was recommended at the Scientific Review Group-recommended level. Prior to the Advisory Council meeting, 1,342 applications requesting $405,716,495 received second-level review through expedited concurrence. All 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 January 24, 2018, 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 206th 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, and Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council