

46th Meeting of the National Institutes of Health (NIH)
Advisory Committee on Research on Women's Health (ACRWH)
Office of Research on Women's Health (ORWH)
Building 31, 6C10
Bethesda, MD
October 23, 2018

Members Present

C. Noel Bairey Merz, M.D.
Wendy R Brewster, M.D., Ph.D.
Geert J. de Vries, Ph.D.
Kimberly D. Gregory, M.D., M.P.H.
Rachel Jones, Ph.D., R.N.
Ana Langer, M.D.
Ana Maria Lopez, M.D., M.P.H.
Carolyn M. Mazure, Ph.D.
Louise D. McCullough, M.D., Ph.D.
David C. Page, Ph.D. (by telephone)
Amy S. Paller, M.D.
Marcia L. Stefanik, Ph.D.
Susan F. Wood, Ph.D. (by telephone)

Guests

Sabra Klein, Ph.D.
Judy Regensteiner, Ph.D.

NIH Leadership Present

Diana W. Bianchi, M.D., Director, **Eunice Kennedy Shriver** National Institute of Child Health and Human Development (NICHD)
Ann Cashion, Acting Director, National Institute of Nursing Research (NINR)
Wilson Compton, M.D., Deputy Director, National Institute on Drug Abuse (NIDA)
George F. Koob, Ph.D., Director, National Institute of Alcohol Abuse and Alcoholism (NIAAA)
Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke

Call to Order and Introductions

Janine Clayton, M.D., NIH Associate Director for Women's Health and Director, Office of Research on Women's Health (ORWH), called the 46th meeting of the Advisory Committee on Research on Women's Health (ACRWH) to order at 9:13 a.m. Elizabeth Spencer, B.S.N., Executive Secretary, ACRWH and ORWH Deputy Director, announced that the meeting was being recorded and videocast. Staff and Committee members introduced themselves.

NIH Leadership Update

Dr. Clayton introduced Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director of NIH, who brought greetings from NIH Director Francis Collins, M.D., Ph.D. Dr. Tabak thanked ACRWH members and ORWH

ORWH Leadership

Janine Clayton, M.D., Director
Elizabeth Spencer, B.S.N., Deputy Director
Margaret Bevans, Ph.D., R.N.
Victoria Cargill, M.D.
Chyren Hunter, Ph.D.
Samia Noursi, Ph.D.

Presenters

James M. Anderson, M.D., Ph.D.
Rebecca DelCarmen-Wiggins, Ph.D.
Wendy M. Kohrt, Ph.D.
Senator Barbara Mikluski
Ambassador Constance Morella
Vivian W. Pinn, M.D.
Griffin P. Rodgers, M.D.
Denise Stredrick, Ph.D.
Lawrence A. Tabak, D.D.S., Ph.D.

staff for their work on the new trans-NIH strategic plan. He noted that a major theme of the document is on teaming and the need for collaboration to bear on the nation's most intractable health problems, such as the current opioid use and misuse epidemic. In response, NIH has established the \$500,000/year Helping to End Addiction Long-term (HEAL) initiative that focuses on enhanced pain management approaches, improved opioid addiction treatments, and overdose reversal. An example of a program funded by HEAL is the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) pilot studies in which the Neonatal Research Network Centers and the Institutional Development Award (IDeA) States Pediatric Clinical Trials Network are partnering to assess prevalence of NOW and current treatment approaches, and to develop common protocols for future studies. To implement HEAL, NIH will collaborate with the Surgeon General, its sister Department of Health & Human Services (HHS) agencies, and local government officials.

Dr. Collins announced NIH's Anti-Sexual Harassment initiative on October 22, 2018 to reduce sexual harassment. This effort includes a new website with information about sexual assault laws and contact information for NIH staff. Dr. Collins will also emphasize this information in an upcoming meeting with Institute/Center (IC) directors as part of NIH's strong stance on sexual assault.

Announcements and Approval of the April 20, 2018 Minutes

Ms. Spencer reminded ACRWH members that they are considered special government employees and subject to the same rules as government employees that are outlined in the Standards of Ethical Conduct for Employees of the Executive Branch, e.g., disclosing all real, potential or apparent conflicts of interest and not engaging in any lobbying activities while attending ACRWH meetings or sponsored events.

The minutes for the April 20, 2018 meeting were approved unanimously.

Ms. Spencer recognized new ACWRH members: Amy Paller, M.D.; Louise McCullough, M.D., Ph.D.; and Ana Langer, M.D. She also thanked the following retiring members for their service: C. Noel Bairey Merz, M.D.; Wei-Jung Chen, Ph.D.; Geert de Vries, Ph.D.; Ana Maria Lopez, M.D., M.P.H.; Carolyn M. Mazure, Ph.D.; and David C. Page, Ph.D.

ORWH Director's Report

Dr. Clayton highlighted transitions in NIH leadership. Bruce J. Tromberg, Ph.D., will become the new Director of the National Institute of Biomedical Imaging and Engineering (NIBIB), replacing former Acting Director Jill Heemskerk, Ph.D., who is now Deputy Director. Patricia A. Grady, Ph.D., R.N., is retiring as Director of the National Institute of Nursing Research; Ann Cashion, Ph.D., R.N., is serving as acting director. Helene M. Langevin, M.D., C.M., will join NIH next month as Director of the National Center for Complementary and Integrative Health (NCCIH). She also honored the women who played a vital role in the establishment of ORWH: Ruth L. Kirschstein, M.D. (1926-2009); Bernadine Healy, M.D. (1944-2011); and Vivian W. Pinn, M.D. Dr. Clayton also reviewed the mission of ORWH and recognized staff members Rajeev Agarwal, Ph.D., and Lisa Begg, Dr.P.H., R.N., who received 2018 NIH Director's Awards.

Research Program: Dr. Clayton shared disturbing data about health trends that are affecting women. Maternal mortality is rising in the United States at the same time it is decreasing globally in both developing regions and in peer countries. The U.S. is falling further behind its peer countries in terms of life expectancy. Premature deaths among those younger than 65 are particularly troublesome, and may be attributed to the ongoing opioid crisis, fueled in large part by the high rate of prescription opioid

consumption. Managing this crisis requires prioritizing the consideration of sex and gender differences. For example, the number of women with opioid use disorder at labor and delivery quadrupled from 1999-2014. The HEAL Initiative, reviewed previously by Dr. Tabak, released a Funding Opportunity Announcement (FOA) entitled Administrative Supplements for Validation of Novel Non-Addictive Pain Targets (NOT-NS-18-1073) that reflected ORWH's work with its NIH colleagues. The FOA instructs applicants: "There is a crucial need to address sex influences in pain research since many pain disorders disproportionately affect women. Inclusion of the description of sex as a biological variable in all the validation experiments is encouraged."

In September, ORWH and the Office of Women's Health at the U.S. Food & Drug Administration (FDA) co-sponsored a meeting of Federal agencies to discuss Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender. Last week, ORWH participated in an NIH conference about sleep that sounded a wake-up call for the importance of sleep to the health of women. In addition, ORWH is serving on the Task Force for Research Specific to Pregnant and Lactating Women (PRGAC) that submitted its final report to Congress on September 26, 2018. Among its key recommendations was the inclusion and integration of pregnant and lactating women in the clinical research agenda.

ORWH supports critical research on women's health and sex/gender influences through a variety of co-funding programs, including the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) mentored career development initiative; other IC co-funds; Specialized Centers of Research on Sex Differences (SCOR); Sex & Gender Administrative Supplements; R56; and U3 awards. ORWH's U3 program for Research on Understudied Issues, Underreported Information, and Underrepresented Populations of Women provides one year of supplemental funding to active NIH parent grants to support research on the influences of sex and gender at the intersection of race/ethnicity and other social determinants of health. In FY 2018, 17 ICOs signed on, and 15 applications were funded for a total of \$2.9 million.

Strategic Vision and Plans: The 2019-2023 Trans-NIH Plan for Research on Women's Health is a roadmap for actualizing the NIH vision for women's health research and women in science careers, i.e., to ensure that women are appropriately represented in biomedical research supported by NIH and to improve the advancement of women in biomedical careers. Dr. Clayton recognized Ambassador Connie Morella and Senator Barbara Mikulski, both whom provided leadership in the establishment of ORWH.

SABV Update: Sex as a Biological Variable (SABV) may be summarized as "NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies." ORWH continues to spearhead SABV dissemination via the Women's Health Research Seminar Series; NIH Sex & Gender in Health & Disease Special Interest Group; and ORWH scientific presentations. ORWH is currently beta-testing a new online course on sex and gender influences in diseases and conditions affecting women, developed in collaboration with the Office of Women's Health, FDA. In addition, ORWH co-sponsored a meeting with the American Dental Education Association on Women's Health in Interprofessional Education and Collaborative Care on June 26, 2018 as part of its goal to train a new generation of professionals who understand the integration of sex and gender into health care.

Building Connections: Barbra Streisand advocated for a better understanding of sex differences to address critical gaps in both women's and men's health care during a fireside chat with Dr. Collins at NIH's Annual J. Edward Rall Cultural Lecture on May 15, 2018. ORWH and its partners have amplified

women's health messaging via coverage in popular media, as well as through scientific publications. An article titled "Inclusion Across the Lifespan: NIH Clinical Policy" by Dr. Clayton; Marie Bernard, M.D., National Institute on Aging (NIA) Director; and Michael Lauer, M.D., Office of Extramural Programs Director in the October 16, 2018 issue of the *Journal of the American Medical Association* (JAMA) has been viewed 4500 times. The fall issue of *Women's Health in Focus* highlights the trans-NIH nature of research on women's health.

Women in Biomedical Careers: ORWH will host the inaugural Ruth L. Kirschstein Memorial Lectureship at this year's annual BIRCWH meeting on November 28, 2018. Judith Greenberg, Ph.D., Deputy Director at the National Institute for General Medical Sciences (NIGMS) published a paper in PNAS on NIH funding longevity by gender. She presented her findings to the NIH Working Group on Women in Biomedical Careers, noting that NIH receives one-third of new applications from women investigators who are as successful as their male counterparts in getting funded, but have slightly reduced longevity. Strategies to address the gender disparity among people holding academic positions should focus on the underrepresentation of women among the initial pool of grantees and their lower rates of new and renewal submissions. ORWH has commissioned a National Academies of Science, Engineering and Medicine study of why women are underrepresented in Science, Technology, Engineering, Medicine, and Mathematics (STEMM) disciplines at pivotal career stages, as a follow-up to its 2007 report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*. Two conferences are planned in conjunction with the study. The first, in September 2019, will be a national conference on the NIH campus with 500 participants expected. The second, in March 2020, will focus on launch of the new report. ORWH has developed a new Science Policy Scholar Travel Award for the 2019 Organization for the Study of Sex Differences (OSSD) meeting in 2019 to support junior investigators focused on women and sex/gender differences who also have an interest in policy. Finally, the 4th annual NIH Vivian W. Pinn Symposium is scheduled for May 15, 2019. Its topic is Improving Maternal Health.

Institute Update: NIDDK

Dr. Clayton introduced Griffin P. Rodgers, M.D., Director, NIDDK, who prefaced his presentation by noting that NIDDK and ORWH have a robust history of collaboration because many diseases that primarily affect women, such as gestational diabetes, urinary tract infections and incontinence, fall within NIDDK's domain. For this presentation, Dr. Rodgers addressed "Gestational and Type 2 Diabetes in Women and Girls: Challenges, Progress, and Paths Forward." The major forms of diabetes are type 1 (5 percent) and type 2 (94 percent). Diabetes impairs the body's ability to respond to insulin, leading to increased glucose that, over time, leads to complications such as cardiovascular disease, blindness, kidney disease, and neuropathy. Treating the complications of diabetes costs about \$325 billion/year. Over one-quarter (7.2 million) of the 30.3 million people who have diabetes are unaware of their disease; among the 84.1 million with prediabetes, 74.3 million are unaware of their status. Women are more aware than men of their disease status. Diabetes disproportionately affects American Indians/Native Americans; African Americans; and Hispanics.

Gestational diabetes mellitus (GDM) is diagnosed during pregnancy; complications occur in about seven percent of pregnancies each year. If uncontrolled, it may lead to high blood pressure, preeclampsia, and an increase risk for subsequent type 2 diabetes for both the mother and her offspring. The prevalence of GDM is increasing, again disproportionately among minorities. For example, between 1989 and 2004, GDM increased among 25-34 year old black women by 197 percent, compared to a 94 percent increase among white women in the same age group.

GDM and type 2 diabetes are distinct but related in girls and women. Obesity, race/ethnicity, age, and genetics are risk factors for both diseases. GDM during pregnancy leads to a higher risk for type 2 diabetes and its complications for the mother, and an increased risk of obesity and type 2 diabetes in their offspring, both girls and boys. GDM is believed to be cause of the current increase in type 2 diabetes in older adolescents. Further research is needed to address important question, such has how large a role the increased prevalence of GDM plays in the reduced mortality rates among women, if there is a sex difference in the offspring of women with GDM in developing type 2 diabetes, and the development of more effective treatments for controlling diabetes in youth.

Dr. Rodgers highlighted four trials in which NIDDK and ORWH collaborated to intervene in the progression from normal health to pre-diabetes to a type 2 diagnosis to the onset of complications. These include the Diabetes Prevention Program (DPP) which compared three approaches—placebo, metformin, and lifestyle—for three years in a study with 3,234 obese or overweight participants with impaired glucose tolerance (IGT) (68 percent female, 45 percent minority). Collaboration with ORWH and NIDDK co-sponsorship allowed more women to be included in the study. The lifestyle intervention consisted of 16 sessions delivered one-on-one over 24 weeks with goals of achieving a 7 percent weight loss and 150 minutes/week of physical activity. Results demonstrated that after four years, lifestyle changes lowered the risk of developing diabetes by 58 percent, compared to a 31 percent reduction in risk among the metformin medication group. This pattern held true across all racial/ethnic groups. Lifestyle was especially effective among older adults, while metformin was especially effective among younger adults. Among women who had given birth, metformin didn't work well in those without GDM but performed about as well as lifestyle changes among women with a history of GDM. Fifteen years post-intervention, 18 percent of those on metformin and 27 percent of those who adopted lifestyle changes are diabetes-free. To extend the reach of this effective program, DPP is now being implemented nationwide in YMCAs using a group counseling approach to lifestyle changes. The next phase of research is to determine the effectiveness of metformin before the onset of disease to prevent cardiovascular disease and cancer, implemented as a partnership between NIDDK, the National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), and NIA, with support from ORWH.

NIDDK is conducting clinical studies addressing type 2 diabetes and diabetes/hyperglycemia during pregnancy. The Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO) was an international study conducted between 2000-2006 that sought to determine if there are adverse perinatal outcomes associated with maternal glucose intolerance less severe than overt diabetes. Results indicated that hyperglycemia was strongly associated with increased birth weight, cord-blood c-peptide, neonatal hypoglycemia, and primary C section. A follow-up study examined long-term sequelae 8-12 years post-delivery. Results indicated a strong relationship between "new" GDM (i.e., no intervention for GDM as then defined) and subsequent type 2 diabetes in the mothers and obesity in the offspring.

SEARCH for Diabetes in Youth has been a U.S. Centers for Disease Control and Prevention (CDC)-NIDDK collaboration since 2000. It's the only source of national data on childhood diabetes among children and young adults. Between 2001 and 2009, the rate of type 1 diabetes among those aged 10 to 19 has increased over 20 percent, while type 2 has increased just over 30 percent. Among whites, over 95 percent of those with diabetes have type 1. In sharp contrast, minority populations show higher rates of type 2 diabetes; among AI/NA groups, the incidence of type 2 diabetes is 68.2 percent

Treatment Options for Type 2 Diabetes in Adolescents and Youth (TOD²AY) studied the impact of metformin, metformin + rosiglitazone, and metformin + intensive lifestyle change on a diverse sample of

overweight youth between 10 and 17. The rationale for the study was that adult drugs had not been tested/approved for youth, coupled with the effects of adolescence on glycemia and metabolism. The results indicated that treatment strategies for adults do not work at all for youth, including girls.

In summary, research has indicated that type 2 diabetes can be prevented or delayed in people at high risk, including women with a history of GDM. There remain many unanswered questions about GDM. Prevention of type 2 diabetes in youth is a high priority due to its aggressive nature; treatment efficacy may differ by gender. Girls with type 2 diabetes may experience even greater adverse pregnancy outcomes than adults with the disease. There is a new initiative underway to enhance understanding of the glycemic profile of pregnancy (RFA-DK-18-018, RFA-DK-18-019).

Discussion: Judy Regensteiner, Ph.D., inquired about NIDDK's plan to study diabetes and women. Dr. Rodgers responded that NIDDK is working on that issue with NHLBI.

ORWH Basic & Translational Research Section: Update

Chyren Hunter, Ph.D., Associate Director for Basic and Translational Research, ORWH, provided an update on ORWH's basic and translational section. She updated ACRWH members on the Specialized Centers of Research on Sex Differences (SCOR), renamed the Specialized Centers of Research Excellence on Sex Differences (SCORE) in FY 2018. It is the only NIH Center program supporting disease-agnostic research on sex differences. There have been three funding opportunities, each with ten to eleven awards. In addition to the name change, FY 18 saw an added requirement to SCORE known as the Career Enhancement Core to educate the scientific community and train the next generation of researchers in the study of sex differences. ORWH partnered with seven ICOs--NIA, NIAAA, NIAMS, NIDA, NIDDK, NIEHS, and NIMH—to co-sponsor RFA-OD-18-004, Specialized Centers of Research Excellence (SCORE) on Sex Differences, the SCORE funding opportunity, using the U54 cooperative agreement mechanism. Applications were reviewed by a Special Emphasis Panel. More than thirty applications were received for FY 18, resulting in six U54 awards covering diverse scientific topic areas. There is currently a Notice of Intent to publish a second SCORE RFA on sex differences (U54 clinical trial optional) to allow additional ICOs and investigators to participate.

The ORWH Sex/Gender Administrative Supplement Program supports three main approaches to increasing sex/gender research in existing NIH grants: Adding new sex/gender to single sex/gender research; adding subjects to an existing study to increase power; or comparative analysis of existing samples/data sets. Since 2013, the ORWH has invested over \$38.3 million in this program and supported 360 Principal Investigators (PIs) with involvement from most ICOs. ORWH plans to continue this Program.

ORWH has collaborated with the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), Office of the Director, to support R56 short-term awards for at-risk investigators involved with high impact research whose applications fall outside normal NIH paylines. Between FY 15- FY 18, ORWH funded 41 PIs for a total investment of \$11.8 million. In 2018, the initiative received the same number of applications as in 2017, but resulted in lower ORWH investment because many ICOs recommitted to funding these at-risk investigators themselves. ORWH is seeking other opportunities to support investigators interested in women's health.

ORWH achieves its mission by engaging stakeholders, i.e., providing SABV FAQs; developing didactic course content and resources; and making presentations to stakeholders in the biomedical community

and at the NIH. Currently, ORWH is developing an interactive e-learning primer on SABV in collaboration with NIGMS. The proposed launch is August 2019.

Discussion: Louise McCullough, M.D., Ph.D., inquired if the number of Sex/Gender Administrative Supplements was declining because investigators are already addressing the requirement in their applications. Dr. Clayton responded that ORWH believes that is the reason.

Biogenetic and Metabolic Consequences of the Menopause Transition

Dr. Agarwal introduced Wendy M. Kohrt, Ph.D., Professor of Medicine at the University of Colorado-Anschutz Medical Campus. Dr. Kohrt has been a SCOR PI since 2012, and will continue that role on a new SCORE. She discussed research on the potential biogenetic and metabolic consequences of menopause.

Potential Consequences of the Loss of Gonadal Function—Working Model: The loss of gonadal function (~51 for women; 70+ for men) impacts other systems in the body and may lead to increased risk of disease. There is a well-studied model on ovarian loss leading to bone loss, leading to osteoporosis. Loss of ovarian function may also affect energy balance, leading to fat gain and thus to increased risk of cardiovascular disease and type 2 diabetes. There is also a shift in where fat is stored and possible changes in the composition of adipose tissue. Finally, the loss of gonadal function has an impact on spontaneous physical activity, which impacts the risk for multiple diseases and conditions.

Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function—Preclinical: Animal studies establish that ovariectomized mice and rats experienced decreased physical activity and reduced metabolic rate, coupled with increased energy intake and abdominal fat gain, indicating metabolic dysfunction. These effects were prevented in preclinical studies by estradiol treatment and by exercise.

Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function—SCOR Results: Dr. Kohrt reported on clinical studies conducted at the Colorado SCOR. In human studies, researchers study the loss of ovarian function by suppressing the release of hormones via gonadotropin releasing hormone agonist therapy (GnRH_{AG}) in premenopausal women. Results in one study indicated that ovarian hormone suppression resulted in decreases in fat-free body mass (FFM) that were prevented by adding back estradiol (E₂), suggesting that the loss of E₂ in women accelerates the loss of muscle mass. It also found significant increases in both subcutaneous and visceral abdominal fat areas among women who received a placebo, but not among those in the added-back estradiol condition. Thus, loss of estrogen appears to affect where fat is deposited in post-menopausal women. Resistance exercise may be helpful in attenuating the decline in FFM that occurred in response to the suppression of ovarian hormones. Examining levels of physical activity among hormone-suppressed women, investigators found that those with added-back E₂ maintained higher levels of physical activity than those treated with a placebo. Another study examined the impact of hormone suppression on resting energy expenditure (REE) and total energy expenditure (TEE) among hormone-suppressed women exposed to add-back of transdermal estradiol, estradiol plus exercise, or a placebo. TEE declined across all groups with no statistically significant differences across conditions. REE, on the other hand, declined among those receiving the placebo; this was prevented by adding back estradiol. Adding resistance exercise decreased FFM, but had no effect on TEE or REE. Thus, there appears to be a change in metabolic efficiency, not simply mass, that occurs in menopause. In unpublished preliminary results of additional research on the effects of resistance exercise, women who received a placebo showed no difference but the hormone-suppressed women showed a decrease in fat-free mass, even if they engaged in resistance exercise. On

the other hand, resistance exercised reduced the increase in fat mass among the hormone-suppressed women. There is no evidence that exercise decrease trunk fat mass in hormone-suppressed women.

SCOR investigators are also exploring the cellular composition of adipose tissue; Dwight Klemm, Ph.D. discovered during a bone marrow transplant procedure in mice that some white adipocyte cells seem to arise from a resident stem cell. He has since been trying to understand the function of these progenitors. These cells travel through the blood stream and end up in adipose tissue where they differentiate into mature adipocytes that are different from typical adipocytes in several characteristics. In animal studies, it appears that the accumulation of these cells in the gonadal fat pad is reduced by the addition of estradiol. In humans, it is hypothesized that these bone marrow-derived adipocytes collect in two fat depots in the body: visceral fat and around the heart. Thus, they represent strong potential for understanding metabolic dysfunction. SCOR investigators are just beginning to study this with human bone marrow transplant patients, and have determined that these cells do, in fact, exist in humans.

SCOR researchers are also examining the impact of loss of ovarian function on brown adipose tissue (BAT), striving to quantify the uptake and metabolism of BAT that plays a role in how the body responds to cold. In unpublished preliminary results, they found a four-fold uptake in BAT among premenopausal women compared to post-menopausal women.

In summary, both preclinical and clinical studies provide consistent evidence for the role of estrogens in the regulation of energy balance. The loss of estrogens may promote fat gain through multiple system-level mechanisms, i.e., decreased resting metabolic rate, decreased physical activity, increased energy intake (some species), and decreased BAT thermogenesis. In animals, exercise prevents the effects of loss of estrogen to increase abdominal adiposity and metabolic dysfunction. Preliminary studies of women suggest resistance exercise may attenuate the loss of lean mass in response to ovarian aging, but not the increase in abdominal adiposity or decrease in resting metabolic rate. Endurance exercise may attenuate fat gain, but not central body fat.

New SCORE Directions: At Colorado SCORE, the scientific focus will be expanded to include the role of Follicle-Stimulating Hormone (FSH) in altered cellular composition and altered peripheral glucocorticoid metabolism, in relationship to the role of estradiol. Blocking FSH has been shown to reduce body fat in animals; Colorado SCORE researchers will be investigating this issue in clinical studies.

Discussion: Dr. Clayton asked if the SCOR investigators have looked at sex-discordant donor-recipient pairs among the bone marrow transplant studies. Dr. Kohrt responded that Dr. Klemm has done this in the mice studies, but the number of human patients is still small and the sex of the donor is often unknown. However, the researchers have asked the Karolinska Institutet in Sweden, which has access to a greater number of patients, to look at that question. Dr. Bairey Merz inquired if there were any differences in calorie intake that might explain the variance in lean and fat body mass in one of the clinical studies. Dr. Kohrt explained that snack boxes were offered during both pre- and post-intervention visits so researchers were able to establish that subjects increased their total calorie consumption, as well as their fat consumption.

NIH Women's Health Research: Remember, Reflect, and Recommit

Dr. Clayton introduced James M. Anderson, M.D., Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives, who said that the new trans-NIH strategic plan provides an opportunity for NIH to rededicate itself to science and to helping women. He recognized and introduced

the trailblazers who helped ORWH advance to where it is today: Dr. Pinn, Ambassador Connie Morella, and Senator Barbara Mikulski.

Vivian W. Pinn, M.D., Scientist Emerita, Fogarty International Center, was the first ORWH Director. She attributed the vision for ORWH to the late Acting NIH Director Ruth L. Kirschstein, M.D. As a new enterprise, ORWH was able to accomplish as much as it did because the Office had Congressional support, notably from Ambassador Morella (then in the U.S. House of Representatives) and Senator Mikulski. Since then, it has been exciting to see Dr. Clayton expand on the original vision. She also noted the importance of having an advisory committee such as ACRWH. She thanked members for their contributions and asked that they continue to be dedicated to the ORWH mission. Constance (Connie) Morella, Ambassador to the Organisation for Economic Co-operation and Development (OECD) (2003-2007) and U.S. Representative (1987-2003), saluted the ACRWH members and ORWH staff for their leadership in women's health, as well as the development of the strategic plan. She acknowledged the leadership of the late Dr. Kirschstein and Dr. Bernardine Healy, noting they would want ORWH to move forward, removing barriers that stand in the way of women achieving and reaching their full potential in science and society. Ambassador Morella applauded NIH leadership for the new sexual assault initiative. Finally, she observed that the creation of ORWH was a bicameral effort. She thanked Dr. Clayton for her leadership now and into the future. Senator Mikulski acknowledged ORWH founders, including Dr. Kirschstein and Dr. Healy, as well as Dr. Pinn and Ambassador Morella. Echoing Ambassador Morella's remarks, Senator Mikulski asserted that Congress worked on a bicameral basis at the time ORWH was created. When she entered Congress, the women's movement was in full swing. Women in Congress asked what was happening to women in research after learning that women were being excluded from clinical trials. On August 22, 1990, leading women in Congress sent a landmark letter to the Acting Director of NIH asking for a public meeting on how best to address research on women's health and requesting that all IC Directors and their leadership teams be present. In the meeting, they asked each Institute about the status of women's inclusion in research at that IC and the reasons why. By executive order, the creation of ORWH was inserted into the appropriations bill amidst strong pushback from the scientific and political establishments. With support of Senators Tom Harkin and Arlen Specter, Congress passed a bill that assured women would be included in research, there would be a research agenda and attention to women's scientific careers. There was also a decision that Congress should not be setting priorities for work to be funded. Instead, Senators Harkin and Specter proposed a fund for innovative research under the guidance of the NIH Director.

2019-2023 Trans-NIH Strategic Plan for Women's Health Research: Goals & Objectives

Denise Stredrick, Ph.D., ORWH, introduced speakers CAPT Margaret Bevans, Ph.D., Dr. Mazure, and Dr. Clayton. Dr. Bevans described ORWH's multi-resource, iterative approach to strategic planning with a strong focus on stakeholder input to identify potential priorities for research on women's health. Core stakeholder groups included the ORWH Strategic Plan Organization Team (SPOT), the Trans-NIH SABV Working Group, the NIH Coordinating Committee for Research on Women's Health (CCRWH), the ACRWH, and the NIH *Raising the Bar* Working Group. Analysis by the final group informed the development of a Request for Information that was available from September 12 to November 10, 2017 for comment. One hundred forty-five comments, almost half (45 percent) from researchers, were organized into 45 broad thematic categories. These 45 categories then informed the development of five strategic goals. The draft plan was then refined through broad NIH involvement, as well as review by external stakeholders: NIH Council of Councils, IC Director meetings, CCRWH, ACRWH Strategic Plan Working Group, and NIH Strategic Plan teams.

Dr. Mazure, speaking on behalf of the ACRWH Strategic Plan Working Group, confirmed the broad and inclusive process to develop the plan, which affirms NIH's commitment to the health of women and addresses a breadth of diseases. She made a motion to close the ACRWH Strategic Plan Working Group, which passed unanimously.

Dr. Clayton introduced the draft goals and objectives of the new strategic plan, as well as its guiding principles. She defined women's health research as research that is relevant to the health of women. The health of women encompasses all diseases and conditions that affect a woman from head to toe and recognizes that individual-level biological factors interact with numerous influences across a woman's life course. Science that will improve the health of women is guided by three principles: Inclusion of women, especially populations known to experience a disproportionate burden of illness; engagement of multiple perspectives, especially researchers with diverse skills, knowledge, and experiences; and consideration of the complex intersection among multiple biological factors and the context of a woman's life. The ultimate aim of advancing science for the health of women requires the pursuit of several goals identified in the draft strategic plan: 1) Advance rigorous research that is relevant to the health of women; 2) Develop methods and leverage data sources that consider sex and gender influences; 3) Enhance dissemination and implementation of evidence to improve the health of women; 4) Promote training and careers to develop a well-trained, diverse, and robust workforce to advance science for the health of women; and 5) Improve evaluation of research that is relevant to the health of women. These goals work in synergy with the NIH-wide strategic plan. Dr. Clayton reported that final approval of the plan for women's research is anticipated in the near future. She encouraged ACRWH members to disseminate and advocate for the plan, as well as to advise NIH on its impact in the "real world."

2019-2023 Trans-NIH Strategic Plan for Women's Health Research: Dissemination, Implementation and Evaluation

Dr. Clayton introduced Samia Noursi, Ph.D., ORWH Associate Director for Science Policy, Planning and Analysis. Dr. Noursi explained that ORWH is beginning the process of planning next steps related to the dissemination, implementation, and evaluation of the new strategic plan. Dissemination will begin as soon as final approval has occurred and will rely on the NIH community, stakeholders, the scientific community, and the public to power the effort. To implement the plan, ORWH will work with all the ICOs to implement the plan in their respective organizations. ORWH will develop an implementation timeline to guide this effort. The goal of the evaluation effort is to create a chain of evidence that collectively shows progress being made and provide meaningful evidence that demonstrates how achievement of the strategic plan goals and objectives contributes to mission accomplishment for both ORWH and NIH.

At Dr. Noursi's request, a motion to establish a new ACRWH Working Group on the Implementation and Evaluation Plan was made and carried unanimously.

Sex and Gender in Health and Disease: Opportunities for the Future

Dr. Clayton introduced Rebecca DelCarmen-Wiggins, PhD., Research Program Officer, ORWH, who presented a concept clearance for a FOA to fund investigator-initiated, interdisciplinary research that focuses exclusively on the consideration of sex and gender and their interaction on health and disease. The rationale is based on landmark developments, including a 2015 workshop on Improving the Health of Women in the United States, the SABV policy, the 21st Century Cures Act, and the new strategic plan.

The new FOA complements existing ORWH funding mechanisms, and reflects the success of a 2010 R21 application that was well-received by 24 ICOs, resulting in 88 awards at a total direct cost of \$11 million.

Sex interacts with gender to influence health and disease. Thus, examples of broad areas for sex and gender integration in the context of disease-specific hypotheses include: Discovering basic biological differences, structural and functional, between females and males; investigating the influence of sex and gender and their interactions on disease prevention, presentation, management, and outcomes; identifying the immediate, mid-, and long-term effects of exposures on health and disease outcomes; promoting research that explores the influence of sex and gender on the connection between the mind and body and its impact on health and disease; and expanding research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health.

Open Discussion

Dr. Clayton invited comments about the implementation of the strategic plan and the new FOA.

General Comments about the FOA: In response to a question from Dr. Langer, Dr. Clayton confirmed that the FOA would encourage interdisciplinary research. Dr. Regensteiner asked for an example of what the FOA might address. Dr. DelCarmen-Wiggins responded that the rate of depression in women is twice that for men, starting at puberty. But the cause for this is unknown, e.g., is it hormonal? Dr. Clayton commented that this FOA will take sex and gender integrative research to a new level. Dr. Clayton asked Dr. McCullough if the FOA would fit into her stroke research; Dr. McCullough responded affirmatively, noting multiple sex and gender reasons for stroke outcomes. Dr. Kohrt commented that the new FOA would complement SCORE funding because it would allow investigators to conduct in-depth studies to follow up their exploratory research. Dr. Stefanik advocated for a lifetime focus and emphasis on the role of adverse early life experiences. Dr. Paller expressed enthusiasm at the prospect of bringing more people into the women's health research arena through the involvement of many ICOs and the opportunity for multi-disciplinary research.

FOA Funding: Susan Wood, Ph.D., asked about how the FOA would be funded. Dr. Clayton responded that ORWH would need to get support from other ICOs; the ORWH role is to be catalyst to promote research on women's health across the trans-NIH portfolio.

Recommendations for Language to Include in the FOA: Dr. Stefanik encouraged greater use of intersectionality in place of binary male/female categories in the approach to the FOA. Dr. Lopez responded that she thought that issue had been addressed in the guiding principle of the strategic plan on the complex relationships among multiple external and internal factors and the context of a woman's life; she recommended that the diagram that appears on Slide 17 of Dr. Clayton's presentation about the strategic plan goals be included in the FOA language. Dr. Langer observed that the measurement of gender is less developed in medicine than in the social sciences, and suggested making the definition more explicit in the new FOA. Dr. Stefanik emphasized the importance of cell biology to sex and gender research; she recommended that the way to engage cell biologists' interest is to state that scientists have been missing some important confounding variables in the traditional approach to doing biology. Dr. McCullough commented that all the genome-wide association studies (GWAS) datasets available to her remove the sex chromosome for software/bio-informatics reasons. Her institution has put together a think tank to address this problem so that sex can be included as a biological variables in future studies.

Award Mechanism: Discussion centered on whether an R21 or an R01 was the better funding mechanism. Dr. Mazure observed that approaching the FOA as an R21 would provide an opportunity to engage ICOs' participation by requiring a smaller commitment of funds and would attract new investigators. However, the short length and minimal funding for an R21 can be limiting. She wondered if it would be possible to provide for a limited number of R01s. Wendy Brewster, M.D., Ph.D., advocated for using the R21 award for the new FOA to help bring in young investigators. Dr. de Vries agreed. Dr. McCollough said she liked the R21 mechanisms in terms of bringing new investigators into the field, but observed that it takes several years to develop a program of research, an argument against the R21. Dr. Bairey Merz agreed. Dr. Mazure recommended focusing on the goal rather than the mechanism. If the goal is to bring more people to the field, an award longer than two years may be needed. Dr. de Vries suggested considering hybrid awards (e.g., the R33) that are in between the R21 and R01. Rachel Jones, Ph.D. argued in favored of R01 awards for the FOA to give investigators sufficient funds to conduct clinical trials, where there are differences in recruitment strategies for men and women. Dr. Lopez concurred with the argument in favor of the R01 award.

Dedicated Review Panel: Dr. de Vries said he is very optimistic about the FOA, and suggested ORWH consider a dedicated review panel to avoid the risk of applications getting lost if reviewed in different panels. Dr. Mazure agreed, as did Kimberly Gregory, M.D. and Sabra Klein, Ph.D., who argued in favor of a standing review committee devoted to sex and gender. Dr. Bairey Merz recommended that an interdisciplinary sex and gender component also be added to traditional study panels.

Strategic Plan: Dr. Lopez lauded the strategic plan's emphasis on developing the workforce, recommending that ORWH partner with the Clinical and Translational Science Awards (CTSAs) in supporting gender-specific research, noting that they have development opportunities for young investigators. Dr. Bairey Merz asked if ACRWH members could cite the strategic plan. Dr. Clayton responded that only the goals and objectives are currently in the public domain. Once the plan has been approved by the NIH Director, she'll send out the full citation.

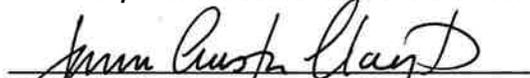
Dr. Clayton asked if ACRWH members had suggestions for topics at future meetings. Dr. Lopez recommended conversations about the intersections of race and sex/gender issues, i.e., genetic variances that may impact understanding of health and disease. Dr. Langer applauded ORWH for choosing the improvement of maternal health as the topic for the next meeting and offered her help.

Closing

Dr. Clayton reminded ACRWH members that the next meeting in April 9-10, 2019. She adjourned the meeting at 3:10 pm.

Certification

We certify that the contents above are accurate and complete.


Janine Austin Clayton, M.D., Director
Office of Research on Women's Health


Elizabeth Spender, B.S.N., Executive Secretary
Advisory Committee on Research on Women's Health

Date 1/23/19

Date 1-20-19