REPORT OF THE NIH INSTITUTES AND CENTERS

National Cancer Institute

Executive Summary

Cancer remains one of the most challenging areas of medicine. In the United States, one in three women will develop cancer within their lifetime, and one in five women will die of their disease, which means that in 2015, an estimated 277,280 women will die from cancer in this country. The most commonly diagnosed cancers among American women include breast, colorectal, and lung cancers. Together, these cancers account for about half of the estimated new cancer cases in this population. These same three cancers are also the leading causes of cancer deaths in women. Although breast cancer is the most commonly diagnosed cancer among women, lung cancer is the leading cause of cancer death in women.

Despite these statistics, there is good news in the fight against cancer. Since the early 1990s, overall death rates from cancer have continued to decrease in both men and women. Among women, cancer death rates decreased an average of 1.4 percent per year from 2001 through 2010. In addition, overall cancer incidence rates among women stabilized from 2001 through 2010. In spite of these important gains, improvement has not been equal in all cancers, which underscores the need for additional research. Also, improvements have not been equal among all populations. Minority and underserved women are burdened by increased rates of cancer incidence and mortality.

As this report highlights, real progress is being made in cancer prevention, early detection, and treatment, which has helped to reduce cancer incidence and mortality. Decreases in colorectal cancer incidence rates, cervical cancer deaths, and mortality for other cancers can be attributed respectively to increases in screening (which can detect and remove precancerous colon polyps), early detection (including improvements in primary prevention, such as the human papillomavirus [HPV] vaccine), and improved treatment strategies (such as combination therapy, targeted drugs, and genetic testing particularly in breast and colon cancers).

Over the past 2 years, National Cancer Institute (NCI)-supported researchers made major strides in a variety of cancers that affect women. Some of the most promising advances include the finding that mutations in the PALB2 gene raise the risk of breast cancer in women by almost as much as mutations in BRCA1 and BRCA2. In addition to raising the risk of breast and ovarian cancer, BRCA gene mutations may contribute to lung tumor risk. A mutated version of the BRCA2 gene was found to raise the risk of getting any type of lung cancer by 85 percent. Daily aspirin use was shown to reduce ovarian cancer risk by 20 percent. Additional studies are needed to explore the risks and benefits for this potential chemopreventive agent and to identify the mechanism by which aspirin may reduce ovarian cancer risk. In reducing cervical cancer risk, data from the NCI Costa Rica Trial showed that less than the standard three-dose regimen of the HPV vaccine may be protective against HPV infection. A noninvasive DNA test is being evaluated that could have clinical impact for screening underserved populations in the United States and for millions of women in poor, underdeveloped countries.

NCI is also advancing basic and translational research related to women's health and conducting population-based studies aimed at identifying risk factors for poor outcomes. In addition, NCI remains dedicated to expediting the dissemination of research advances, new knowledge, and beneficial interventions to the scientific community and diverse public audiences via numerous resources related to women's health. Additional information on women's health issues related to cancer can be found on NCI's award-winning Web site: http://www.cancer.gov.

Introduction

The American Cancer Society (ACS) estimates that 277,280 women in the United States will die from cancer in 2015. Breast, colorectal, and lung cancers are the most commonly diagnosed cancers among American women, collectively accounting for approximately half of the estimated new cancer cases in this population. Breast cancer is the most common, accounting for 29 percent of all new cases, while lung cancer accounts for 13 percent and colorectal cancer accounts for 8 percent. These three cancers are also the leading causes of cancer deaths in women.

Overall cancer incidence rates among women stabilized from 2001 through 2010. When averaged across this period, breast cancer incidence rates declined 1.0 percent per year, though they did not change from 2006 through 2010. However, there have been declines in other cancers common among women. From 2006 through 2010, average incidence rates per year decreased for colorectal cancer, 4.0 percent; ovarian cancer, 2.9 percent; lung cancer, 1.8 percent; and cervical cancer, 1.2 percent. Steady declines in cancer incidence among women have also been observed for lymphoma and cancers of the brain, bladder, and stomach.

In addition to the stabilization of the overall incidence rates of cancer, overall death rates have continued to decrease in both men and women since the early 1990s. From 2001 through 2010, cancer death rates in women decreased an average of 1.4 percent per year. In the same period, average death rates per year declined for colorectal cancer, 2.9 percent; stomach cancer, 2.7 percent; breast cancer, 1.9 percent; cervical cancer, 1.7 percent; oral cavity and pharynx cancer, 1.6 percent; ovarian cancer, 1.6 percent; leukemia, 1.3 percent; and lung cancer, 0.8 percent (Edwards et al., 2014).

These data indicate real progress in cancer control. Primary prevention, early detection, and improved treatment have resulted in the vast majority of changes. Decreases in cervical cancer deaths primarily are due to early detection of premalignant lesions, with incidence rates expected to drop dramatically in the coming years due to improvements in primary prevention, including the human papillomavirus (HPV) vaccine. The decrease in colorectal cancer incidence rates largely reflects increases in screening, which can detect and remove precancerous polyps. Decreases in mortality for many cancers, particularly breast and colon cancers, can be attributed to improved treatment strategies, such as combination therapy, targeted drugs, and genetic testing.

Unfortunately, improvement has not been equal in all cancers. Incidence rates were steady or increased from 2001 through 2010 for two HPV-associated cancers (oropharynx and anus). This underscores the need for additional prevention efforts for HPV-associated cancers, including efforts to increase vaccination coverage. Moreover, with many minority and underserved women burdened by increased rates of cancer incidence and mortality, improvements have not been equal among all populations.

NCI conducts and supports research, training, health information dissemination, and other programs focused on the cause, diagnosis, prevention, and treatment of cancer, as well as rehabilitation and continuing care for patients with cancer. NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, especially those cancers with high incidence or mortality among women, as well as cancers that affect both genders to a similar degree. This research focuses on all stages of disease, from prevention through cancer survivorship, and ranges from molecular and subcellular basic science experiments to population-based studies and community-based interventions.

NCI also is committed to disseminating research advances to the scientific community and the public and has developed numerous resources related to women's health. The award-winning NCI Web site, Cancer.gov (http://www.cancer.gov), is a key Institute vehicle for disseminating information to a diverse range of audiences; NCI also provides a Spanish-language version of its Web site, Cancer.gov en español (http://www.cancer.gov/espanol). NCI's Cancer Information Service provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public. U.S. residents can reach English- or Spanish-speaking NCI information specialists by calling toll-free 1–800–4–CANCER (1–800–422–6237). An instant-messaging service called LiveHelp is also available on the NCI Web site.

Although far from comprehensive, the following pages provide a representative sampling of the activities and accomplishments of NCI relative to women's health in FY 2013 and FY 2014. Disease areas included in this report are brain, breast, cervical, endometrial, lung, oropharyngeal, ovarian cancer, Burkitt lymphoma, and AIDS-associated malignancies.

NCI Women's Health Officer

The NCI Women's Health Officer facilitates communication across the Institute and promotes collaboration between NCI and other National Institutes of Health (NIH) Institutes and Centers, Federal agencies, and nongovernmental organizations. The Women's Health Officer develops and disseminates reports and information on NCI's research and research progress on cancers in women and coordinates NCI's responses to agency requests for information.

Accomplishments and Activities

All Cancers

Female Cancer Rates Declining. According to NCI's *Annual Report to the Nation on the Status of Cancer, 1975–2010* (Edwards et al., 2014), female cancer rates declined 1.4 percent per year from 2004 through 2010, which was a turnaround from an increase of 0.3 percent per year from 1995 to 2004. These shifts have been attributed primarily to the reduced prevalence of cigarette smoking in the United States. Lung cancer continues to be the leading cause of cancer death among women in the United States, with approximately 80 percent of lung cancer deaths among women due to smoking. (The Web site http://www.women.smokefree.gov is a resource targeted specifically to women to help prevent and stop tobacco use among women.) It is anticipated that there will be further decreases in lung cancer in future years, based on reduced tobacco consumption among women.

This program maps to ORWH Strategic Plan Objective 5.1

Women Who Followed Nutrition and Physical Activity Guidelines Had Lowered Risk of Cancer. An NCI-supported Women's Health Study by Thomson et al. (2014) used data from more than 65,000 postmenopausal women and found that women who followed the ACS *Guidelines on Nutrition and Physical Activity for Cancer Prevention* lowered their risk for many types of cancer significantly. The women who followed the guidelines most closely had a 17 percent lower risk of any cancer, a 22 percent lower risk of breast cancer, and a 52 percent lower risk of colorectal cancer. The women who best adhered to the guidelines were also 27 percent less likely to have died during the time frame of the study.

This program maps to ORWH Strategic Plan Objective 5.5

AIDS-Related Malignancies

Treatment

Drug-Resistance Mutations Following Exposure to Single-Dose Nevirapine. Low-frequency nevirapine (NVP)-resistant variants have been associated with virologic failure of initial NVP-based combination antiretroviral therapy in women with prior exposure to single-dose NVP (sdNVP). Boltz et al. (2014) found the risk of virologic failure on NVP-based combination antiretroviral therapy from NVP-resistant variants differs between sdNVP-exposed and sdNVP-unexposed women. This difference may be driven by drug-resistance mutations emerging after sdNVP exposure that are linked on the same viral genome.

This program maps to ORWH Strategic Plan Objectives 1.6, 3.5

Brain Cancer

Biology

Type I Insulin-Like Growth Factor Receptor May Mediate Brain Metastasis. Brain metastasis is a common cause of mortality in cancer patients, yet potential therapeutic targets remain largely unknown. The type I insulin-like growth factor receptor (IGF-IR) plays a role in the progression of breast cancer and is being investigated in the clinical setting for various types of cancer. Using an in vivo experimental brain metastasis model, Saldana et al. (2013) found that IGF-IR knockdown brain-seeking cells are less likely to establish brain metastases. Also, they demonstrated that the malignancy of brain-seeking cells is attenuated with picropodophyllin, an IGF-IR-specific tyrosine kinase inhibitor. Together, these data suggest that the IGF-IR is an important mediator of brain metastasis and its ablation delays the onset of brain metastases in this model system.

This program maps to ORWH Strategic Plan Objective 1

Breast Cancer

Biology

Third Gene (PALB2) Is an Indicator of Breast Cancer Risk. A study carried out by Antoniou et al. (2014) at 14 international centers found that mutations in the PALB2 gene raise the risk of breast cancer in women by almost as much as mutations in BRCA1 and BRCA2. Previous data had indicated that mutations in PALB2 were linked to breast cancer and many genetic tests already screen for them, but it had not been clear to what extent these mutations raised a carrier's odds of developing the disease.

This program maps to ORWH Strategic Plan Objective 1.1

Transcription Factor that Suppresses Breast Cancer Metastasis. GATA3 is a transcription factor that specifies

and maintains mammary luminal epithelial cell fate. Its expression is lost in breast cancer, correlating with a worse prognosis in human patients. Researchers demonstrate that GATA3 promotes differentiation, suppresses metastasis, and alters the tumor microenvironment by inducing miR29b expression. The discovery published by Chou et al. (2013) that the GATA3-miR29b axis regulates the tumor microenvironment and inhibits metastasis makes it a target for therapeutic intervention in breast cancer.

This program maps to ORWH Strategic Plan Objective 1.1

Potential Druggable Target for Aggressive Triple-Negative Breast Cancer. Gonzalez et al. (2014) identified EZH2 overexpression as significantly associated with triple-negative breast cancers, a biologically aggressive subtype of breast cancer characterized by the absence of estrogen and progesterone receptor expression as well as the HER2 receptor. EZH2 is the catalytic subunit of PRC2, which silences gene transcription through histone methylation. EZH2 protein is upregulated in several malignancies where its oncogenic activity is thought to be primarily mediated by silencing tumor suppressor genes. In this study, researchers were able to show that EZH2 activates the Notch1 signaling pathway, which leads to the expansion of the stem cell pool, leading to accelerated breast cancer initiation and growth. Hence, targeting EZH2 may be an important target to halt triple-negative breast cancer progression.

This program maps to ORWH Strategic Plan Objectives 1.7, 3.1

Exploring the Role of an Inflammatory Protein in Breast Cancer Development. Aberrant expression of an inflammatory protein, nitric oxide synthase 2 (NOS2), may enhance the progression and metastasis of an aggressive and less common form of breast cancer, known as the estrogen receptor-negative type of disease. In this work, Heinecke et al. (2014) used tumor xenografts (human tumor cells transplanted into mice) to mimic an aggressive tumor microenvironment that included inflammation, nutrient deprivation, and hypoxia (inadequate oxygen in body tissue). The researchers hope that a better understanding of how NOS2 influences estrogen receptor-negative breast cancer tumor expression will lead to an approach, when coupled with drug inhibition of NOS2, that could provide evidence to clearly determine whether NOS2 has an important role in breast cancer disease progression in women.

This program maps to ORWH Strategic Plan Objectives 1.7, 2.2

Brachyury: A Possible Driver of Tumor Cell Invasion, Metastasis, and Drug Resistance. The epithelial-mesenchymal transition (EMT) has been implicated as an important process in tumor cell invasion, metastasis, and drug resistance. Brachyury, a transcription factor, has recently been described as a driver of EMT of cancer cells. Palena et al. (2014) found the overexpression of brachyury in breast carcinomas was associated with poor prognosis. They also demonstrated that brachyury-specific T cells can lyse human breast carcinoma cells. This study provides the rationale for the use of a vaccine targeting brachyury for the therapy of human breast cancer, either as a monotherapy or in combination therapies.

This program maps to ORWH Strategic Plan Objectives 2.1, 3.5

CD44 as a Prognostic Marker for Breast Cancer Treatment Outcomes. CD44 is a transmembrane glycoprotein involved in numerous cellular functions, including cell adhesion and extracellular matrix interactions. Researchers found CD44 is prognostic marker for overall survival in a randomized trial on breast conservation with 25-year follow-up. These findings published by Dan et al. (2014) illustrate the potential utility of CD44 as a marker for early stage breast cancer. Subgroup analysis in patients with lymph node involvement revealed CD44 positivity was strongly associated with increased survival, suggesting a potential role of CD44 in decision making for axillary management.

This program maps to ORWH Strategic Plan Objective 3.5

Screening

Using Nanotechnology to Detect and Isolate Metastatic Breast Tumor Cells from Blood. Primary tumor cells travel through the bloodstream before the appearance of detectable metastatic lesions. The analysis of these circulating tumor cells (CTCs) in blood may provide unprecedented opportunities for metastatic risk assessment and investigation. Halo et al. (2014) have developed gold nanoparticles coated with highly oriented DNA molecules called NanoFlares that fluorescently detect the complementary messenger RNA biomarkers of CTCs. Using these nanoparticles, they have detected as few as 100 live breast cancer cells per milliliter of human blood and isolated these cells for further growth and analysis. This approach may enable the genetic analysis of CTC subpopulations

on an individual basis, providing opportunities for cancer diagnosis, prognosis, and personalized therapy.

This program maps to ORWH Strategic Plan Objectives 2.4, 2.5, 3

Treatment

Yoga May Help Overcome Fatigue After Breast Cancer. Fatigue interferes with daily activities for approximately one-third of cancer survivors. Exercise helps recovery after cancer treatment, but fatigue can make working out hard, even years after treatments have ended. Yoga can help reduce fatigue for breast cancer survivors, according to an NCI-funded randomized study by Kiecolt-Glaser et al. (2014). The researchers recruited women who had completed cancer treatment within 3 years. All were yoga novices. The women practicing yoga reported approximately 60 percent less fatigue than the women who did not, and their measures of inflammation were 13 percent to 20 percent lower. Moreover, the longer they practiced yoga, the greater their improvement.

This program maps to ORWH Strategic Plan Objective 2.5

Reducing Resistance to Hormonal Therapies in Breast Cancer. Entinostat is an agent that targets resistance to hormonal therapies in estrogen receptor-positive breast cancer. In a randomized placebo-controlled phase II study published by Yardley et al. (2013), the researchers evaluated entinostat combined with the aromatase inhibitor exemestane versus exemestane alone. Median overall survival improved to 28.1 months with entinostat/exemestane versus 19.8 months with the placebo. Entinostat added to exemestane is generally well tolerated and demonstrated activity in patients with estrogen receptor-positive advanced breast cancer in this study. Acetylation changes may provide an opportunity to maximize the clinical benefit of entinostat.

This program maps to ORWH Strategic Plan Objectives 1.7, 3.1

Breast Cancer Survivors Face Long-Term Unemployment After Adjuvant Chemotherapy. Women who get chemotherapy for breast cancer may end up unemployed for a long period. The women in this study who received chemotherapy were less likely to be still working 4 years later, compared with women who skipped chemotherapy (38 percent jobless versus 27 percent jobless, respectively). The findings suggest that even though women want to get back to work as soon as possible, chemotherapy may be changing their lives more than anticipated. The researchers conclude that patients who are deciding on whether to receive chemotherapy need to understand the potential long-term consequences of receiving treatment, including possible implications for their employment and financial outcomes (Jagsi, Hawley, et al., 2014).

This program maps to ORWH Strategic Plan Objective 3

Enhancing Effectiveness of Radiofrequency Ablation with Nanoparticle Delivery of Chemotherapeutics. Moussa et al. (2014), investigators from the NCI Alliance for Nanotechnology in Cancer, have conducted animal studies to combine radiofrequency ablation (RFA) with micellar (20 nm) or liposomal (100 nm) preparations of doxorubicin or quercetin. The purpose of the study was to enhance effects of RFA treatment on larger tumors. It was found that smaller particles have superior deeper tissue penetration, while larger long-circulating particles result in greater overall long-term intratumoral drug accumulation and reduced tumor growth.

This program maps to ORWH Strategic Plan Objective 2.2

Outcomes

Double Mastectomy Did Not Result in Longer-Term Survival than Less Invasive Lumpectomy Followed by Radiation. Women with breast cancer who opt for a double mastectomy do not increase their chances of survival, according to research supported by the Tobacco Control Research Branch, Division of Cancer Control and Population Sciences (DCCPS). Having both breasts removed did not extend patients' lives any more than having cancerous lumps removed followed by radiotherapy. The findings by Kurian et al. (2013) are based on a study of 189,734 women in California with the disease. Ten years after having both breasts removed, 18.8 percent of women had died, compared with 16.8 percent of those who had a lumpectomy, then radiation.

This program maps to ORWH Strategic Plan Objective 2.5

Prevention

Fruit and Vegetable Consumption Linked to Lower Risk of Breast Condition for Teen Girls. Benign breast disease increases the risk of breast cancer later in life; women who have benign breast disease are one and a half to two times more likely to develop breast cancer than women without

it. According to a recent NCI-supported study, teenage girls who eat more colorful fruits and vegetables are less likely to develop benign breast disease as young adults. Boeke et al. (2014) concluded that consumption of these fruits and vegetables might be a way to prevent benign breast disease.

This program maps to ORWH Strategic Plan Objectives 2.5, 3

Risk Factors

Obesity Promotes Aggressive Breast Cancer. The study has found that among postmenopausal women, obese women tend to have larger, more aggressive breast tumors than lean women. Arendt et al. (2013) show that during obesity, the adipocytes (fat cells) within human and breast tissues recruit and activate macrophages (a subtype of immune cell), which enable angiogenesis and create a microenvironment conducive for the growth of the tumor.

This program maps to ORWH Strategic Plan Objectives 1.8, 3

New Evidence Linking Smoking to Increased Risk of Breast Cancer. Postmenopausal women who smoke or have smoked in the past may have an increased risk of breast cancer compared with women who have never smoked. Nyante et al. (2014) confirmed this association in more than 186,000 women enrolled in the NIH–American Association of Retired Persons Diet and Health Study, of whom about 7,500 developed invasive breast cancer during almost 10 years of follow-up. A major strength of the study was that the authors controlled for alcohol consumption, which is known to increase the risk of breast cancer and is more common among smokers.

This program maps to ORWH Strategic Plan Objectives 3.5, 3.6, 3.7, 3.8

Associating Urinary Estrogens and Estrogen Metabolites with Premenopausal Breast Cancer Risk. Estrogens and estrogen metabolism are thought to be associated with premenopausal breast cancer risk but evidence is limited. Eliassen et al. (2012) examined 15 urinary estrogens/estrogen metabolites and breast cancer risk among premenopausal women in a case-control study nested within the Nurses' Health Study II. The data suggest that most mid-luteal urinary estrogen metabolite concentrations are not positively associated with breast cancer risk among premenopausal women. The inverse associations with parent estrogen metabolites and the parent estrogen metabolite/nonparent estrogen metabolite ratio suggest that women with higher urinary excretion of parent estrogens are at lower risk.

This program maps to ORWH Strategic Plan Objective 3.1

Burkitt Lymphoma

Risk Factors

***Plasmodium falciparum* Infection Is Associated with EBV Reactivation in Pregnant Women Living in Malaria Holoendemic Area of Western Kenya.** Daud et al. (2014) found that Epstein-Barr virus (EBV) loads in pregnant women with malaria were elevated in comparison to women without evidence of *P. falciparum* infection during pregnancy. The loss of control of EBV latency following *P. falciparum* infection during pregnancy and the subsequent increase in EBV load contribute to greater shedding of EBV in maternal saliva and breast milk and thus increased risk of endemic Burkitt lymphoma.

This program maps to ORWH Strategic Plan Objectives 3.3, 4.6

Cervical Cancer

Biology

Researchers Identify Major Genetic Drivers of Cervical Cancer. Although HPV is an identified factor in cervical cancer, the key human gene drivers of this disease remain unknown. Using gene network reconstruction, Mine et al. (2013) found that cell cycle and antiviral genes serve as major drivers of cervical cancer. This suggests that chromosomal gains drive activation of antiviral genes and contribute to virus elimination, which synergizes with cell cycle dysregulation. These findings may help explain the paradox of episomal HPV decline in women with invasive cancer who were previously unable to clear the virus.

This program maps to ORWH Strategic Plan Objectives 1.1, 1.6

Screening

8 Million U.S. Women Skip Cervical Cancer Screening. According to a study published by Benard et al. (2014), 11.4 percent (approximately 8 million) of women who should be screened for cervical cancer reported that they had not been screened in the past 5 years. Health insurance seemed to be an important factor, with more than 23 percent of women without health insurance and 25 percent of those without a

regular doctor or other health care provider reporting that they had not had a screening. Rates were also higher among minorities. More than half of women diagnosed with cervical cancer cases have never or rarely been screened.

This program maps to ORWH Strategic Plan Objectives 2.5, 3.9

HPV Test for Primary Cervical Cancer Screening. Genital HPVs are a group of more than 40 related viruses and are the most common sexually transmitted infections. Approximately 14 "high-risk" HPV types are associated with cervical cancer. About 10 percent of women infected with high-risk HPV develop a persistent infection that may put them at risk of cancer. Virtually all cervical cancers are caused by HPV infections, with just two types, HPV 16 and HPV 18, responsible for approximately 70 percent of cervical cancers. In April 2014, the U.S. Food and Drug Administration (FDA) approved the first HPV DNA test, the cobas HPV Test, for women 25 or older to assess the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about a woman's risk for developing cervical cancer in the future. Using a sample of cervical cells, the test detects DNA from 14 high-risk HPV types. It specifically identifies HPV 16 and HPV 18, while concurrently detecting 12 other types of high-risk HPVs. Based on results of the cobas HPV Test, women who test positive for HPV 16 or HPV 18 should have a colposcopy. Women testing positive for 1 or more of the 12 other high-risk HPV types should have a Pap test to determine the need for a colposcopy. Data supporting the use of the cobas HPV Test as a primary screening test for cervical cancer included the ATHENA trial, a study of more than 40,000 women 25 years old or older undergoing routine cervical exams. The study results showed that the cobas HPV Test is safe and effective for use as either a co-test or a primary screening tool for cervical cancer. The results of the cobas HPV Test should be used together with patient screening history, risk factors, and current medical practice guidelines for cervical cancer screening.

Unnecessary Pap Tests Common in Older Women. The U.S. Preventive Services Task Force, the American Cancer Society, the American College of Obstetricians and Gynecologists, and other medical groups recommend a Pap smear every 3 years until age 65. After age 65, further testing has been shown to provide little to no benefit for women with a history of negative Pap tests and no previous cancer or precancerous lesions. Despite those recommendations, millions of American women, including those who have had hysterectomies, continue to be unnecessarily screened for cervical cancer. The findings underscore the need to reframe the idea of the annual exam and to focus on appropriate screenings (Kepka, Breen, King, Benard, & Saraiya, 2013).

This program maps to ORWH Strategic Plan Objectives 3.6, 3.8

Cervical Cancer Rates Are Much Higher in Older Women than Previous Estimates. Rositch, Nowak, and Gravitt (2014) found that cervical cancer rates are much higher in older women than previously estimated: Approximately 1.9 cases occur for every 10,000 women—rather than the previous estimate of 1.2 cases per 10,000 women—and the rate peaks in women ages 65 to 69 years, rather than 25 years earlier, as was previously thought. African-American women had the highest cervical cancer rates, at more than 5 cases for every 10,000 women in ages 65 to 69—an increase of 126 percent over the previous estimate. These latest data excluded the 20 percent of women who had hysterectomies, which previous studies had not; that skewed the previous data, because few if any of these women would develop cervical cancer. Because these data show a high and nondeclining rate of cervical cancer in women over the age of 60 to 65 years, when women are eligible to exit screening, the authors concluded that risk and screening guidelines for cervical cancer in older women may need to be reconsidered.

This program maps to ORWH Strategic Plan Objectives 3.6, 5.5

Negative HPV Test Result Is Better Predictor of Low Cervical Cancer Risk than Negative Pap Test. Based on a study that included more than 1 million women enrolled in Kaiser Permanente Northern California's health care system, NCI investigators determined that a negative test for HPV infection compared to a negative Pap test provides greater safety, or assurance, against future risk of cervical cancer. That is, women who test negative on the HPV test have an extremely low risk of developing cervical cancer. Research by Gage et al. (2014) found that the risk of developing cervical cancer within 3 years following a negative HPV test result was about half the already low risk following a negative Pap test.

This program maps to ORWH Strategic Plan Objectives 1.6, 2.5

Multiple Biopsies Are Superior to a Single Biopsy in Detecting Cervical Cancer Precursors. NCI researchers found that performing multiple biopsies during a procedure

known as colposcopy—visual inspection of the cervix—is more effective than performing a single biopsy of the worst-appearing area for detecting cervical cancer precursors. Women with abnormal results on cervical cancer screening, which is usually done via scraping cells from the surface of the cervix, are referred for colposcopy and biopsy to detect cervical cancer precursors (typically classified as high-grade squamous intraepithelial lesions [HSIL]). The biopsy results determine whether excision of the lesion is required. Colposcopy with a single biopsy can fail to detect HSIL. A multiple biopsy approach may help to detect disease early and avoid repeated biopsies for women with initial negative findings (Wentzensen et al., 2014).

This program maps to ORWH Strategic Plan Objective 2

Prevention

Development of the Next-Generation HPV Vaccine. HPV 9-valent vaccine, recombinant (Gardasil 9), covers five additional HPV types that cause approximately 20 percent of cervical cancers. These HPV types were not covered by previously FDA-approved HPV vaccines. This new nonvalent HPV vaccine has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal, and anal cancers. In a randomized, controlled clinical study conducted in the United States and internationally with approximately 14,000 females, Gardasil 9 was shown to be 97 percent effective in preventing cervical, vulvar and vaginal cancers caused by the five additional HPV types. Gardasil 9 also is as effective as the previous Gardasil vaccine for the prevention of diseases caused by the four shared HPV types. Due to the low incidence of anal cancer caused by the five additional HPV types, the prevention of anal cancer is based on Gardasil's demonstrated effectiveness of 78 percent and additional data on antibodies in males and females who received Gardasil 9. Gardasil 9 is administered as three separate injections, with the initial dose followed by additional injections given 2 and 6 months later. Gardasil 9's full potential for benefit is obtained by those who are vaccinated prior to becoming infected with the HPV strains covered by the vaccine. In December 2014, FDA approved Gardasil 9 for the prevention of certain diseases caused by the nine types of HPV. The new vaccine is approved for use in females aged 9 to 26 and males aged 9 to 15. In February 2015, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices issued its recommendations on the use of the vaccine.

Fewer Doses of HPV Vaccine Result in Immune Response Similar to Three-Dose Regimen. Safaeian et al. (2013) reported that two doses of a HPV vaccine, trademarked as Cervarix, resulted in similar serum antibody levels against two of the most carcinogenic types of HPV (16 and 18), compared to a standard three-dose regimen. Among women who received only one dose, antibody levels were also high and remained stable 4 years after vaccination. The results suggest that fewer doses of an HPV vaccine may confer necessary long-term protection against new infection. This study was part of the NCI Costa Rica Vaccine Trial, a randomized clinical trial designed to evaluate vaccine efficacy against cervical HPV16/18 infection and related disease.

This program maps to ORWH Strategic Plan Objectives 1.6, 2.5, 4.2, 4.6

Treatment

Developing Vaccines to Destroy HPV-Infected Cervical Cancer Cells. Cancers resulting from HPV, including cancers of the cervix, vagina, anus, and oropharynx, disproportionately affect women. Despite effective strategies to screen or prevent cervical HPV disease, cervical cancer remains the third leading cause of cancer in women worldwide. A longstanding goal of immunotherapy has been to develop therapeutic vaccines that would generate durable antiviral cytotoxic T cells (CTLs) that would destroy HPV-infected cervical cancer cells. Recent studies are beginning to shed light on the immunologic obstacles posed by the virus and the microenvironment and how they might be overcome. In particular, recent findings have demonstrated that peripheral therapeutic vaccination to HPV antigens could induce a robust tissue-localized antiviral CTL immune responses (Maldonado et al., 2014; Wang, Hung, Huh, Trimble, & Roden, 2015).

This program maps to ORWH Strategic Plan Objectives 1.6, 2.3, 2.7

Treatment Trial Demonstrates Addition of Bevacizumab to Chemotherapy Prolongs Overall Survival of Advanced Cervical Cancer. The NCI-funded NRG Oncology conducted a randomized controlled 2 × 2 factorial clinical trial examining the role of the

antiangiogenesis agent, bevacizumab, in combination with chemotherapy (comparison 1) and in comparison to treatment with carboplatin/paclitaxel with the non-platinum-containing regimen of topotecan and paclitaxel (comparison 2). This was tested in women with advanced, noncurable disease at presentation or newly recurrent or metastatic cervical cancer. A statistically significant prolongation of progression-free disease and overall survival was observed with the additional of bevacizumab to chemotherapy. These data led to FDA approval of the bevacizumab/chemotherapy combination for this group of cervical cancer patients. This is the first new treatment approved for cervical cancer in more than a decade.

This program maps to ORWH Strategic Plan Objectives 2.7, 5.2

Endometrial Cancer

Biology

Improving Endometrial Cancer Treatment by Identifying Progesterone Resistance Mechanisms. Endometrial cancer is a hormonally regulated tumor. Although 50 percent of patients respond well to progesterone therapy, this therapy, which is well tolerated and spares fertility, is not widely embraced. This is primarily because clinicians cannot reliably identify women who will respond to it. In this study, the researchers use a mouse model of endometrial cancer to elucidate mechanisms that cause progesterone resistance. The endometrium has two distinct cell types: the epithelium and stroma, two distinct cell types with unique functions and responsiveness to steroid hormones. The model that the investigators have used has the potential to identify strategies that can broaden the clinical utility of hormonal therapy in this disease (Janzen et al., 2013).

This program maps to ORWH Strategic Plan Objective 1.7

Lung Cancer

Biology

BRCA Gene Mutations May Contribute to Lung Tumor Risk. In addition to raising the risk of breast and ovarian cancer, BRCA gene mutations may contribute to lung cancer risk. A version of the BRCA2 gene that, when mutated, can increase the risk of developing breast and ovarian cancers also raises the risk of lung cancer. The study included genetic data from 75,750 lung cancer patients and controls. Those with a relatively rare version of BRCA2 found in about 2 percent of the population had a 26 percent increased risk of developing breast cancer but an 85 percent higher chance of getting any type of lung cancer and a 2.5-fold increased risk of developing an aggressive, hard-to-treat lung cancer known as squamous cell carcinoma. The researchers did not see an association to lung cancer with other BRCA2 variants (Wang et al., 2014).

This program maps to ORWH Strategic Plan Objectives 1.1, 3.5

Oropharyngeal Cancer

Screening

Promising Biomarker for Predicting HPV-Related Oropharyngeal Cancer. Kreimer et al. (2013) found that antibodies against HPV may help identify individuals who are at greatly increased risk of HPV-related oropharyngeal cancer. In their study, at least 1 in 3 individuals with oropharyngeal cancer had antibodies to HPV, compared to fewer than 1 in 100 individuals without cancer. When present, these antibodies were detectable many years before the onset of disease. These findings raise the possibility that a blood test might one day be used to identify patients with this type of cancer. The study was conducted by NCI in collaboration with the International Agency for Research on Cancer (IARC).

This program maps to ORWH Strategic Plan Objective 3.5

Prevention

HPV Vaccine Protects Against Oral HPV Infection. NCI researchers found that women who received a vaccine targeting two types of the HPV that cause 70 percent of cervical cancers had the added benefit of protection against oral HPV infection, which can lead to cancer of the tonsils and throat (oropharyngeal cancer). It had been previously established that the vaccine prevents genital and anal HPV type 16 and 18 infections and related disease in addition to cervical cancer. Before this study by Herrero et al. (2013), the efficacy of the vaccine against oral HPV infections was unknown. This study was part of the NCI Costa Rica Vaccine Trial, a randomized clinical trial designed to evaluate vaccine efficacy against cervical HPV16/18 infection and related disease.

This program maps to ORWH Strategic Plan Objectives 1.6, 4.2, 4.6

Ovarian Cancer

Biology

Ovarian Cancer Proteomic Data Available. The Clinical Proteomic Tumor Analysis Consortium aims to comprehensively characterize the proteome of tumors that have been previously genomically analyzed by the Cancer Genome Atlas and integrate this data to develop a more complete view of the biology of ovarian cancer. By analyzing phosphoproteomic (unique modified proteins) data, researchers have identified two pathways that were upregulated in patients with short overall survival, independent of their protein levels, potentially informing the use of antiangiogenic therapies. All data are publicly available to the biomedical research community at http://proteomics.cancer.gov.

This program maps to ORWH Strategic Plan Objectives 1.3, 2.3, 2.9, 6

Validating Genetic Targets for Ovarian Cancer Using Nanocomplexes and siRNAs. A large group of NCI-supported researchers, including members of the Alliance for Nanotechnology in Cancer, are participating in an effort to study the essentiality of more than 11,000 genes in more than 100 human cancer cell lines. These researchers are systematically silencing individual genes to identify genes necessary for cancer cell survival and provide candidate targets for treatment. To enable prioritization of targets, Alliance investigators developed an approach for the in vivo validation of targets using a modular nanoparticle small interfering RNA (siRNA) delivery platform to silence genes in tumor models and look for effects on tumor growth inhibition. This approach is ideal for gene targets that are considered undruggable by small molecule therapeutics. It has been used to validate the ovarian cancer oncogene ID4 and another class of potential cancer targets, CYCLOPS genes, that decrease cancer cell survival when suppressed (Nijhawan et al., 2012; Ren et al., 2012).

This program maps to ORWH Strategic Plan Objective 1

Treatment

Olaparib and Carboplatin Safe for Patients with Breast or Ovarian Cancer. Researchers conducted a phase I/Ib study of olaparib and carboplatin (AUC5) in BRCA1 or BRCA2 mutation–associated breast or ovarian cancer. They found that olaparib (400 mg) every 12 hours on days 1 to 7 with AUC5 is safe and has activity in these patients. In addition, the results published by Lee et al. (2014) suggest that the expression levels of the protein FOXO3a before treatment may be predictive for response to therapy.

This program maps to ORWH Strategic Plan Objective 2.5

Combination of Olaparib with Cediranib Prolongs Disease-Free Survival in Platinum-Sensitive Recurrent Ovarian Cancer. A randomized phase II study reported marked improvement in progression-free survival in women with platinum-sensitive recurrent ovarian cancer who received the combination of olaparib and cediranib rather than single-agent olaparib treatment. This extramural/intramural collaboration included biomarker exploration that showed a potential role for measuring circulating endothelial cell induction to predict clinical benefit. NRG Oncology is developing phase III trials to confirm and register the activity of the targeted agent combination for treatment of both platinum-sensitive and platinum-resistant ovarian cancer.

This program maps to ORWH Strategic Plan Objectives 2.5, 3.5

Prevention

Daily Aspirin May Cut Ovarian Cancer Risk in Women. An NCI study by Trabert et al. (2014) found that regular aspirin use may reduce ovarian cancer risk by 20 percent. In the largest study to date to examine the possible association, the researchers analyzed data pooled from 12 large epidemiological studies to investigate whether women who used aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen have a lower risk of ovarian cancer. These 12 studies (9 from the United States) evaluated the benefit of these drugs in nearly 8,000 women with ovarian cancer and nearly 12,000 women who did not have the disease. The study suggests that aspirin regimens, proven to protect against heart attack in men and stroke in women, may reduce the risk of ovarian cancer as well. However, the authors emphasized that these findings should not influence current clinical practice. Additional studies are needed to explore the delicate balance of risk-benefit for this potential chemopreventive agent and to identify the mechanism by which aspirin may reduce ovarian cancer risk.

This program maps to ORWH Strategic Plan Objectives 2.5, 4.2

NCI Study Examines Outcomes from Surgery to Prevent Ovarian Cancer. A study of women at high risk

of ovarian cancer but with no clinical signs of the disease who underwent risk-reducing salpingo-oophorectomy (RRSO) found cancer in the removed tissues of 2.6 percent of the participants. RRSO is a surgical procedure in which a woman's ovaries and fallopian tubes are preventively removed. The participants included women known to carry a harmful mutation in the BRCA1 or BRCA2 gene, as well as women considered at high risk because of a strong family history of the disease. Cancer was detected in tissues from 4.6 percent of the women who carried a BRCA1 mutation, 3.5 percent of those with a BRCA2 mutation, and 0.5 percent of women who had a family history but did not carry a BRCA1 or BRCA2 mutation. These cancer risk estimates provide the best available information for high-risk women considering RRSO (Sherman et al., 2014).

This program maps to ORWH Strategic Plan Objectives 3.5, 5.1, 5.5

Some High-Risk Women May Benefit from Removal of Ovaries as Young as Age 35. An NCI-supported study by Finch et al. (2014) found that women who inherit mutations in certain high-risk genes that sharply increase the risk of breast or ovarian cancer can reduce their risk of death by 77 percent by having their ovaries removed by age 35. For women who carry the higher-risk BRCA1 gene, the researchers reported that the chance of already having ovarian cancer rose from 1.5 percent at age 35 to 4 percent at age 40. After age 40, the risk jumped to 14 percent by age 50. In contrast, the researchers said carriers of the related BRCA2 gene could safely delay surgery into their 40s. The study found only one case in a woman younger than 50. This new study included 5,787 BRCA carriers from Canada, the United States, and parts of Europe. Researchers tracked their health for an average of 5½ years and found 186 who eventually developed either ovarian cancer or related fallopian tube or peritoneal cancer.

This program maps to ORWH Strategic Plan Objectives 3.5, 3.9

Other Activities

Science, Technology, Engineering, and Mathematics (STEM) Efforts

Sallie Rosen Kaplan Postdoctoral Fellowship for Women Scientists. Recent observational, longitudinal, and intervention studies have shown women in science are significantly more likely to leave research careers earlier than men, specifically at the transition from a mentored scientist to an independent investigator. The Sallie Rosen Kaplan Fellowship is equipping NCI's female postdoctoral fellows for the competitive nature of the job market and helping them transition to independent research careers through a highly competitive, annual, 1-year program to strengthen leadership skills by providing additional mentoring opportunities, networking, seminars, and workshops. The program is for current female NCI postdoctoral fellows training at NCI's intramural research settings in Bethesda, Rockville, Gaithersburg, and Frederick, MD.

This program maps to ORWH Strategic Plan Objective 6.2

Funding Initiatives, Workshops, and Conferences

Comprehensive Partnerships to Advance Cancer Health Equity. The Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) are long-term, mutually beneficial collaborations between underrepresented-serving institutions and NCI-designated Cancer Centers (CCs) aimed to augment diversity in the cancer and cancer health disparities research workforce and improve outreach efforts in racially and ethnically diverse communities. Within CPACHE, each partnership supports full research projects designed to increase participation of institutions serving underserved communities and increase the involvement and effectiveness of CCs in developing research, education, and outreach programs in cancer health disparities. Select examples of full CPACHE research projects related to women's health and health disparities follow:

- **Vanderbilt University, Tennessee State University and Meharry Medical College CPACHE Partnership: *Increasing HPV Vaccine Utilization Among African-American Girls Through Social Marketing.*** This project is developing and testing the feasibility and impact of a culturally appropriate social marketing intervention targeting African-American girls and their parents to increase use and completion of the HPV vaccine series. The study follows the model of community-based prevention marketing, which combines social marketing theories and techniques with community-based participatory research

approaches to guide the planning and implementation of evidence-based strategies for addressing public health concerns. Researchers hypothesized that HPV vaccine initiation and completion will be higher for African-American girls ages 11 to 18 who received the intervention compared to those who did not receive the intervention.

- **Tuskegee University, University of Alabama and Morehouse School of Medicine CPACHE Partnership: *Chemopreventive and Therapeutic Activity of* Withania somnifera *and Its Mechanism of Action in Human Breast Cancer*.** Recently, interest in safe, economically feasible, effective herbal extracts for the prevention and treatment of breast cancer has increased. *Withania somnifera* (WS), commonly known as ashwagandha, has been used for many years in traditional medicine in the treatment of tumors, arthritis, and stress. Preliminary data has shown that daily administration of a root extract of WS causes 99 percent growth inhibition of breast cancer cells xenografted in mice. The main goal of this project is to determine a safe and efficacious dose of WS. This study has the potential to provide a basis for the clinical use of a safe and efficacious antitumor drug. By reducing the doses of standard drugs and the cost of treatment, such a drug could provide effective therapy and reduce the suffering of breast cancer patients due to the side effects of currently used anticancer medicines and treatments.

African Organization for Research and Training in Cancer Beginning Investigator Grant for Catalytic Research Awards. The cancer burden in Africa is predicted to rise with breast and cervical cancers as the most common types of cancers inflicting African women. In 2009, NCI partnered with African Organization for Research and Training in Cancer (AORTIC), a nongovernmental organization promoting cancer control, to support exploratory data collection by African scientists engaged in cancer research. This collaboration, titled AORTIC Beginning Investigator Grant for Catalytic Research, focuses on furthering research related to cancers prevalent in Africa. NCI, through the Center for Global Health (CGH), provides funding support for each research project and AORTIC administers the grants. NCI has funded 12 research projects since 2010—6 per award cycle. Of the grants awarded, five address breast and cervical cancer. The following is a list of the research projects for FY 2013 to FY 2015:

- Survival from genetic and generic susceptibility to invasive breast carcinoma in HIV-positive and HIV-negative black South African women;
- Cold coagulation versus cryotherapy for immediate treatment of women who test positive to visual inspections with acetic acid and Lugol's iodine in rural African settings; and
- Sociocultural factors on health behavior towards early detection of breast cancer on women who were exposed to breast cancer education in Ghana.

This program maps to ORWH Strategic Plan Objective 4

Partnership with Office of HIV/AIDS Malignancies. The NCI Office of HIV/AIDS Malignancies partnered with CGH to fund research projects focused on HIV/AIDS malignancies, such as cervical cancer and Kaposi's sarcoma. As a result, CGH has been able to support research projects focused on non-HIV/AIDS-related malignancies, such as breast cancer.

This program maps to ORWH Strategic Plan Objectives 1.6, 4

Human Papillomavirus Research. NCI supports research investigating the molecular mechanisms of HPV infection, carcinogenesis, and genetic and nongenetic factors that influence susceptibility to HPV infection, persistence and progression to neoplasia. The importance of specific immune mechanisms in clearing HPV infections and the effects of immunodeficiency, especially with HIV coinfection, are additional focus areas. Defining robust markers of immunity associated with resistance to infection and markers associated with HPV clearance among infected individuals are priorities. The following projects are examples of these efforts:

- **Exploring the Increase in HPV-Positive Oropharynx Cancers.** The incidence of HPV+ oropharyngeal cancer (affecting the middle part of the throat, including the soft palate, the base of the tongue, and the tonsils) in the United States increased more than threefold between 1988 and 2004. The basis for this increase is being explored through assessing behavior and lifestyle factors, HPV prevalence, natural history of infection, and pathogenesis. The basis for the improved prognosis is also being evaluated.

- **Predicting Which HPV Infections Will Progress to Cancer.** NCI's Study to Understand Cervical Cancer Early Endpoints and Determinants and the HPV Persistence and Progression Cohort are designed to develop a method to identify biomarkers to distinguish HPV-infected lesions that are likely to progress to cancer from those destined to regress.
- **HPV Vaccine Dosage and Efficacy, Second-Generation Vaccines, and HPV Vaccine Uptake:**
  - NCI and ORWH are continuing to collaborate on a large, community-based HPV vaccine trial in Costa Rica to evaluate the long-term impact of vaccination against HPV-16/18 and the immunological mechanisms involved in long-term vaccine efficacy. Ten years of follow-up are planned to provide a detailed assessment of long-term protection by the vaccine. Results have already demonstrated high efficacy in preventing new infections with HPV, a lack of efficacy in treating established HPV infections, and a much greater impact of vaccination on women under 20 compared with women 24–25 years of age, presumably reflecting a higher prevalence of established infection prior to vaccination. The trial demonstrated evidence of some cross-protection against carcinogenic types related to HPV-16/18 not specifically covered by the vaccine formulation and demonstrated the efficacy of a novel adjuvant (ASO4). The trial also demonstrated excellent safety, protection against anal HPV infection, and suggested that one or two vaccine doses evoke substantial immune responses and efficacy.
  - Additional NCI-supported efforts are exploring the potential of candidate therapeutic vaccines, the potential of candidate second-generation preventive vaccines, and small molecules that can inhibit HPV. This includes an October 2014 NCI investment of $3.5 million for further development of a second-generation HPV vaccine by investigators at the Medical University of Vienna. The award was made through NCI's PREVENT Cancer Preclinical Drug Development Program within the NCI Division of Cancer Prevention. Preclinical tests have demonstrated broader effectiveness of this vaccine against a range of high- and low-risk types of HPV compared to currently available vaccines. The new vaccine also aims to protect against strains of HPV that cause skin warts.
  - In October 2014, NCI provided 1-year supplement awards to 18 NCI-designated cancer centers to support research aimed at increasing HPV vaccine uptake by girls and boys ages 11–17.

This program maps to ORWH Strategic Plan Objectives 1, 2

Cervical Cancer Screening with Human Papillomavirus Testing. Also known as ESTAMPA, this is a multicentric study of cervical cancer screening and triage with HPV testing. The study will screen 50,000 women in 10 Latin American countries with HPV testing and compare triage approaches to include visual, cytological, and molecular, that can follow HPV testing to make an HPV-based screening program efficient, affordable, and sustainable. The study is sponsored by IARC with partial support from CGH and the Pan American Health Organization (PAHO). CGH provides $150,000 in funding for training and capacity building over 3 years (FY 2014–FY 2017). Experts from NCI also participate in the data safety monitoring committee.

This program maps to ORWH Strategic Plan Objectives 3, 4

President's Cancer Panel Releases 2012–2013 Report, Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer. During 2012–2013, the panel explored underuse of HPV vaccines and ways to accelerate vaccine uptake and protect today's children as well as future generations against cancers caused by HPV. The panel sought the input of diverse stakeholders, including government and nongovernmental organization leaders, researchers, health care providers, public health professionals, advocates, and health communication experts. Through four workshops, the panel identified barriers to HPV vaccine uptake and discussed steps to overcome them. The panel's report presents a multipronged strategy to accelerate vaccine uptake in the United States and globally. The recommendations of the report have been endorsed by the HHS National Vaccine Advisory Committee.

This program maps to ORWH Strategic Plan Objective 5

Cancer Detection, Diagnosis, and Treatment Technologies for Global Health: Supporting the Development of Low-Cost Technologies for Low- and Middle-Income Countries. CGH supports developing and validating low-cost technologies to increase access to cancer prevention, screening, detection, diagnosis, and treatment, especially in rural areas with limited infrastructure. Prevention, early detection, and treatment are vital to the successful treatment of many women's cancers. However, much of this depends on effective technologies, many of which are not suitable for use in low-resource settings due to expense, dependency on extensive medical infrastructure, or both. This situation warrants translational efforts to develop appropriate technologies that could help improve cancer treatment in resource-poor settings.

CGH is coordinating a trans-NCI effort to stimulate the development of low-cost, portable technologies for global health. This initiative has the potential to increase early detection, diagnosis, and minimally invasive treatment of cancer in low-resources settings. In FY 2014, NCI funded four projects related to women's cancers and the National Institute of Biomedical Imaging and Bioengineering expanded funding to sponsor a fifth award. The following projects related to women's health were funded by NIH in FY 2014 as part of this effort:

- Performance, safety, and efficacy of a new cryotherapy device for cervical dysplasia;
- CryoPen, an innovative treatment for cervical precancer in low-resource setting;
- Point-of-care diagnostic tools to improve global cervical cancer control programs;
- Improving specificity of HPV screen-and-treat in South Africa; and
- Low-cost automated ultrasound for breast cancer detection and diagnosis.

This program maps to ORWH Strategic Plan Objectives 3.9, 4.6

Pilot Collaborations in Global Cancer Research at NCI-Designated Cancer Centers. CGH and the NCI Office of Cancer Centers developed a funding opportunity to promote research collaborations between NCI-designated cancer centers with institutions in low- and middle-income countries (LMICs) to stimulate cancer research pilot programs and expand the international reach of the cancer centers. The scope of these pilot proposals was broad and included a range of research projects, trainings, advanced technologies, development of clinical research networks, and other focus areas that support the development of cancer research capacity. In FY 2013 and FY 2014, CGH supported the following two projects that focused on low-cost technology and the building of research capacity and networks in women's cancers:

- **A Low-Cost Optical Imaging Tool for Cervical Cancer Prevention.** The proposal addresses the significant unmet need for simpler, more cost-effective cervical cancer prevention methods for Brazil and other LMICs. It includes a prospective clinical study testing an innovative, low-cost optical imaging tool developed by collaborators at Rice University. This tool allows for point-of-care diagnosis and treatment of cervical dysplasia using a single-visit, see-and-treat approach. To complement the clinical study, the proposal includes a 2-day symposium and other educational activities focused on increasing research capacity and collaboration.
- **Building Cooperation and Capacity for Cervical Cancer Research.** In response to the challenge of cervical cancer screening in sub-Saharan Africa, the University of North Carolina at Chapel Hill, working through the Center for Infectious Disease Research in Zambia, is extending their established cervical cancer prevention service platform in Zambia using visual screening techniques (i.e., visual inspection with acetic acid and digital cervicography).

This program maps to ORWH Strategic Plan Objectives 3.9, 4

United States–Latin America Cancer Research Network. CGH coordinates the development of research initiatives and international research networks to decrease the global burden of cancer, facilitate cancer research, and develop research infrastructure in LMICs. Female breast and cervical cancers are generally considered to be the most important cancers among women in the Americas. Incidence and mortality rates of both cancers are increasing annually in parallel to global trends. In 2009, NCI established the United States–Latin America Cancer Research Network (US-LA CRN) to increase cancer research capacity in Latin America. In 2011, US-LA CRN launched a breast cancer research study titled Molecular Profiling of Stage II and III Breast Cancer in Latin American Women Receiving

Standard of Care Treatment. Participating investigators are studying the molecular profile distribution of invasive stage II and III breast cancer among Latin American women to improve diagnosis and treatment, correlate molecular subtypes with long-term survival and response to therapy, and identify indolent-disease subpopulations of cancer patients. CGH is using its training program, along with advanced technology and a capacity-building program, to implement this study. In FY 2014, NCI spent $500,000 and the total award for FY 2013 was $3,075,000. CGH has been collaborating with NCI divisions to leverage resources and incorporate technical expertise into the project.

This program maps to ORWH Strategic Plan Objectives 3, 4

United States Agency for International Development Partnership for Enhanced Engagement in Research Health Program. Modifying some common behaviors can help women reduce their risk for certain cancers, including lung cancer. CGH partnered with the U.S. Agency for International Development for the Enhanced Engagement in Research Health program to support research into maternal and neonatal health and tobacco use in Indonesia. NCI, through CGH and DCCPS, provided financial and technical support. The following projects are specific to women's health:

- Impact of reduced in-home secondhand smoke exposure on low birth weight prevalence and neonate health; and
- Effects of air pollution (including tobacco) in early life on infant and maternal health.

This program maps to ORWH Strategic Plan Objective 4

Women's Cancer Summits. The CGH Women's Cancer Program is an important part of NCI's efforts to build capacity for women's cancer control in LMICs. In FY 2013 and FY 2014, the program coordinated regional Women's Cancer Summits to help build regional networks of advocates and health care providers that could facilitate breast and cervical cancer education and awareness efforts. The summits were developed to train health care professionals and community advocates about breast and cervical cancer, the key elements of cancer control programs, and the role of advocates in working with health care professional and policymakers in implementing cancer control efforts. The workshops were conducted over 2–3 days in different host countries, giving the host countries the opportunity to exchange experiences and develop action plans around creating and implementing comprehensive women cancer control plans. The goals of the Women's Cancer Program include the following:

- Increase breast and cervical cancer awareness among health care professionals, community leaders, and advocates;
- Build a community of health care providers that can foster the development of women's cancer control programs and regional networks of advocates to work with health care professionals and policymakers to decrease the burden of women's cancer in the developing world; and
- Raise education and awareness.

This program maps to ORWH Strategic Plan Objectives 4.1, 4.6, 5.4

Role of Testing for the Human Papillomavirus in Reducing the Global Cancer Burden Workshop. CGH partnered with PAHO in FY 2014 to sponsor a workshop with HPV test manufacturers. The purpose of this workshop was to exchange information on available HPV tests for PAHO member States to consider for their health programs and discuss the challenges pertaining to implementing new HPV testing technologies in LMICs including training, technical support, and expense.

This program maps to ORWH Strategic Plan Objectives 4, 5

National Cervical Cancer Meeting in Costa Rica. CGH led a national cervical cancer meeting in Costa Rica in FY 2014 to disseminate the results and experiences of NCI's Guanacaste Epidemiologic Project (GEP), in coordination with the Ministry of Health of Costa Rica, Caja Costarricense de Seguro Social, and PAHO. The outcomes of the meeting included the following:

- Coordination of technical assistance from NCI, PAHO, IARC, CDC, and ACS in developing and implementing a national policy concerning human resources involved in HPV prevention;
- Assistance in establishing an HPV/cervical cancer education and communication plan;
- Sharing of HPV vaccine clinical trials results by NCI and GEP;

- Support for the HPV vaccine cost-effectiveness study including screening strategies such as the ProVac initiative;
- Technical support for scientific workshops pertaining to different areas of cervical cancer screening and vaccination; and
- Development of a proposal for revised screening guidelines by representatives from the Costa Rican Ministry of Health, Caja Costarricense del Seguro Social, NCI, GEP, and PAHO.

This program maps to ORWH Strategic Plan Objectives 4, 6

Asia-Pacific Economic Cooperation Regional Workshop on Enabling Sustainable Economic Advancement for Women Through Cervical Cancer Prevention and Control. CGH worked with the Office of Global Affairs at the U.S. Department of Health and Human Services, the U.S. Department of State, and the Cancer Hospital Chinese Academy of Medical Sciences to develop this workshop, which occurred in Beijing on August 16, 2014. The workshop's goals included disseminating information to public health experts and policymakers in the Asia-Pacific region on the state of the science with regard to cervical cancer prevention and control (including HPV vaccine and HPV screening) and to develop policy recommendations and tools for Asia-Pacific Economic Cooperation economies to drive toward substantial reduction of cervical neoplasia.

This program maps to ORWH Strategic Plan Objective 5

Measuring Estrogen Exposure and Metabolism Workshop. In March 2014, NCI investigators participated in a workshop titled Measuring Estrogen Exposure and Metabolism, held in Bethesda, MD. The workshop provided an opportunity for experts to discuss how to improve and standardize methods for assessing estrogen exposure and metabolism in both epidemiologic and clinical research. A major focus was the need for improved methods for breast cancer research, prevention, and treatment. The workshop closed with the development of guiding principles for future research directions and clinical guidelines.

This program maps to ORWH Strategic Plan Objective 4.1

Technical Assistance

National Cervical Cancer Screening Policy. CGH assisted the Ministry of Health of El Salvador in revising their national cervical cancer screening policy to include HPV testing and cytology triage testing in women 30 to 50 years of age and cytology screening in women 20 to 29 years of age. Assistance also included building consensus with key stakeholders for the new guidelines.

This program maps to ORWH Strategic Plan Objective 4.6

HPV Test-Based Screening Program Work Plan. CGH helped the Ministry of Health of Guatemala create a work plan for rolling out a new HPV test-based screening program, beginning in the capital city and expanding as resources permit.

This program maps to ORWH Strategic Plan Objective 5

Health Disparities

Minorities Are Most Vulnerable to Financial Slide After Breast Cancer. An NCI-funded study by using SEER data found that black and Latina breast cancer patients were more than twice as likely as white women to have lingering medical debt and to skip treatments because of costs. Based on surveys of 1,500 women diagnosed with mostly early-stage breast cancers, researchers found that up to one-quarter were struggling financially as a result of their disease. Cancer patients face direct costs, such as copayments for prescription medications, visit copays, and coinsurance, as well as indirect costs, such as lost income from time off work, transportation for treatment, and childcare. Minority populations might be especially at risk due to insufficient employee health benefits, cultural barriers, and poor health literacy—especially given that Spanish-speaking Latinas were at the greatest risk for declining financial status (Jagsi, Pottow, et al., 2014).

This program maps to ORWH Strategic Plan Objectives 3.9, 4, 5

Genetic Variant May Protect Latinas from Breast Cancer. A genetic variant that is particularly common in some Hispanic women with indigenous American ancestry appears to drastically lower the risk of breast cancer. The findings, published by Fejerman et al. (2014) may explain why Latinas have lower rates of breast cancer than other Americans. While many genome-wide association studies

have looked for associations with breast cancer in women of European descent, this was the first such study to include large numbers of Latinas. The finding highlights the existence of genetic risk factor differences between racial groups and ethnicities. Understanding these variations could shed light on who is most at risk for breast cancer.

This program maps to ORWH Strategic Plan Objectives 1, 3

Studies Confirm Obesity-Breast Cancer Link for Black and Hispanic Women. According to studies by John et al. (2015a, 2015b), more than one in two black women and nearly one in two Hispanic women in the United States are obese. Recently, two NCI-supported studies found that obesity increases the risk of certain types of breast cancer in postmenopausal black and Hispanic women. One study of more than 3,200 Hispanic women found being overweight or obese increased the risk for estrogen receptor-negative and progesterone receptor-positive breast tumors among postmenopausal women. The other study included more than 15,000 black women and found that being overweight or obese increased postmenopausal women's risk of estrogen receptor-positive breast cancer by 31 percent. It also found that the risk was nearly double among black women who were lean as young adults and gained weight in adulthood.

This program maps to ORWH Strategic Plan Objectives 1, 3

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National Eye Institute

Executive Summary

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

Clinical research demonstrates that a significant majority of ocular diseases affect women more frequently than men. These conditions include glaucoma, optic neuritis, cataracts, dry eye, Sjögren's syndrome, corneal endothelial dystrophy, age-related macular degeneration, idiopathic intracranial hypertension, thyroid eye disease, and myopia.

NEI's research and initiatives in FY 2013–2014 addressed the NIH Strategic Plan for Women's Health and Sex Differences. For example, Goal 3 reads, "Actualize personalized prevention, diagnostics, and therapeutics for girls and women, including i.) conducting developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span (3.1); ii.) studying sex/gender differences in the aging process (3.6); and iii.) conducting research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life (3.8)."

NEI studies of hormone factors in such conditions as intracranial hypertension, eye diseases of aging women and the role of dietary supplements in eye health in aging women are also examples that satisfy the goals and objectives of ORWH. Below is a summary of vision research findings for which significant sex or gender differences were reported during FY 2013–2014.

Women's Health Research Report

Accomplishments—Highlights

Corneal Diseases

Corneal Endothelial Dystrophies. Corneal endothelial dystrophies are diseases of the endothelium that usually affect both eyes and are more common in women than men. These dystrophies affect the innermost layer of the cornea including Descemet's membrane and the endothelium, which are the layers of the cornea closest to the inner structure of the eye. If endothelial cells are diseased or absent, permanent corneal edema, loss of corneal transparency, and eventual blindness may occur. For patients who do not respond to nonsurgical intervention, methods to surgically replace abnormal corneal tissue have advanced considerably.

NEI-supported scientists are attempting to determine why endothelial function deteriorates following cell loss, age, or trauma. Delineating the optimal conditions for the tissue culture of corneal endothelium will help evaluate the problems involved in transplanting these cultured cells and assuring their survival. With further refinement of endothelial culture techniques, it will be possible to determine whether cell cycle stimulatory and inhibitory factors arise from other cells and whether the endothelium can be induced to repair itself. Parallel gene therapy studies are being pursued in animals with the aim of developing vectors to deliver factors therapeutically to the eyes of patients with the disease.

External Ocular Diseases

Dry Eye. Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition that may feel like a stinging or burning sensation in the eye and, if left untreated, may result in blurred vision or vision loss. Dry eye results from a reduction in secretion of fluid by the lacrimal glands or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty

components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, such as Sjögren's syndrome, lupus, and rheumatoid arthritis but also occurs in association with aging, medications, exposure to the environmental, and eye surgery, including laser correction surgery. Dry eye affects roughly 2 million Americans and is the most common complaint to present in the ophthalmologist's office, with 10 percent to 20 percent of adults in the United States suffering from it. It appears to be more common in women than in men, particularly postmenopausal women.

Despite the prevalence of dry eye, treatments have met with limited success. Restasis, a drug that has been approved by the U.S. Food and Drug Administration (FDA), has been shown to increase natural tear production in the eye; however, this drug is not very effective and works for only some people. Another treatment for severe dry eye is the surgical insertion of lacrimal or punctal plugs to block the eyes drainage ducts keeping the tears in place. Supporting better treatments for dry eye, NEI has funded a Small Business Innovative Research Grant for an FDA-approved Phase 1 clinical trial to evaluate the efficacy and safety of a new drug, P-321 Ophthalmic Solution, in relieving the symptoms of moderate to severe dry eye disease.

Dry Eye Assessment and Management Study (DREAM). NEI is currently funding a Phase III clinical trial called DREAM, which will examine the effectiveness of omega-3 supplementation treatment for dry eye disease (DED). Despite being a widespread, growing problem with serious consequences, at present, DED is inadequately treated. Because omega-3 fatty acids have been shown in laboratory studies, animal models, and some human studies to ameliorate inflammatory reactions and are widely available over the counter, they are gaining in popularity to combat or prevent diseases associated with inflammation, including DED. But as with any treatment, results of a large, randomized, double-blind clinical trial are needed to assess efficacy and safety. The study is currently recruiting participants.

Sjögren's Syndrome Registry. Sjögren's syndrome is a chronic autoimmune disease that occurs primarily in women and attacks the salivary and lacrimal glands resulting in severe dry eye. NEI continues to cofund, with the National Institute of Dental and Craniofacial Research and ORWH, the Sjögren's Syndrome International Collaborative Clinical Alliance, a group that is developing an International Sjögren's Syndrome Registry. The purpose of this registry is to promote cutting-edge research in the area of Sjögren's syndrome with emphasis on diagnosis, epidemiology, causes, prevention, and treatment. The coordinating center is at the University of California, San Francisco, and sites have been established in the United States, Argentina, China, Denmark, Japan, India, and the United Kingdom. All sites continue to recruit patients, which includes the use of the standardized Baseline Eye Exam Form and Baseline Eye Exam Standard Operating Procedures developed by the consortium.

Thyroid Eye Disease. Graves' eye disease, also known as thyroid eye disease, is an autoimmune condition that causes hyperthyroidism and affects 2 percent of all women (7:1 compared to men) between the ages of 20 and 40. Excessive thyroxine is produced from the enlarged thyroid glands causes swelling of the muscle and other tissues around the eye resulting in proptosis (bulging of the eye), corneal exposure, optic nerve compression, and ultimately loss of vision. Current treatments of thyroid eye disease are only marginally effective, and therefore, research into the pathogenic mechanisms and discovery of potential new therapeutic targets is underway.

Lens

Cataracts. Cataracts are a clouding of the eye's natural lens, which lies behind the iris and the pupil and is the most common cause of vision loss in people over the age of 40. A recent study on the Swedish population reports that cataracts are more prevalent in postmenopausal women than in men at similar ages. The study showed that women who receive hormone replacement therapy (HRT) to counter the drop in estrogen levels after menopause were at greater risk for developing cataracts and that the longer a woman takes HRT, the greater the severity of the cataracts.

Estrogen receptors have been detected in the eye's lens, and naturally occurring (endogenous) estrogen appears to protect the eye from cataract, along with guarding cardiovascular and other body systems before menopause. However, exogenous estrogens like those used in HRT do not function the same way. For instance, other studies show that HRT increases C-reactive protein levels, a test used to evaluate one's risk of coronary artery disease, and is now associated with greater risk of the development of

cataracts. Taken together, the population study and the biochemical data suggest a possible role for estrogen in cataract development.

Retinal Diseases

Age-Related Macular Degeneration (AMD). AMD is the leading cause of blindness and visual impairment among elderly individuals in the United States. The macula is a specialized region near the center of the retina responsible for the high-resolution vision that permits activities such as reading. Several genetic and environmental risk factors have been identified with this condition; among those is female sex, which has been associated with a higher prevalence of AMD in many population-based studies.

One study in the Archives of Ophthalmology, looking at AMD in women participating in the Nurses' Health Study, showed an association between women who received hormone replacement therapy after menopause and 34 percent higher risk of early AMD, whereas a 48 percent lower risk of the late-stage neovascular form of the disease was observed. The Korea National Health and Nutrition Examination Survey revealed that age, duration of lactation, and duration of oral contraceptive pills are associated with late AMD. These findings suggest a role for estrogen in the pathogenesis of AMD as well as to facilitate screening of patients at risk and the prevention of AMD among the postmenopausal women.

Age-Related Eye Disease Study (AREDS). AREDS is a multicenter clinical trial and epidemiological study designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and other studies suggested that lutein or zeaxanthin and omega-3 long chain polyunsaturated fatty acids might also have benefits in AMD and cataract. A second study, AREDS 2, confirm this hypothesis. A multicenter clinical trial, the Complications of Age-related Macular Degeneration Prevention Trial, assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision.

Optic Neuropathies

Glaucoma. Primary open angle glaucoma (POAG) is a leading cause of irreversible blindness worldwide, yet the pathogenesis of this condition remains unknown. The Nurses' Health Study (NHS), supported by various branches of NIH, has contributed considerably to research on POAG. The NHS started in 1976 when 121,000 registered female nurses from across the United States agreed to complete biennial questionnaires regarding lifestyle and health. Among women 65 years of age or older, entering menopause at age 54 years or later was associated with a 47 percent reduced risk of POAG compared to entering menopause between ages 50 and 54. Furthermore, postmenopausal hormone (PMH) use consisting of estrogen and progesterone was associated with a 42 percent reduced risk of high-tension POAG. Circulating estrogen strongly modulates the expression of endothelial nitric oxide synthase (NOS3). In a gene association study involving participants of the NHS and the Health Professionals Follow-up Study, significant relations between common NOS3 gene variants and POAG were found in women but not in men. Significant interactions between four NOS3 gene variants and PMH use in high tension POAG were also noted. Finally, anthropometric studies indicate an inverse relation between body mass index (BMI) and the risk of normal tension variant of POAG in women but not in men. Perhaps higher circulating estrogen levels in women with higher BMI contribute to this inverse relationship. Collectively, these data support the notion that circulating estrogen levels play a role in the pathogenesis of POAG.

Women in the NHS and the Genetic Etiology of POAG (GEP) contributed DNA specimens to a projected aimed at new gene discovery for POAG. The GEP is a clinic-based sample of POAG cases and controls located mostly in New England. Specimens from NHS and GEP contributed to a genome-wide association study (GWAS) of POAG as part of the Glaucoma Genes and Environment Initiative (GLAUGEN). NEI funded the formation of the GLAUGEN case control group, while the National Human Genome Research Institute supported genotyping efforts. Genotyping in GLAUGEN is complete, quality control filters have been applied and data analysis is ongoing. A second GWAS within the NEI Glaucoma Human Genetics Collaboration (NEIGHBOR) consisting of approximately 2,000 POAG cases and 2,000 controls is currently underway. The NEIGHBOR consortium is headed at

Harvard University and Duke University with several contributing centers. The high throughput genotyping efforts in GLAUGEN and NEIGHBOR will help define the genetic architecture of POAG. Members of the Women's Health Study (WHS) will serve to confirm some of the new gene discoveries in GLAUGEN and NEIGHBOR. The WHS consists of more than 26,000 women who completed a genome-wide scan and have completed biennial questionnaires regarding lifestyle behavior and health. POAG cases identification in WHS is ongoing.

Idiopathic Intracranial Hypertension. Idiopathic intracranial hypertension (IIH) typically occurs in women of childbearing age and the incidence is 1/100,000 in normal-weight women and 20/100,000 in obese women. The disease is characterized by an increase in intracranial pressure (more than 250 mm of water); the cause is unknown but involves obstruction of cerebral venous outflow. The most common symptoms are headaches and visual problems, including diplopia, blurred vision, and transient and permanent vision loss.

Recently, an NEI-funded treatment trial coordinated by the Neuro-Ophthalmology Research Disease Investigator Consortium demonstrated the efficacy of an inexpensive glaucoma drug to treat women with IIH. The results showed that acetazolamide (Diamox) can help preserve and actually restore vision for patients with IIH when combined with a moderate but comprehensive weight loss plan.

Optic Neuritis. Optic neuritis is a demyelinating inflammation of the optic nerve, which is highly associated with multiple sclerosis, a disease that causes inflammation and damage to nerves in the brain and spinal cord. This disease is more common is women than men, and NEI is working with ORWH to cofund projects to further our understanding of the disease process. Ongoing studies include the comparative analysis of gender-mediated effects in animals of the opposite sex (female). These data demonstrated degeneration of the optic nerve in multiple sclerosis is more pronounced in females and showed a temporally and quantitatively different responsiveness to pharmacotherapy treatment. Research priorities are aimed at using gender-specific datasets to develop novel intervention strategy and successful subsequent translation to the clinics.

Myopia

Nearsightedness, or myopia, is the most common refractive error of the eye and has become more prevalent in recent years. Epidemiological data in humans indicates that myopia is more prevalent and tends to develop earlier and more severely in females than in males. There is increasing evidence that sex hormones may also play an important role. NEI is continuing to work with ORWH by cofunding projects to investigate the influence of systemic sex hormones on ocular growth and myopia in animal models.

Initiatives

NEI and the National Advisory Eye Council (NAEC) have established a 5-year strategic plan: Vision Research, Needs, Gaps, and Opportunities, which completed a report in August 2012. This report provides a comprehensive review of the highlights of recent progress in vision research and the emerging needs, gaps, and opportunities that lie ahead for improving visual health and preventing blindness. This includes research on diseases that are known to have a higher incidence and prevalence in women than in men.

The NEI Audacious Goal Initiative (http://www.nei.nih.gov/audacious) is focused on regenerating neurons and neural connections in the eye and visual system. In consultation with the 2014 NAEC, NEI initiative is targeting the photoreceptor and retinal ganglion cells, because the loss of either cell type by disease or injury leads to severe visual disorders and blindness. This includes loss of photoreceptor cells such as AMD or damage to retinal ganglion cells (RGC) resulting in glaucoma or optic nerve pathologies, all of which are conditions that are more pronounced in women. One challenge in vision research is how to restore vision by promoting photoreceptor cell and RGC survival as well as optic nerve regeneration. In addition to therapies that may slow or prevent the death of these cells, retinal stem cell replacement therapies also hold promise and may be used to integrate rod and cone photoreceptors and/or retinal ganglion cells into diseased retinas and form the appropriate connections with the remaining neurons. Studies that promote research aimed at restoring these connections to visual centers of the brain are encouraged.

Moreover, studies that gather comprehensive knowledge of (1) the molecular basis of ocular health and disease and use that knowledge to improve diagnosis, treatment, and

prevention of eye disease; (2) translational basic research into clinical studies; (3) use of clinical, epidemiological, and statistical tools to identify populations at risk of blinding eye diseases and visual disorders; and (4) evaluation of new therapeutics to improve vision are encouraged by NEI. However, all proposed projects should include a group of animals or humans of the opposite sex (female) for comparative analyses of gender-mediated effects and treatment outcomes.

National Heart, Lung, and Blood Institute

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for research, training, and education to promote the prevention and treatment of heart, lung, blood, and sleep (HLBS) disorders and enhance the health of all individuals. As reflected in its Strategic Plan, the Institute's broad goals are to:

- Improve understanding of the molecular and physiological basis of health and disease and to use that understanding to develop better approaches to disease diagnosis, treatment, and prevention;
- Improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis, and treatment; and
- Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

The diseases within NHLBI's portfolio do not discriminate; they affect both men and women, and people of all races. For example, diseases of the heart constitute the leading cause of death for women in the United States, accounting for 22 percent of deaths among women (Centers for Disease Control and Prevention [CDC], 2014). Some diseases affect a greater proportion of women than men (e.g., chronic obstructive pulmonary disease, or COPD); and others affect women almost exclusively (e.g., lymphangioleiomyomatosis, or LAM). Moreover, even for diseases that affect equal numbers of women and men, the consequences may be greater for women. For example, while heart failure affects about 2 percent of men and women, there were 40,000 more new cases of heart failure (NHANES 2009 to 2012), 21,000 more hospitalization discharges for heart failure (Hospital Discharge Survey), and 9,000 more deaths from the condition for women than men (CDC WONDER, 2013). Such data highlight the need for research that is inclusive of both men and women and provide insights into when sex- and/or gender-specific research is needed. For these reasons, NHLBI has made research to address gaps in knowledge of how to diagnose, prevent, and treat disease in women a top priority. This research agenda spans basic, translational, clinical, population, and implementation science. Understanding the role of sex in health and disease is not only critical to improving women's health but also is the basis for sound science. Research on sex as a fundamental biologic variable will shed light on health and disease processes that will ultimately impact both men and women.

This report highlights a variety of research results, programs and solicitations, and educational activities in areas of women's health that align with the Institute's mission. Especially notable are the Institute's efforts to explore sex differences in the basic biology and physiology of the cardiovascular and respiratory systems as well as the roles of sex hormones in health, disease, and treatment response. For example, recent research has begun to uncover the molecular mechanisms that underlie sex differences in the production of certain proteins that may impact heart function, sex-race-genotype interactions in susceptibility to asthma, the role of estrogen in abdominal aortic aneurysm and differential responses to some medications, and the pathways of disease and biomarkers of disease severity

and response to drug treatment in LAM, a disease that disproportionately affects women.

NHLBI is also diligent in ensuring that its clinical research projects include adequate representation of women. This effort has included not only careful monitoring of recruitment for clinical trials and other studies but also support of certain studies conducted entirely in cohorts of women, such as the landmark Women's Health Initiative, insights from which have dramatically changed the use of postmenopausal hormone therapy in this country. Finally, NHLBI strives to ensure that the results of this diverse portfolio are shared with the community so that women can take steps to reduce their risks of disease and improve their health with programs such as *The Heart Truth*®.[1]

Accomplishments and Activities

Preeclampsia

Preeclampsia (PE) is diagnosed when a pregnant woman develops high blood pressure and protein is found in the urine after 20 weeks of pregnancy. It occurs in about 10 percent of all pregnancies and, if left untreated, can develop into eclampsia (the onset of seizures) and may lead to death of the mother and/or fetus. Two new studies have identified methods that may allow for earlier detection of the condition than with current tests. In one of these studies, researchers discovered that the disease involves misfolded proteins and that doctors can infer the presence of these misfolded proteins from a specific urine test (Buhimschi et al., 2014). In the study, women who developed PE requiring induction of delivery were positive for this test before traditional indicators of the disease arose. Thus, further development of this test may enable earlier detection of the condition. In a separate study, researchers identified a protein, epidermal growth factor-like domain 7 (EGFL7), that is under-produced in humans with PE (Lacko et al., 2014). Researchers were able to detect the lower levels of the protein in a mouse model of the disease prior to the onset of the typical signs of PE, suggesting that the levels of this protein might serve as an early biomarker of the condition. Early detection of PE may prove beneficial if researchers can devise methods of arresting the condition before it progresses too far; the only current treatment for PE is induction of delivery, which carries the risks of a preterm birth.

[This research addresses ORWH Strategic Plan Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," Objective 3.4: "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."]

Sex-Dependent Differences in Heart Cells

Premenopausal females have a reduced risk of death from cardiovascular disease (CVD) compared with men of a similar age. Researchers have sought to elucidate the molecular underpinnings of this natural protection from heart disease with the hope of extending it to both postmenopausal women and men of all ages. Because the cardioprotective advantage women have disappears after menopause, when estrogen production declines, scientists have hypothesized that estrogen is responsible for the protection from heart disease. Researchers are investigating this hypothesis and trying to reconcile it with studies that indicate that postmenopausal therapy with estrogen increases the risk of CVD. These conflicting findings have required scientists to deeply explore the molecular pathways that are driving sex differences in heart function to see why premenopausal women are protected from heart disease. One such study recently examined why the levels of endothelial nitric oxide synthase (eNOS) differ between male and female hearts, whether this relates to estrogen, and how it might contribute to cardioprotection in females (Evangelista, Deschamps, Liu, Raghavachari, & Murphy, 2013). The researchers found that levels of a particular microRNA that regulates protein production were lower in female versus male mouse heart cells and were responsible for increased eNOS levels in females. The increased eNOS levels in turn affect a calcium channel, which could contribute to sex differences in heart function. In addition,

[1] *The Heart Truth*, its logo, *The Red Dress, Red Dress*, and *Million Hearts* are registered trademarks of HHS. National Wear Red Day is a registered trademark of HHS and the American Heart Association.

the gene for this microRNA is regulated by an estrogen receptor, suggesting estrogen affects production of the microRNA. Although this study did not completely reveal how estrogen affects heart function, it adds an important piece to a growing mosaic of understanding that should eventually enable doctors to more effectively treat CVD in women and men.

[This research addresses ORWH Strategic Plan Goal 1, "Increase sex differences research in basic science studies," Objective 1.2: "Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems." This research is also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Obesity

In the United States, one in three adults is considered obese, and obesity increases the risk of coronary heart disease, stroke, high blood pressure, sleep apnea, and other conditions. Although women are at greater risk of developing obesity than men, attempts to study the biological basis for this difference have been hampered by a lack of female animal models that effectively mimic diet-induced human obesity. To overcome this barrier to research, researchers recently tested a candidate model organism for diet-induced human obesity: a mouse genetically engineered to express the human form of the PXR gene, which produces a receptor that appears to contribute to obesity (Spruiel et al., 2014). The researchers found that female mice engineered in this manner and fed a high-fat diet developed obesity more rapidly than mice with the mouse form of the PXR gene. The genetically engineered female mice that were fed a normal diet also exhibited biological differences from the normal mice that had the same diet. These findings suggest that the genetically engineered mice may serve as effective model organisms, allowing researchers to study exactly how PXR contributes to obesity and how its effects differ between male and female mice. Such studies could help shed light on why human females are more susceptible to obesity and may even point to novel therapeutic approaches for women and men.

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies," Objective 1.6: "Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS, and urinary tract and sexually transmitted infections."]

Abdominal Aortic Aneurysm

Abdominal aortic aneurysms (AAAs) are characterized by localized ballooning of the abdominal aorta, possibly leading to rupture and/or death in minutes. AAAs are more common in men than in women, and research has suggested that females are to some extent protected from the development of this condition due to the anti-inflammatory effects of estrogen. It was unclear whether the protective effect of estrogen was due to circulating estrogen or locally produced estrogen in the aortic wall. To answer this question, researchers recently studied the effect of aromatase, an enzyme required for estrogen synthesis, on AAA (Johnston et al., 2014). Aromatase—and estrogen—are produced in the ovaries and in tissues throughout the body, including the aortic wall. The researchers found that production of estrogen in peripheral tissues, including the aortic wall, contributes roughly half of the protection against AAA. This finding has clinical significance: If researchers can determine how to target the aromatase in the aortic wall and increase its expression, such an approach could be used to stimulate localized estrogen production and could treat both males and females at risk for AAA. This approach would have the advantage of avoiding the effects of systemic estrogen exposure, which is feminizing in males and can be harmful in postmenopausal women.

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies," Objectives 1.6 and 1.7: "Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS, and urinary tract and sexually transmitted infections;" and "Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions such as lupus and cardiovascular diseases and to predominantly sex-specific diseases such as breast cancer and uterine fibroids." This research is also responsive to congressional interests in CVD and stroke and in sex differences in basic, applied, and clinical research.]

Women's Ischemia Syndrome Evaluation (WISE)

NHLBI created the WISE study in 1996 to increase scientific knowledge about ischemic heart disease in women, a condition characterized by reduced blood supply to the heart. The WISE study showed that in women, cholesterol plaque may not build up into major blockages, instead spreading evenly throughout the artery wall. As a result, when doctors conduct diagnostic coronary angiography on women, injecting a dye into the arteries and then taking X-ray images of the heart arteries to measure blood flow, the results often suggest that these women have clear arteries, incorrectly indicating low risk for a heart attack. Because of this shortcoming of angiography when used in women, WISE has the goals of developing accurate diagnostic approaches for ischemic heart disease detection in women; improving understanding of the ways in which heart disease develops in women, including the significance of ischemia without coronary blockages in women; and evaluating the influence of hormones on ischemic heart disease development and diagnosis.

A recent study found that in 298 women with chest pain but no evidence of obstructive plaque buildup, the women had a high reading for a particular test (the corrected Thrombolysis in Myocardial Infarction frame count [cTFC]) that was associated with an increased risk of hospitalization for angina (chest pain caused by reduced blood flow to the heart) (Petersen et al., 2014). The cTFC diagnostic method involves an angiography in which doctors count the number of X-ray frames that elapse until the dye arrives in the bed of the vessel of interest; in this way, the method provides a measurement of flow speed, which implies the degree of narrowing of the artery. Although further studies are needed to confirm the finding that a high cTFC predicts a higher risk of hospitalization in women with chest pain, this discovery suggests that this diagnostic method might prove helpful in informing future care of these patients.

[This research addresses ORWH Strategic Plan Goal 2: "Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs," Objective 2.1: "Encourage the development of technologies that will address sex-based differences at all scales of detail, from the nanometer to the whole person." This research is also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Menopausal Predictors of Cardiovascular Disease

Menopause is known to increase the risk of CVD, but it is unclear whether symptoms of early menopause are associated with a quickening of the development of atherosclerosis (hardening of the arteries). To study this issue, researchers checked for indicators of atherosclerosis in women between the ages of 42 and 58 who exhibited early menopause (Wolff et al., 2013). The women were part of a large multicenter trial called Kronos Early Estrogen Prevention Study (KEEPS). Although previous reports had found that 4 percent of early postmenopausal women in KEEPS had unexpected asymptomatic atherosclerosis, the Wolff study found no association between estrogen levels or menopausal symptoms and the presence of atherosclerosis. However, the researchers did find that palpitations and depression (two symptoms of menopause), but not other self-reported symptoms, may signal future coronary artery calcification. Further observation is required to better understand the predictors of cardiovascular outcomes.

[This research addresses ORWH Strategic Plan Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," Objective 3.1: "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span." This research is also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Sex- and Age-Dependent Drug Responses

Preclinical research has shown sildenafil—an inhibitor of cGMP-specific phosphodiesterase 5 (PDE5)—to have a protective effect during cardiac stress and heart failure. Evidence of therapeutic sildenafil efficacy in males has been reported. However, efficacy in females is unclear. A large, multicenter, placebo-controlled trial called RELAX showed that females, many more than 50 years

old and postmenopausal, failed to show any benefit when sildenafil was used to treat heart failure (Murphy & Steenbergen, 2014).

Sasaki et al. investigated whether sex- and age-dependent estrogen levels may explain the variable efficacy of sildenafil observed in this clinical trial (Sasaki et al., 2014). Estrogen is present in premenopausal females, and it helps make the cGMP molecule that PDE5 targets. Sasaki et al. studied sildenafil treatment in a mouse model of cardiac failure and compared its efficacy in males, females with ovaries, and females without ovaries. Ovary removal mimics a no-estrogen postmenopausal state. They found that sildenafil was protective in male mice. Surprisingly, sildenafil was protective in female mice with ovaries, but not in female mice without ovaries that were more male-like due to their lack of estrogen. Interestingly, sildenafil efficacy was restored when estrogen was given to female mice without ovaries.

Sex-dependent differences are known to influence the response to drugs. This research shows sildenafil efficacy to be estrogen-dependent in females, despite being estrogen-independent in males. These results suggest that the age-dependent changes in certain factors, in this case estrogen, also may be an important factor to consider when designing studies and interpreting results.

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies," Objective 1.6: "Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS, and urinary tract and sexually transmitted infections." This research is also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Lung Diseases

Sex Differences in Asthma

Women with asthma describe more symptoms and worse asthma-related quality of life than men, despite having similar or better pulmonary function. Current guidelines focus on assessing asthma control but lack information about whether sex-specific approaches to asthma assessment should be considered. Investigators reviewed data from four trials published by the American Lung Association Asthma Clinical Research Centers to determine if sex differences in asthma control or symptom profiles exist. The investigators evaluated response to questionnaires about asthma and determined that women with poorly controlled asthma were more likely to report symptoms such as nocturnal awakenings, activity limitations, and shortness of breath, as well as worse asthma-related quality of life and more asthma-related symptoms. Women were also more likely to report feeling bothered by symptoms such as coughing or environmental triggers. This study suggests that clinicians should take sex into account when assessing asthma treatment options (McCallister et al., 2013).

Lymphangioleiomyomatosis (LAM) Pathways Determined

LAM is a destructive lung disease found primarily in women and associated with increased activity of the mammalian target of rapamycin complex 1 (mTORC1). Studies have demonstrated that the drug rapamycin, which targets mTORC1, is partially effective in treating LAM, but it is not curative. Studies have also indicated that pregnancy worsens LAM, suggesting that estrogen may play a role in its disease progression. Researchers used a LAM patient–derived cell line to show that estrogen increases the activity of pathways that control cell growth and certain cell-type changes involved in wound healing and tumor cell spread. These results suggest that targeting these estrogen-dependent pathways may inhibit certain kinds of fibrosis and may be an effective add-on to rapamycin for treating LAM (Gu et al., 2013). Another study of the role of estrogen in LAM development found that estrogen increased the expression of cyclooxygenase-2 (COX-2), which increased levels of prostaglandins that are known to exert hormone-like effects throughout the body. LAM patients had significantly higher prostaglandin in the blood than healthy women, suggesting a potential role for prostaglandins in the development of the disease. The study therefore suggests that COX-2 and prostaglandin pathways may be novel therapeutic targets for LAM (Li et al., 2014).

[This research addresses ORWH Strategic Plan Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," Objective 3.1: "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."]

Factors Affecting Sirolimus Therapy in LAM Patients

Young et al. studied 87 patients from the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial to identify new biomarkers for LAM severity and responsiveness to the drug sirolimus. Investigators report that VEGF-D levels—a factor that promotes blood vessel growth and tumor spread—decreased in some patients treated with sirolimus but not in placebo-treated patients. Sirolimus-treated patients were then separated into two groups—those whose VEGF-D decreased compared with placebo (VEGF-D responders) and those whose did not (VEGF-D non-responders). Young et al. compared lung function between the VEGF-D responders and non-responders by assessing how much air could be exhaled before and after 12 months of sirolimus treatment. They found that lung function improved in 65 percent of VEGF-D responders versus 27 percent of VEGF-D non-responders. Identification that VEGF-D blood levels are a potential biomarker for disease severity and treatment response can better define the benefits and risks of sirolimus therapy in LAM patients (Young et al., 2013).

Sex Differences in Cystic Fibrosis (CF)

Overall birth prevalence of CF in the United States (1 in 3,700) is distributed equally in male and female babies, yet multiple epidemiologic studies have indicated that females have a disadvantage in CF morbidity and mortality. CF is caused by a mutation in the CF transmembrane conductance regulator (*ctfr*) gene leading to a defect in chloride and bicarbonate ion transport in the lungs. This results in thick and viscous mucus in the airways, which impairs ciliary motion and leads to a relentless cycle of infection and inflammation that causes structural changes and tissue damage. Investigators found that after puberty, the pulmonary exacerbation rate increased in adolescent girls relative to boys with CF, supporting a role for sex hormones. This study suggests that sex-dependent hormone signaling pathways may be a therapeutic target for CF lung disease (Sutton, Rosenbluth, Raghavan, Zheng, & Jain, 2014).

[This research addresses ORWH Strategic Plan Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," Objective 3.1: "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."]

Blood Disorders

Genetic Pain Susceptibility in Sickle Cell Disease (SCD)

Patients with SCD experience episodes of acute pain, with severe pain accounting for 90 percent of disease-related hospitalizations. Sex is a known factor for acute pain episodes in SCD. Earlier genomic studies identified tetrahydrobiopterin (BH4) and the *GCH1* gene, which ultimately controls BH4 production, to be associated with pain. Belfer et al. examined *GCH1* variation in people of African ancestry, specifically those with SCD, to determine genetic susceptibility to pain. They examined the genotypes of 281 adult patients with SCD from the Bethesda Sickle Cell Cohort Study and identified three out of six *GCH1* variants to be associated with pain. One of the variants, rs8007267, was more prevalent in SCD and in those with pain. Belfer et al. confirmed that this variant also was associated with patients having SCD and severe pain episodes from the Cooperative Study of Sickle Cell Disease. In contrast, this variant has been reported to be pain protective in people of European descent. They also showed that patients with rs8007267 had elevated BH4 levels, which also was associated with increased pain perception. Belfer et al. observed a stronger association of rs8007267 and two other *GCH1* variants in females with severe pain events, but not in males. This work suggests *GCH1* and BH4 are involved in sickle cell anemia pain, possibly in a sex-dependent way. Also, this work highlights how the same genetic variant can cause race-specific molecular responses and clinical outcomes (Belfer et al., 2014).

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies," Objective 1.1: "Encourage genetic and epigenetic studies to identify sex differences in gene expression."]

Sleep Disorders

Sleep Apnea

Obstructive sleep apnea is a prevalent sleep disorder characterized by obstruction of the upper airway during

sleep. It was traditionally recognized in middle-aged, obese men but is now known to occur in women and people who are lean. Sleep apnea has been associated with inflammation and the activation of specific molecules that lead to the synthesis of C-reactive protein in the liver. This, along with insulin resistance, links sleep apnea to cardiometabolic complications. Researchers studied those with mild-to-moderate sleep apnea and found that middle-aged men with mild-to-moderate sleep apnea have worse inflammatory and metabolic profiles than women. One explanation may be that visceral fat, which has more vessels, nerves, and many inflammatory and immune cells, is the strongest predictor of sleep apnea in males, whereas in females, total fat is more strongly associated with sleep apnea. These findings suggest that inflammatory and metabolic abnormalities in sleep apnea should be examined separately in men and women (Gaines et al., 2014).

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies," Objective 1.6: "Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS, and urinary tract and sexually transmitted infections."]

Education/Outreach Activities

The Heart Truth® [2]

The Heart Truth® is a national health education program to promote heart disease prevention among women. It seeks to raise awareness that heart disease is a serious health issue for U.S. women, increase knowledge of the risk factors that render women susceptible to heart disease, and encourage women to talk to their doctors, learn their personal risk, and take action to reduce it. The program uses the iconic *Red Dress*® to impart the awareness message. Awareness of the Red Dress symbol has grown considerably since its launch. In 2010, about 60 percent of women were aware of the *Red Dress* (The Heart Truth, 2010). Women who reported seeing or hearing about the *Red Dress* or *The Heart Truth* campaign were substantially more likely than other women to take at least one risk-reducing action as a result (up from 35 percent in 2008 to 57 percent in 2010) (The Heart Truth, 2010).

Raising awareness about risk has done more than just inform women; it motivates them to act. Women who know that heart disease is their leading cause of death were 35 percent more likely to be physically active and 47 percent were more likely to report weight loss than those who were unaware (Mosca et al., 2006). *The Heart Truth* is sponsored by NHLBI and involves collaboration through public-private partnerships with professional associations and other organizations and with other components of HHS, including ORWH, the Centers for Disease Control and Prevention's Million Hearts® initiative, and the HHS Office on Women's Health.

The Heart Truth's strategic framework is built on three pillars: national-level awareness-raising activities, community activation, and partnerships. From this framework, multiple tactics are developed, implemented, and evaluated to achieve *The Heart Truth*'s objectives. National-level partnerships and activities, such as National Wear Red Day®, are designed to raise awareness of heart disease and its risk factors among American women. Community activation, including *The Heart Truth* Community, Action Grant Program (supported by a public–private partnership between NHLBI and the Foundation for NIH), and the Champions Trainings (supported by the HHS Office on Women's Health), provides community-level education to women of color and low income. Using multicultural, science-based resources, these programs help motivate women to make healthy lifestyle and behavior changes. These programs also equip health educators and women's health advocates to plan and implement heart health awareness and education programs in their communities.

Partnerships with a wide variety of organizations—community, media, corporate, government, nonprofit, and health professional—leverage *The Heart Truth*'s outreach to its target audience, amplify the program's key evidence-based, public health messages, and support national activities and community programming. Over the past decade, the program has contributed to an increased

[2] *The Heart Truth*, its logo, *The Red Dress, Red Dress*, and Million Hearts are registered trademarks of HHS. National Wear Red Day is a registered trademark of HHS and the American Heart Association.

awareness among women that heart disease is their leading cause of death—a 2012 American Heart Association survey showed that such awareness nearly doubled over the past 12 years, from 30 percent to 56 percent (Mosca et al., 2006).

[These activities address ORWH Strategic Plan Goal 5: "Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research," Objective 5.3: "Expand strategic alliances and partnerships with key national and international organizations to maximize the communication and impact of women's health research."]

Inclusion

Researchers are uncovering a number of sex differences with regard to various aspects of HLBS disorders. These findings encompass differences in risk factors, symptoms, diagnosis, response to preventive and therapeutic interventions, and prognosis. The long-running Framingham Heart Study continues to yield comparisons of CVD risk in three generations of women and men, and the Jackson Heart Study and the Hispanic Community Health Study are expected to provide sources of data on gender differences in minorities. NHLBI also has a long history of supporting research on women-only cohorts and strives to ensure sex-specific analyses are conducted in its clinical trials.

The Women's Health Initiative (WHI)

WHI is a major long-term research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women: CVD, cancer, and osteoporosis. It enrolled more than 160,000 women in now-completed clinical trials and one observational study. It provided follow-up until March 2005, with optional enrollment in the WHI Extension Study for continued observation through 2015, with a further 5-year extension study in the planning stages.

The main objectives are to take advantage of the large WHI cohort to explore factors contributing to CVD burden in aging women (and conversely, the absence of CVD in healthy successful aging); increase data-sharing, dissemination, and mentoring of new investigators; continue to facilitate ancillary studies, consortium, and Centers for Medicare & Medicaid Services validation and health resources utilization studies; and leverage the WHI cohort to launch a new generation of large, simple, low-risk prevention trials focused on the health of older women.

WHI included two randomized clinical trials of postmenopausal hormone therapy—a study of estrogen plus progestin (E+P) in women who had an intact uterus and a study of estrogen alone in women who had undergone a hysterectomy. Both were designed to test the hypothesis that long-term use of hormone therapy could reduce heart disease risk. The E+P trial was halted ahead of schedule in July 2002. Compared with women taking a placebo, study participants taking hormones experienced higher rates of heart attack, stroke, blood clots, and invasive breast cancer. Although the women taking hormones had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable. In March 2004, the estrogen-alone trial also was halted ahead of schedule. After an average of nearly 7 years of treatment, estrogen therapy had no effect on heart disease risk, but it increased risk of stroke and of blood clots in the legs. No evidence of elevated breast cancer risk was found, and a favorable effect on bone health emerged. On balance, however, the trial indicated that postmenopausal hormone therapy should not be prescribed for chronic disease prevention. Following release of these findings, use of postmenopausal hormone therapy in the United States declined dramatically.

Researchers recently determined that the investment in this WHI clinical trial resulted in a return of $140 in net economic value for each dollar invested in the trial (Roth et al., 2014). The analysis found that the guidance provided by the WHI clinical trial results led to the following achievements:

- 76,000 fewer cases of CVD;
- 4.3 million fewer combined hormone therapy users;
- 126,000 fewer breast cancer cases;
- 145,000 more quality-adjusted life years; and
- Direct medical expenditure savings of $35.2 billion.

This analysis reveals that large public research investments can yield considerable clinical and economic value.

[This research addresses ORWH Strategic Plan Goal 3, "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," Objective 3.1: "Conduct

developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."]

Analysis of WHI data continues to yield numerous publications on health issues of concern to postmenopausal women such as coronary heart disease, heart failure, hypertension, nutrition, venous thromboembolism, diabetes, breast and other cancers, osteoporosis, and cognitive function. For example, the NIH-funded WHI Strong & Healthy Study will be testing the hypothesis that a centralized, public health intervention designed to increase and/or maintain physical activity levels will reduce major cardiovascular events among older women. A closely related ancillary study, Objective Physical Activity and Cardiovascular Health in Women Aged 63 and Older, has been completed. Its goals were to increase understanding of the health of aging women and, specifically, to determine whether objective measurement of physical activity is associated with CVD events and total mortality. Another industry-funded clinical trial embedded among the WHI cohort will test whether cocoa extract and/or multivitamins may reduce the risk of heart disease and stroke in older adults. The WHI Long Life Study, launched in 2012, conducted in-person visits with 8,000 older WHI participants. The data and blood collected in this study will establish a new baseline from which numerous studies on aging and health/disease can be initiated.

Sex-Dependent Disease Management in Diabetes and Coronary Artery Disease

Previous studies have suggested that sex influences clinical outcome in patients with coronary artery disease (CAD). However, other studies that have adjusted for sex differences in clinical characteristics and disease management have reported similar outcomes between men and women. To clarify this issue, Tamis-Holland et al. examined outcome differences in 2,368 patients in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (Tamis-Holland et al., 2013). Management strategies for CAD and type 2 diabetes were similar for all studied patients. After adjusting for baseline differences, Tamis-Holland et al. found that more women reported angina and had a statistically lower Duke Activity Status Index (DASI) score at the 5-year follow-up, even though they had less severe CAD than men. Investigators note that more women reported depression and inadequate social support, factors that may account for the lower self-reported functional capabilities. As expected with less severe CAD, women received fewer bypass grafts during coronary artery bypass surgery than men. Rates of death, myocardial infarction, and stroke were similar between men and women. These findings suggest that clinical outcomes are the same for men and women with CAD and type 2 diabetes when disease management is standardized between genders. However, despite similar management, women had higher rates of self-reported angina, lower DASI scores, and ineffective statin treatment for controlling bad LDL cholesterol. This study highlights that gender-specific differences in CAD and type 2 diabetes management can confound otherwise similar disease outcomes. More work is necessary to determine whether this holds true for patients with more severe CAD who were ineligible for BARI 2D.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

One of NHLBI's enduring principles is the "training and nurturing of a diverse biomedical workforce," critical to ensuring that the success of NHLBI research continues into the future. Data from the NIH Office of Extramural Research show that only 30 percent of NIH-funded principal investigators are women. Therefore, increasing the representation of women in this pipeline is a top priority. In order to truly address this problem, it is critical to understand the barriers that women face in pursuing academic research careers. NHLBI recently funded a study that is examining biases faced by women who are both physicians and researchers. Specifically, investigators are conducting surveys of career development awardees to determine which resources, as well as individual and institutional characteristics, are associated with academic success (e.g., publication, attainment of independent funding, satisfaction, promotion, and retention within academic medicine), as well as to identify which factors primarily mediate gender differences in these outcomes. This study's findings can be used to inform future NHLBI efforts to develop initiatives to improve the

career development opportunities for women in science, technology, engineering, and mathematics.

NHLBI is supporting female faculty through administrative supplements to existing NHLBI research grants to update their existing research skills and knowledge. The Re-Entry Program supports individuals with high potential to re-enter an active research career after taking time off for family responsibilities or other qualifying circumstances. The aim of these supplements is to encourage such individuals to re-enter research careers within the NHLBI mission areas. It is anticipated that at the completion of the supplement, the re-entry scientist will be in a position to apply for a career development (K) award, a research award (R), or some other form of research support.

Funding Initiatives, Workshops, and Conferences

Requests for Applications

The Women's Health Initiative: Regional Centers
https://www.fbo.gov/index?s=opportunity&mode=form&id=5e208a9cb7df3bbf35e0523fa414a2aa&tab=Core&_cview=1

Limited Competition: Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes as Predictors of Increased Risk Factors for Cardiovascular Disease (U10)
http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-13-014.html

Conferences and Working Groups

NHLBI Working Group: Sex Bias in Cardiovascular Research

NHLBI held a working group meeting to examine the topic of sex bias in cardiovascular research on September 22, 2014, in Bethesda, MD. The working group gathered leading scientists in the field, who discussed the current knowledge and identified scientific gaps and challenges related to sex differences in non-clinical and clinical research in CVD. The working group identified five recommendations that should enable and enhance CVD research in both sexes:

- Demystify assumptions about the difficulty of studying sex as a biological variable and educate the community about the importance of sex balance in research.
- Develop tools and resources for studying sex differences in CVD.
- Foster basic research on sex differences in health and disease.
- Develop guidelines for sex-based basic, clinical, and translational research design that highlight strategic experimental design considerations for researchers who would like to incorporate sex as a variable in their projects.
- Develop metrics for tracking the implementation of these recommendations.

[This research addresses ORWH Strategic Plan Goal 1, "Increase sex differences research in basic science studies," Objective 1.9: "Incorporate sex/gender considerations into discussions in scientific conferences and meetings." The meeting was also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Optimizing Cardiovascular Health of Women: Public Health Challenges and Scientific Opportunities

NHLBI held a scientific roundtable discussion on February 13, 2015, in New York, NY, which brought together leading researchers and advocates in the field of women's heart health. The goals of the meeting were to envision the desired future state of research, clinical care, and public health in cardiovascular health for women and help identify what needs to be done to achieve these goals.

[This research addresses ORWH Strategic Plan Goal 1, "Increase sex differences research in basic science studies," Objective 1.9: "Incorporate sex/gender considerations into discussions in scientific conferences and meetings." The meeting was also responsive to congressional interest in CVD and stroke and sex differences in basic, applied, and clinical research.]

Health Disparities

Racial and Ethnic Minorities

Recent U.S. health statistics highlight the importance of studying HLBS diseases in diverse populations (CDC, 2014).

- Diseases of the heart account for 22 percent of deaths (1st or "leading" cause) in White women, 23 percent (1st) in black women, 20 percent (2nd) in Hispanic women, 21 percent (2nd) in Asian or Pacific Islander women, and 17 percent (2nd) in American Indian or Alaska Native women.
- Cerebrovascular disease (stroke) accounts for 6 percent (4th) of deaths in White women, 6 percent (3rd) in black women, 6.0 percent (3rd) in Hispanic women, 8 percent (3rd) in Asian or Pacific Islander women, and 4 percent (7th) among American Indian or Alaska Native women.
- Chronic lower respiratory diseases account for 7 percent of deaths (3rd) in White women, 3 percent (6th) in black women, 3 percent (7th) in Hispanic women, 3 percent (8th) in Asian or Pacific Islander women, and 5 percent (6th) among American Indian or Alaska Native women.
- CVD affects a higher percentage of Blacks, an estimated 48 percent of Black women and 46 percent of Black men, compared with any other race (NHANES 2009 to 2012).
- Among Black women, the prevalence of angina pectoris was 5 percent (compared to the overall estimate of 3.3 percent), and 7 percent of Black women suffer from coronary heart disease, second only to White males.

NHLBI supports an extensive portfolio of studies focused on the health issues of racial and ethnic minorities and on disparities that exists between minority and majority populations. Of particular relevance are large epidemiological studies that enable detailed study of diseases and their associated risk factors in defined groups. The Jackson Heart Study, initiated in 1998, addresses CVD prevalence, severity, and mortality among black women and men living in the Jackson, MS, area. The Multi-Ethnic Study of Atherosclerosis, initiated in 1999, is investigating the prevalence, correlates, and progression of subclinical CVD in a cohort that includes White, Black, Hispanic, and Asian Americans. The Hispanic Community Health Study (HCHS), initiated in 2006, is collecting data on a wide variety of conditions—including heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment—in Latinos. Participants are Mexican Americans, Puerto Ricans, Cuban Americans, and Central/South Americans. The NHLBI-supported Strong Heart Study has been seeking to understand CVD mortality and risk factors among Native Americans since 1988. Due to the importance of genetics in the occurrence of CVD, the Strong Heart Study has most recently been focusing on identifying genetic factors that contribute to risk of cardiovascular and other diseases that affect Native communities.

The Hispanic Community Health Study

The HCHS study recently reported that among Hispanics, a higher percent of women self-reported COPD and asthma. Fifty percent more Hispanic women ages 45 to 64 years old and 30 percent more Hispanic women ages 65 to 74 years old reported that they suffered from COPD compared with Hispanic men. Asthma was reported by 65 percent more Hispanic women ages 45 to 64 years old and 90 percent more Hispanic women ages 65 to 74 years old compared with Hispanic men. These data reveal the opportunity for future research into possible causes of health disparities among the Hispanic community to inform the development of targeted interventions (Study of Latinos, 2013).

In addition to these large epidemiological studies, NHLBI supports individual projects that are addressing health disparities.

Efficacy of Weight-Loss Strategies in Black and White Females

More than 30 percent of women are obese, and approximately 60 percent of Black women are obese. Group therapy and Internet-based educational tools are successful weight-loss strategies. However, group sessions are less effective for Black women, and the efficacy of Internet-based tools is unknown in minority populations. To examine the efficacy of these weight-loss strategies in both Black and White women, investigators randomized 199 nondiabetic women to receive Internet wellness information

(WI) alone or in combination with nutrition education group sessions provided at work (WI+GS) (Carnie et al., 2013). Both groups also had access to exercise rooms with aerobic exercise equipment at work. The study investigators measured the subjects' weight and fat mass at the outset of the study, after 3 months, and after 6 months. At the 3-month check-in, members of the WI+GS group had lost significantly more weight than those in the WI group. However, at 6 months, members of the WI group had erased the difference, losing roughly the same amount of weight over the 6 months as the WI+GS group members. Both Black and White women lost similar amounts of weight and fat mass. The study leaders concluded from these results that for the WI+GS group, weekly weigh-ins and nutrition education sessions focusing on weight loss for the initial 3 months were of value and that a move to monthly sessions and a shift in instructional focus to weight loss maintenance for the remaining 3 months were premature for many subjects. Although the magnitude of weight and fat loss for the groups was modest, the study also shows the potential value of work-based weight-loss interventions in improving the health of employees and reducing the costs of disease and absence from work. However, the study authors noted that 30 percent of those initially approved for the program dropped out before the 6-month mark, most commonly because they did not have time to use the workplace exercise equipment. This result suggests a work-based weight-loss program may need other design elements to work for more people.

Study Links Sex, Race, and Genotype in Asthma Risk

Sex-specific differences in asthma have been shown to exist, and gene studies have suggested that sex-genotype interactions affect asthma risk, although this has not yet been explored on a genome-wide level. Investigators performed male- and female-specific genome-wide association studies in 2,653 males and 2,566 females with asthma, and 3,830 non-asthma controls from European American, African-American, African Caribbean and Latino populations. Six sex-specific asthma risk loci were identified; two were male-specific, four were female-specific, and all were ancestry-specific. The most significant locus in European Americans was interferon regulatory factor 1 (IRF1) on chromosome 5, which appears to be a strong candidate region for male-specific asthma susceptibility. The investigators also found in Latinos a female-specific association in a protein called RAP1GAP2, found on chromosome 17. This study highlights the need to consider sex-race-genotype interactions when assessing asthma susceptibility (Myers et al., 2014).

[This research addresses ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies;" Objective 1.1: "Encourage genetic and epigenetic studies to identify sex differences in gene expression."

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National Institute on Aging

Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other dementias, implications of ovarian aging, menopause and menopausal hormone therapy (MHT), osteoporosis, physical disability, and other diseases and conditions. During FY 2013 and FY 2014, NIA-supported researchers made important progress in a number of women's health-related areas, including:

Reproductive Health and Menopause. Research continued through the Study of Women's Health Across the Nation (SWAN) and other studies on health across the menopausal transition. For example, although previous studies have suggested an association between use of selective serotonin reuptake inhibitors or tricyclic antidepressants and bone loss, SWAN investigators found no association with bone loss at the hip, femoral head, or spine among participants who began either class of drug at midlife. SWAN investigators also reported that vasomotor symptoms such as hot flashes may last 7 years or longer across the menopausal transition and identified a number of factors associated with age at final menstrual period. In addition, investigators with the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Network found in a randomized clinical trial that healthy menopausal women taking a low dose (75 mg/day) of the antidepressant venlafaxine or low-dose oral 17β-estradiol had fewer and less severe hot flashes than those taking a placebo.

Cognitive Health. A number of investigators reported on vascular risk factors for age-related cognitive decline in women. For example, investigators with the Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-Cog) developed a model that stratified risk for cardiovascular disease and cognitive decline, incorporating education level, age, ethnicity, and genetic indicators; these differences may point to phenotypes for cardiovascular disease risk. Breast cancer chemotherapy and long-term depression were also singled out as possible risk factors for cognitive decline in older women.

Alzheimer's Disease. Recent estimates suggest that nearly two-thirds of individuals diagnosed with Alzheimer's disease are female, possibly because women, on average, live longer than men. At the same time, the majority of studies conducted in the United States have not observed sex differences in the *incidence* of Alzheimer's disease, although some studies have shown a higher incidence of Alzheimer's disease among women after around age 80. Recent reviews have explored possible reasons for these phenomena, including differences in brain structure, differential effects of the APOE ε4 genotype (the most common genetic risk factor for late-onset disease), and differences in education between men and women in the age cohorts currently at greatest risk.

Behavioral and Social Research. NIA-supported researchers found that moving from a maternity leave with limited coverage to one with comprehensive coverage around the birth of a first child reduces late-life depression. In addition, they explored differential long-term effects of different forms of childhood abuse on men and women.

Ongoing research initiatives focusing on women's health include the Women's Health Initiative Study of Cognitive Aging (WHISCA), which investigates both on-trial and long-term post-trial effects of exposure to MHT on cognitive aging within the context of the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative (WHI) more generally; a Specialized Center of Research on Sex Differences, cofunded with ORWH, to explore the intersection of sex, vascular dysfunction, and cognitive decline; and the SWAN Sleep Study, in which investigators from four SWAN sites are examining sleep patterns and factors that may affect sleep during the menopausal transition.

In addition, NIA supports a number of communication and education activities related to women and aging, career development activities, and research on the specific health concerns of minority women.

Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases

with age. In 2010, women accounted for 57 percent of the population age 65 and over and for 67 percent of the population age 85 and over. However, despite living longer, older women are more likely to report depressive symptoms or limitations in physical function, are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), and live in poverty at a disproportionately high rate (Federal Interagency Forum on Aging-Related Statistics, 2012). American women also lag significantly behind their counterparts in other higher-income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared to other industrialized countries (National Research Council Panel on Understanding Divergent Trends in Longevity in High-Income Countries, 2011). In fact, life expectancy has fallen 3 to 5 years behind other developed nations, including France, Italy, Spain, Switzerland, Australia, and Japan (National Research Council and Institute of Medicine, 2013).

NIA supports a diverse portfolio of research on older women's health, including studies on:

- Cognitive and emotional aging
- Alzheimer's disease and other types of dementia
- Menopause and MHT
- Osteoporosis and hip fracture
- Physical disability
- Caregiver burden
- Decline in function of older women
- Age-related muscle loss
- Cancer in older women
- Demography and economics of aging
- Ovarian hormone influences on brain structure and function
- Mechanisms of ovarian aging, including premature ovarian failure
- Sex differences in aging and age-related health conditions

A Women's Health Liaison in the Office of Planning, Analysis, and Evaluation coordinates communication and reporting on NIA activities related to women's health and serves as liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and new research initiatives with a particular emphasis on women, are described below.

Accomplishments and Activities

The Male–Female Survival Paradox: Still More Questions than Answers. In general, women live longer than men in much of the world, and this gap increased throughout most of the Western world during the first three-quarters of the 20th century. The reasons are unclear, but researchers have proposed that behavioral factors, particularly smoking and excessive alcohol consumption among men, may be partially responsible. In addition, women's fertility rates have steadily dropped, reducing the numbers of deaths in childbirth in the developed world. NIA-supported researchers recently compared life expectancy among men and women born in 1850–1910 in Utah, where—due to the influence of the Church of Jesus Christ of Latter-Day Saints (LDS)—men are less likely to drink alcohol or smoke and women are more likely to bear higher numbers of children, to life expectancy in Sweden and Denmark (where the Church of LDS was slower to take hold, and from where a significant number of Utah's original settlers emigrated). Although the investigators hypothesized that because of these factors, the Utah sex differential in mortality would be small and lower than in Sweden and Denmark, they found that the difference in cohort life expectancy was similar or larger in Utah when compared with Denmark or Sweden. This finding supports previous hypotheses that lifestyle factors alone are insufficient to explain the differentials in male versus female survival in developed nations.

Women's Aging and Health: Findings from the Study of Women's Health Across the Nation

NIA's flagship study of women's health is SWAN, an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to post-menopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in Caucasian,

African-American, Chinese, Japanese, and Hispanic women. Findings from SWAN have greatly enhanced understanding of women's health across the menopausal transition; for example, SWAN investigators recently reported that vasomotor symptoms such as hot flashes may last 7 years or longer across the menopausal transition, with African-American women experiencing the longest duration of such symptoms; this information will enable physicians to provide more accurate information to their patients about what to expect during the transition. In addition, the investigators identified a number of factors associated with age at final menstrual period: Higher educational level, prior oral contraceptive use, and higher weight at baseline, as well as being employed, not smoking, consuming alcohol, participating in more physical activity, and having better self-rated health over follow-up, were significantly associated with later age.

Selected findings from SWAN in FY 2013 and FY 2014 include the following:

Depression and Anxiety. Although the majority of women do not become depressed at midlife, depressive symptoms and major depressive disorder (MDD) are more common in perimenopausal women than in premenopausal women, and some studies have suggested an increased risk of depressive symptoms in the postmenopausal period, as well. SWAN investigators have found that women with a prior history of MDD or an anxiety disorder, a family history of MDD, concurrent health difficulties, or vasomotor symptoms are at increased risk of developing MDD during the menopausal transition. Women who experienced high levels of anxiety prior to the transition were found to continue to do so, while women who initially experienced low levels of anxiety often experienced a "surge" of anxiety symptoms in late menopause or immediately afterward.

Long-Term Effects of Trauma and Abuse. A history of child sexual abuse was associated with greater intima media thickness—a sign of subclinical cardiovascular disease—in women at midlife. In addition, a history of childhood abuse and neglect was related to overall elevated inflammation in mid-life women, possibly mediated through obesity, and physical abuse during childhood was associated with development of metabolic syndrome at midlife.

Cardiovascular Disease. SWAN investigators found that women who drink wine in moderation (about one glass per day) have lower levels of C-reactive protein, fibrinogen, factor VII, and plasminogen activator inhibitor—markers of cardiovascular risk—than women who drank no or little wine. Chronic financial strain and lower educational attainment were associated with subclinical cardiovascular disease among mid-life women. Investigators also found that hysterectomy with or without ovarian conservation is not a key determinant of cardiovascular risk either before or after elective surgery in midlife.

Exercise and Physical Activity. SWAN investigators have added to an extensive body of evidence supporting the benefits of exercise and physical activity. For example, physical activity was associated with higher peak femoral neck strength relative to load in premenopausal and early perimenopausal women. Greater levels of habitual physical activity were associated with more favorable sleep characteristics among mid-life women, including those experiencing vasomotor symptoms. However, modest increases in physical activity were associated with subsequent self-reported hot flashes within a 48-hour monitoring period, particularly among women reporting depressive symptoms or anxiety. Interestingly, this association was only observed between physical activity and self-reported hot flashes—not hot flashes detected via sternal skin conductance monitor.

Bone Health. Among non-Caucasian SWAN participants, higher education—but not higher income—was associated with lower incidence of nontraumatic bone fracture; the reasons for this association are unclear but remain under study. Although previous studies had suggested an association between use of selective serotonin reuptake inhibitors or tricyclic antidepressants and bone loss, SWAN investigators found no association with bone loss at the hip, femoral head, or spine among participants who began either class of drug at midlife.

Sleep. U.S.-born daughters of Hispanic/Latina, Chinese, and Japanese immigrants were more likely to report sleep complaints than their first-generation ethnic counterparts, and women with higher levels of language acculturation (i.e., they were more likely to speak, read, and consume media in English) had greater chances of reporting any sleep complaint compared to those with less language acculturation. Experiences of chronic everyday discrimination were independently associated with both

subjectively and objectively measured poor sleep. Poor sleep quality was also associated with aortic calcification, an early sign of heart disease.

Non-Hormonal Treatment for Menopausal Symptoms. Researchers with the MsFLASH Network, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition, found in a randomized clinical trial that healthy menopausal women taking a low dose (75 mg/day) of the antidepressant venlafaxine or low-dose oral 17β-estradiol had fewer and less severe hot flashes than those taking a placebo. Interestingly, when MsFLASH investigators pooled data from two completed trials, they found that trial participants assigned to the placebo group reported clinically significant improvement throughout treatment with a time course similar to improvement with active drug. A meaningful number of participants in the placebo group sustained a clinically significant response after stopping placebo pills. The results suggest that nonspecific effects are important components of treatment and warrant further studies to optimize their contributions in clinical care.

Basic Mechanisms of Ovarian Aging

For many years, researchers believed that women's ovaries contained a non-renewing and ever diminishing supply of eggs. However, NIA-supported researchers have made the startling discovery that the ovaries of adult mammals possess a rare population of germline stem cells. These cells initiate a differentiation program that ultimately results in the generation of new oocytes that interact with the surrounding ovarian soma to form new follicles throughout the reproductive life span. This finding suggests that menopause is driven by an age-related decline in ovarian stem cell function rather than simply depletion of the follicular reserve endowed at birth. It is still not fully understood how ovarian stem cells interact with their surrounding environment, so in September 2013, NIA convened an expert workshop in which scientists reviewed the state of the science in the field and generated suggestions for moving forward.

The Menopausal Transition, Menopausal Hormone Therapy, and Cognitive Health

Although the number of women prescribed MHT continues to decline, a recent nationally representative survey showed that more than 8 million American women continue to use MHT, with women older than 60 continuing to account for more than one-third of MHT use in the United States. Meanwhile, the long-term effects of estrogen-containing MHT on cognition, including the association between MHT use and Alzheimer's disease, remain the subject of intense scientific scrutiny. The question of whether MHT promotes, protects against, or does not influence risk of cognitive decline or Alzheimer's and related dementias has proven to be extremely complex, with timing and duration of treatment, specific hormones prescribed, and environmental factors all implicated to some degree in each woman's individual risk profile.

Observational studies have long suggested that use of estrogen-containing MHT is associated with a reduced risk of Alzheimer's disease. However, among participants in WHIMS, conjugated equine estrogens (CEE) plus the progestin (progesterone-related hormone) medroxyprogesterone acetate (MPA) increased dementia risk, but not risk of mild cognitive impairment, in women 65 and older. While WHISCA showed that CEE/MPA worsens verbal memory, it found that CEE alone had no influence on cognition. These findings have been replicated in several randomized clinical trials. The apparent negative effect of CEE/MPA on verbal memory does not appear to be age dependent. Studies testing the long-term effects of natural estrogen and progesterone on dementia and cognitive outcomes are in progress.

In the past several years, NIH-supported investigators have begun to explore whether hormone use by younger postmenopausal women near the time of menopause reduces dementia risk or whether WHIMS findings should be generalized to younger women. Some research suggests that MHT may be beneficial if taken during a critical window near menopause, but it may be associated with increased risk when initiated in later life. Recent results from the NIH-supported Cache County Study support this "window of opportunity" hypothesis: In this study, women who used any type of hormone therapy within 5 years of menopause

had 30 percent less risk of Alzheimer's disease, especially if use was for 10 or more years. By contrast, Alzheimer's disease risk was not reduced among those who had initiated MHT 5 or more years after menopause. Instead, rates were increased among those who began estrogen-progestin compounds within the 3 years preceding the Cache County Study baseline evaluation. At the same time, however, NIA intramural researchers with the WHI Study of Younger Women found no cognitive benefit or risk associated with estrogen therapy (CEE) in women who started treatment when they were between 50 and 55 years of age and continued it for an average of 7 years. Research is ongoing in this area.

Vascular Risk Factors for Age-Related Cognitive Decline and Cognitive Impairment

Cardiovascular disease and cognitive decline are related conditions with distinct sex differences in morbidity and clinical manifestations, response to treatments, and mortality. In a recent review, NIA-supported investigators suggest that hypertensive pregnancy disorders and menopause activate vascular components such as platelets and leukocytes to release cell-membrane derived microvesicles that are potential mediators of changes in cerebral blood flow. This may ultimately affect cognition in women as they age (Miller et al., 2013).

For example, mid-life vascular risk factors influence later cognitive decline and Alzheimer's disease. The decrease in serum estradiol levels during menopause has been associated with cognitive impairment and increased vascular risk, such as high blood pressure, which independently contributes to risk of cognitive dysfunction and Alzheimer's disease. Recently, investigators with the NIA-supported KEEPS-Cog reported on the extent to which various vascular risk factors relate to cognition in healthy, middle-aged, recently postmenopausal women. They found that higher systolic blood pressure early in the postmenopausal period was weakly related to poorer performance in auditory working memory and attention, although other cognitive domains were not affected by blood pressure. This relationship was not associated with hormone levels. KEEPS investigators also developed a model that stratified risk for cardiovascular disease and cognitive decline, incorporating education level, age, ethnicity, and genetic indicators. They note that these differences may point to phenotypes for cardiovascular disease risk. Evaluating the evolution of phenotypes could in turn clarify preclinical disease and screening and preventive strategies.

Pregnancy-Related Hypertension Shows Long-Term Effects. The National Heart, Lung, and Blood Institute (NHLBI) reports that high blood pressure problems occur in 6 percent to 8 percent of all pregnancies in the United States (NHLBI, n.d.), and NIA-supported investigators have found that pregnancy-related hypertension may be associated with poorer health outcomes later in life. In one study, investigators found that a history of hypertension in pregnancy is associated with elevated C-reactive protein, a marker of inflammation and often a sign of cardiovascular disease levels later in life. In a separate study, investigators found that pregnancy-related hypertension is an independent risk factor for peripheral arterial disease later in life. Both of these findings are independent of traditional cardiovascular disease risk factors and body mass index, and taken together they suggest that women who develop high blood pressure during pregnancy represent an at-risk group for later cardiovascular problems.

Other Risk Factors for Age-Related Cognitive Decline

Breast Cancer Chemotherapy May Harm Cognition, but Chemoprevention May Help. NIA-supported investigators performed functional magnetic resonance imaging on women undergoing chemotherapy for breast cancer prior to initiation of treatment, 1 month after treatment was complete, and 1 year later. They found decreased functional connectivity within the brain 1 month after chemotherapy, although connectivity had partially returned to baseline in some areas of the brain 1 year after chemotherapy was complete. The study participants also reported subjective memory complaints 1 month and 1 year after chemotherapy. These findings suggest a detrimental effect of chemotherapy on brain functional connectivity that may be related to subjective cognitive changes. In a separate study, investigators found that tamoxifen, which is often used in the prevention and treatment of breast cancer, improved performance in some cognitive domains among postmenopausal women who had been administered anticholinergic drugs, which can induce mild, temporary cognitive dysfunction. Women

with the APOE ε4 genotype—who are at highest risk for Alzheimer's disease—showed the greatest benefit of tamoxifen treatment. Because a loss of activity in the brain's cholinergic system is a hallmark of Alzheimer's disease, this finding that tamoxifen may attenuate cholinergic dysfunction will require further study.

Long-Term Depressive Symptom Burden Is Associated with Risk of Cognitive Decline and Dementia. Depressive symptoms and cognitive outcomes are strongly interrelated. However, although rates of depressive symptoms often fluctuate during late life, little is known about the impact of long-term cumulative depressive symptom burden on cognitive decline and dementia in older adults. Investigators with the Study of Osteoporotic Fractures (see below) found that among women followed into their 80s and 90s, cumulative depressive symptom burden over nearly 20 years was strongly and independently associated with worse cognitive functioning, greater cognitive decline, and higher chances of developing dementia or mild cognitive impairment.

Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia among people 65 and older, and it is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. As many as 5.1 million people 65 and older in the United States suffer from Alzheimer's disease, depending on how it is measured, and scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue (Hebert, Weuve, Scherr, & Evans, 2013).

The prevalence of Alzheimer's disease is significantly higher among women than among men; recent estimates suggest that nearly two-thirds of individuals diagnosed with the disease are female (Hebert et al., 2013), perhaps because women, on average, live longer than men. At the same time, the majority of studies conducted in the United States have not observed sex differences in the *incidence* of Alzheimer's disease, that is, in the rate of developing the disease; however, several American studies, and most European and Asian studies on the subject, have shown a higher incidence of Alzheimer's disease among women after around age 80 (Mielke, Vemuri, & Rocca, 2014). The potential reasons for this are complex and may include differences in brain structure, differential effects of the APOE ε4 genotype (the most common genetic risk factor for late-onset disease), and differences in education between men and women in the age cohorts currently at greatest risk (Mielke et al., 2014; Rocca, Mielke, Vemuri, & Miller, 2014). Notably, a recent study found amnestic mild cognitive impairment, often a precursor condition to Alzheimer's disease, was more common in men than in women, suggesting that sex differences in disease course may exist; for example, the investigators hypothesize that women may transition from mild cognitive impairment to dementia later in life than men but more abruptly (Petersen et al., 2010).

Behavioral and Social Research

Childhood Trauma and Metabolic Syndrome in Men and Women. NIA-supported investigators found that a history of emotional and physical abuse increases the risk of developing metabolic syndrome for both sexes, whereas a history of sexual abuse is a predictor for women only. For both sexes, individuals who experienced more cumulative abuse have a greater risk of developing metabolic syndrome. Adult socioeconomic status partially explains the association between childhood abuse and metabolic syndrome, while maladaptive stress responses and unhealthy behaviors further explain the association. Among the potential mediators, poor sleep quality was a significant pathway for men and women, while stress-induced eating was a significant pathway for women only. These findings suggest that the well-documented health consequences of early life trauma may vary by the nature of the trauma, the victim's sex, and the coping mechanisms that he or she employs.

Do Maternity Leave Benefits Protect Against Later-Life Depression? Social policies may have unanticipated health consequences. In a recent study of women age 50 and older, NIA-supported investigators linked data from eight countries in the Survey of Health, Ageing, and Retirement in Europe to data on maternity leave legislation from 1960 to 2010. They found that moving from a maternity leave with limited coverage to one with comprehensive coverage around the birth of a first child reduces late-life depression scores by 14 percent. Other recent evidence suggests that an increase in the length of maternity leave entitlements is associated with a decrease in depressive symptoms in the first 6 months after childbirth; these findings suggest that the benefits may endure for much longer.

Initiatives

Ongoing Research Initiatives

Menopause and Beyond: The Study of Women's Health Across the Nation. SWAN is an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to post- menopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in Caucasian, African-American, Chinese, Japanese, and Hispanic women. SWAN is unique in that the period of follow up spans the menopausal transition, the final menstrual period, and post-menopause in order to characterize how the menopausal transition influences health outcomes at older ages. Over two decades, SWAN investigators have collected a wealth of clinical data and biospecimens that represent an important research resource for further studies of menopause.

Funded initially in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research, and ORWH and supports Objective 3.1 of the ORWH Strategic Plan, "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."

The SWAN Sleep Study. SWAN investigators from four sites are examining sleep patterns and factors that may affect sleep during the menopausal transition. Although sleep disruptions, insomnia, and breathing-related sleep disorders increase as women age, little is known about how sleep changes as women progress through the menopausal transition. The goals of Sleep I, the baseline phase, were to (1) characterize sleep disturbances in a large, multi-ethnic sample of mid-life women; (2) characterize relationships among menopausal characteristics (for example, vasomotor symptoms and bleeding) and sleep disturbances; (3) evaluate the influence of psychobiological factors on the sleep-menopause relationship; and (4) establish baseline data for Sleep II, the longitudinal phase of this research study. The major goals of Sleep II, currently in progress, are to identify (1) potential predisposing, precipitating, and perpetuating factors for chronic sleep disturbances during the menopausal transition and (2) adverse effects of sleep disturbances on subsequent health status during the early post-menopausal period.

MsFLASH Network. In 2008, NIA, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Center for Complementary and Alternative Medicine, and ORWH, established the MsFLASH Network, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. The MsFLASH network is composed of five clinical research centers and a data coordinating center. Different approaches are being studied for efficacy against hot flashes and night sweats in diverse groups of women in trials with either placebo or usual-care control groups. Investigators are also looking at effects on other symptoms at middle age, including sleep disturbance, mood disorder, vaginal dryness, and sexual function. A number of different treatment strategies were studied, including antidepressants, yoga, low-dose estrogen gel, and exercise.

Hormones, Menopause, and the Aging Brain. NIA-supported investigators continue to study the mechanisms through which estrogen and related hormones work on the brain, as well as the effects of different forms of MHT on cognition. These efforts support ORWH Strategic Plan Objective 1.5, "Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders." Ongoing initiatives exploring the effects of age-related hormone changes and MHT on the brain include:

- **Women's Health Initiative Memory Study.** NIA supports the continued cognitive follow-up of women who participated in WHIMS, an ancillary study to the WHI randomized clinical trials of the effects of postmenopausal hormone therapy on a variety of health outcomes in older women. In addition, WHIMS investigators are performing cognitive assessments on women who were between 50 and 54 years old when they participated in the WHI randomized hormone trials and are now almost 70 years old.
- **Women's Health Initiative Study of Cognitive Aging.** While WHIMS focuses on the effects of MHT

on the risk and progression of Alzheimer's disease and other dementias, WHISCA assesses the effects of hormone treatment on memory, cognition, and mood in non-demented WHIMS volunteers age 65 and older who had been randomized to hormone therapy or placebo within the WHI trial. More than 12,000 longitudinal assessments have been performed for 2302 WHISCA participants. In addition to allowing assessment of hormonal effects on cognitive aging, this database also allows more general investigation of risk and protective factors for cognitive decline in older women. Since almost half of the women have also participated in the WHIMS-MRI study, this database also allows investigation of variation in brain volumes and brain lesion burden in relation to cognitive change.

- **Perimenopause in Brain Aging and Alzheimer's Disease.** The goal of this large, long-running program is to determine how the brain changes during the perimenopausal transition and how these changes can lead to development of early risk factors for developing Alzheimer's disease. The goal of these studies is the early identification of those at greatest risk for developing Alzheimer's disease and the window of opportunity for interventions to prevent Alzheimer's disease in those at greatest risk postmenopausal women.

Bone Health. NIA continued to support the multicenter Study of Osteoporotic Fractures (SOF), which has collected 20 years of prospective data about osteoporosis that has served as the basis for many findings about osteoporosis and aging in women 65 and older. In addition to fractures, SOF has tracked cases of breast cancer as well as total and cause-specific mortality. The data include measures of bone mineral density, hormones, strength and function, cognition, sleep, medication use, health habits, and much more. Although initially most of the study participants were Caucasian, in 1997 SOF enrolled an additional 662 African-American women who are now seen with the original cohort. The participants, who are now in their 80s and 90s, continue to be assessed every 2 years, and data are available to qualified researchers for further analysis. NIA also supported basic research projects on bone health in women, including the role of sex steroids on bone health and the identification of genes that influence peak bone mineral density in men and women.

Early Versus Late Intervention Trial with Estradiol (ELITE). Understanding the effect of MHT on the progression of subclinical atherosclerosis, especially in young postmenopausal women, continues to be an important public health issue. Investigators with ELITE evaluated whether 17β-estradiol (estrogen) reduces the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium (lining of blood vessels) is relatively healthy versus later when the endothelium has lost its responsiveness to estrogen. The investigators also tested whether 17β-estradiol reduces the progression of cognitive decline if initiated soon after menopause. A manuscript detailing findings is in development.

Ovarian Cancer Pathogenesis and Drug Resistance. NIA intramural investigators are working to elucidate clues to the pathogenesis of ovarian cancer, one of the most common gynecological malignancies in women, with particular attention to a family of proteins known as claudins. Evidence is mounting that the proteins claudin-3 and claudin-4 may represent useful markers for the detection and diagnosis of ovarian cancer. The same research team is also identifying genes associated with resistance to drugs that are commonly used to treat ovarian cancer.

Sex and Gender Analyses

NIA supports research to identify and elucidate sex and gender differences in aging and age-related disease and dysfunction. New and ongoing initiatives, which are broadly responsive to ORWH Strategic Plan Objective 3.6, "Study sex/gender differences in the aging process," include:

- A large program grant that innovatively combines informative animal models, high-quality human data, and sophisticated demographic analyses to generate a deeper understanding of the basis for sex differences in health and survival and opportunities to reduce these differences.
- A Specialized Center of Research on Sex Differences, cofunded with ORWH, to explore the intersection of sex, vascular dysfunction, and cognitive decline. By focusing on women who have experienced a hypertensive pregnancy event, preeclampsia, and menopause, these studies will identify which women might benefit from early treatments to sustain cognitive health across their life transitions.

- Projects under several 2012 program announcements soliciting research applications on the biodemography of aging. Biodemography, the integration of demographic and biological theory and methods, provides an innovative tool for understanding the impact of aging on health and longevity. Investigators will use evolutionary and life history theories as a framework for investigating individual and population-level factors that underlie changes in life span and healthy life expectancy, including sex and population differentials in late-life frailty and mortality.

Sex and gender analyses are included in many NIA basic and clinical studies, and several studies focus specifically on sex and gender differences in older age. These include:

- The Interventions Testing Program, which supports the testing of compounds with the potential to extend the life span and delay disease and dysfunction in a genetically heterogeneous mouse model of aging. All interventions are tested in both male and female animals, and sex differences in response to several compounds have been identified.
- A study aimed at developing a social and biodemographic approach to studying sex differences in health and longevity.
- A study to examine whether the rate of telomere shortening in leukocytes is associated with risk of insulin resistance in adults and forecasts mortality in the elderly and whether the rate of telomere attrition is faster in men than in women and faster in postmenopausal women than in premenopausal women.

Communications and Education Initiatives

Many of the topics covered by NIA publications are of special interest to women. Recent communications activities include:

- Online and social media outreach to promote NIA women's health research. For example, NIA staff worked with influential bloggers to disseminate evidence-based messages about menopause and hormones.
- Development and distribution of evidence-based consumer publications on women's health topics, including Menopause AgePage, Hormones and Menopause, and Menopause: Time for a Change.
- NIHSeniorHealth page within new topic Health Immunizations and Screenings, Recommended Screenings for Women 50+.
- Participation in a video with NIH ORWH: Studying Both Sexes with NIH's National Institute on Aging's Interventions Testing Program.
- "Inside NIA" blog post by Marie A. Bernard: Join the Women of Color Research Network.

Health Disparities

Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Institute on Minority Health and Health Disparities. Minority aging research is conducted throughout the Institute's programs, and much of this research has relevance to the health needs of minority women. Examples of current programs and projects include:

- SWAN, which explores a number of health parameters among Caucasian, African-American, Chinese, Japanese, and Hispanic women.
- The MsFLASH Network, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition, which has successfully recruited sufficient numbers of African-American women to gather baseline data to analyze for differences by race and ethnicity in perimenopause/menopause characteristics.
- The Healthy Aging in Neighborhoods of Diversity across the Life Span study, a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations.

Career Development

NIA actively encourages participation of women in its training and career development initiatives. In addition, the Institute supports a research study examining the barriers women face in careers in biomedical research in universities and research centers and cofunds the University of Maryland Building Interdisciplinary Research Careers in Women's Health Program, which has

a research emphasis on women and aging. The NIA Deputy Director also cochairs the NIH Women of Color Research Network, which was created to provide women of color and supporters of their advancement in the biomedical sciences information about the NIH grants process, advice on career development, and a venue or forum for networking and sharing information.

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National Institute on Alcohol Abuse and Alcoholism

Executive Summary

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the primary U.S. agency for conducting and supporting research on the causes, consequences, prevention, and treatment of alcohol abuse, alcoholism, and alcohol problems. NIAAA provides leadership in the national effort to reduce alcohol-related problems by:

- Conducting and supporting alcohol-related research in a wide range of scientific areas including genetics, neuroscience, epidemiology, prevention, and treatment.
- Coordinating and collaborating with other research institutes and Federal programs on alcohol-related issues.
- Collaborating with international, national, State, and local institutions, organizations, agencies, and programs engaged in alcohol-related work.
- Translating and disseminating research findings to health care providers, researchers, policymakers, and the public.

According to the Centers for Disease Control and Prevention, excessive alcohol consumption is the third-leading cause of preventable death in the United States. Untreated alcohol problems cost the United States an estimated $184.6 billion per year in health care, business, and criminal justice costs and cause more than 100,000 deaths. Studies indicate that women consume lower levels of alcohol and are less likely than men to drink daily or to engage in binge patterns of use. For example, in 2011, an estimated 47.1 percent of females aged 12 or older were current drinkers, which was lower than the rate for males (56.8 percent). However, women are more sensitive than men to the physiological effects of alcohol, achieve higher blood alcohol concentrations, have a higher risk for the development of alcohol-related diseases, and show a higher vulnerability to alcohol dependence.

NIAAA-funded preclinical studies in animal models have begun to reveal the mechanisms underlying sex/gender differences in drinking behaviors and related problems. In the past 2 FYs, scientific areas related to Goal 1 and Goal 2 of the NIH Strategic Plan for Women's Health Research have undergone significant advances in knowledge.

NIAAA also maintains a strong program of research that examines how the presence of other medical conditions, along with environmental and social factors, can lead to different patterns of alcohol abuse and health vulnerabilities in girls and women throughout their lives. Scientists now recognize that human biology and behavior continue to change throughout life, which in turn affects individuals' drinking patterns and their decisions to alter drinking habits or to seek help for alcohol-use problems. A life span perspective will allow researchers to identify how the emergence and progression of drinking behavior is influenced by changes in biology, psychology, and exposure to social and environmental inputs over a person's lifetime, and vice versa. This approach will help discover life stage–appropriate strategies for developing individualized prevention and treatment programs for girls and women that fulfill Strategic Plan Goal 3.

The following report highlights NIAAA's recent activities and accomplishments in biomedical and behavioral research related to women's health. The accomplishments fall into six research categories: (1) gender differences; (2) alcohol use, pregnancy, and fetal alcohol spectrum disorders (FASD); (3) alcohol and violence; (4) prevention and treatment for women; (5) women and other disorders; and (6) women, alcohol use, and cancer.

Accomplishments and Activities

Sex Differences (Preclinical)

Females Are More Likely to Exhibit Comorbid Anxiety with Alcohol Abuse Compared to Males (co-funded by ORWH) (Objective 1.5). Alcohol abuse has a high comorbidity with depression and anxiety disorders, with a higher rate in females. This is consistent with the idea that females exhibit a different response to chronic stress. ORWH recently provided an administrative supplement

to an NIAAA grant to study the sensitivity of female mice to alcohol-induced anxiety- and depression-like behaviors and to examine plasticity within the 5-HT system following alcohol exposure. This supplemental study will provide a systematic examination of chronic ethanol vapor exposure on anxiety- and depression-like behavior in female mice and, through the use of slice physiology, will provide the first characterization of how alcohol impacts 5-HT–regulated emotional circuitry in the female brain. 5-HT neurons respond to stress differently depending on sex. Results obtained from this study will clarify neurobiological mechanisms of sex dependent differences in anxiety related to alcohol dependence and may provide insights needed for developing effective alcohol dependence therapies for females.

Sex Differences in Stress-Alcohol Interactions (Objective 1.5). This project addresses sex differences in how stress and alcohol alter activity of neurons in the amygdala, a brain region involved in both stress and alcohol dependence, and how these neuroadaptations affect the tendency to relapse to alcohol drinking. The main findings to date are that basolateral amygdala stimulation of central amygdala excitatory postsynaptic potentials in female rats are less sensitive to inhibition by alcohol, and that there is a greater chance, compared with males, that female neurons will be excited or unaffected, rather than inhibited, by acute alcohol application. In addition, female neurons demonstrate adaptation of phosphodiesterase 10a (PDE10A) expression over a longer, but not shorter, interval—suggesting that females may be more sensitive to modulation of alcohol intake by PDE10A inhibitors. Understanding sex differences in alcohol-induced neuroadaptations of stress-responsive brain regions, such as the amygdala, is of great importance for development of therapies to more effectively treat alcohol use disorders in both males and females.

Sex Differences in Alcohol Drinking in Response to Stress (Objective 1.6). This recently awarded study investigates whether females are more susceptible than males to alcohol's anxiolytic and sedative properties and therefore more likely to find this drug rewarding during or after particularly stressful situations. Though the clinical association between stress and drinking is well substantiated, the factors that mediate the relationship between stress and drinking are poorly understood. These studies will test the overriding hypothesis that females are more sensitive to stress and that this liability is modulated by gonadal hormones and the opioid peptide beta endorphin. Males and females have somewhat different factors contributing to addiction, so a better understanding of these influences will promote more effective targeted alcoholic treatment and intervention.

Sex Differences in Regulation of Alcohol Intake by Purinergic P2X4 Receptors (Objective 1.5). This project tests the role of purinergic receptors (P2X4Rs) within the brain dopamine reward system in regulation of alcohol intake. The preliminary findings suggest that male mice lacking the p2rx4 gene drink significantly more alcohol and are less sensitive to alcohol-induced loss of righting reflex than wild-type controls. This study will extend the investigation to female mice and use both genetic and pharmacological approaches to understand the role of P2X4Rs in alcohol intake, neurophysiology, and behavior in male and female mice. The outcomes of the study will provide novel insights to the molecule cascade linking the role of P2X4Rs to alcohol intake and the potential sex interaction with P2X4R genotype in regulation of alcohol consumption.

Gender Differences (Clinical)

Gender Differences Related to Alcohol Use During Adolescent Brain and Behavioral Development. This newly funded R01 grant will use a multi-modal brain imaging approach (structural and functional magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy) to follow a group of adolescents before they initiate any form of drinking and then follow them longitudinally. In addition to structural and functional brain imaging, a variety of clinical and neuropsychological assessments will also be collected to understand healthy adolescent brain and behavioral development and the factors associated with the initiation of alcohol use in the adolescent period. It is hypothesized that brain and behavioral development will be more disrupted in adolescent females who use alcohol than in male users and that both groups will show impairments relative to those adolescents who did not begin drinking.

Gender Differences in Behavioral and Emotional Functioning in College Drinkers. This newly funded career development award will provide training and research experiences for the principal investigator to further her development as an independent researcher to study men and women college students with functional neuroimaging and behavioral assessments in relation to their use of alcohol. The research study will investigate the neural and behavioral correlates of emotion-related impulsivity in first-year college drinkers that may serve as predictors of alcohol-related problems 2 and 3 years later in college. The analyses will involve investigation of possible gender differences. It is hypothesized that women who are heavy drinkers will show more disruption of inhibitory control on a go/no-go task when presented with distracting emotional information.

Sex Differences in the Neurobehavioral Consequences of Alcoholism. The effects of alcoholism among women remain understudied. The proposed work addresses this gap in knowledge by assessing cognitive and emotional processing in detoxified treatment-seeking alcoholic men and women as well as community controls and by exploring whether emotional and/or cognitive deficits observed during treatment are related to psychosocial adaptation in early recovery. By studying both men and women, the project is designed to reveal clinically relevant sex differences and inform research and treatment development.

Alcohol Use, Pregnancy, and Fetal Alcohol Spectrum Disorders

Sex Differences in Executive Function in a Rodent Model of FASD (Objective 1.5). FASD is a leading cause of intellectual and developmental disabilities that continues to be a significant medical and societal problem in the United States and abroad. A feature of FASD that has received much attention in the human literature over the past decade is impairment of executive function (i.e., prefrontal-cortex-dependent cognitive processes such as attention, working memory, conceptual set shifting, and inhibitory learning). Although impairment of executive function is well established in human FASD, it has not been well documented in rodent models. This study examines whether a well characterized, widely accepted, and highly specific test of prefrontal executive function in rodents, the attentional set shifting task, is impaired by developmental alcohol exposure in male and female Long-Evans rats. The proposed experiments will provide key insights into the specific mechanisms implicated in FASD-related executive function deficits and could enable the discovery and development of interventions for FASD.

Alcohol and Violence

Effects of Alcohol Intoxication and Rumination on Partner Aggression. Both men and women can be victims of interpersonal violence; however, women are much more likely to be victims of interpersonal violence. This recently funded study will examine the individual and interactive effects of alcohol intoxication and in vivo use of rumination and reappraisal on partner aggression among heterosexual dating couples. Participants will be at least 21 years old, report at least social drinking, and be in a committed relationship of at least 4 months. This study will examine the influence of acute alcohol intoxication and emotion regulatory strategies in contributing to two intimate partner aggression (IPA) outcomes: a behavioral measure of partner aggression and self-reported IPA. Findings from this study will inform on important situational risk factors for IPA perpetration and provide knowledge to guide development of intervention, prevention, and treatment programs specifically designed for women.

Alcohol Intoxication and Neurocognitive Processing Effects on Intimate Partner Violence (IPV). This project investigates the role of acute alcohol intoxication and neurocognitive processing in predicting IPV. Findings indicate that while neither alcohol intoxication nor a history of IPV perpetration independently predicted increased aggression during anger arousal, a significant interaction emerged such that only individuals with a history of IPV and who were intoxicated exhibited increased aggressive verbalizations during anger arousal. Unexpectedly, attentional processing did not predict the expression of aggression during anger arousal or mediate the interactive effects of alcohol intoxication and IPV on aggression. Results revealed that alcohol intoxication predicted decrements, which reflects the cost of shifting attention. Findings also highlight the importance of targeting alcohol use for both women and men in the treatment of IPV as well as developing interventions that attempt to increase the saliency of inhibitory cues to reduce IPV.

Prevention and Treatment for Women

Substance Abuse, Mental Health, and Health in Homeless Women in Primary Care (Objective 3.9). Samples of homeless women have shown upwards of two-thirds have had alcohol or combined alcohol and drug-use problems during the last year. Half or more of homeless women with substance abuse issues have been reported to have a mental health condition, primarily depression. In addition, there is evidence that problematic alcohol and drug use are associated with high-risk sexual practices, poor overall health, lower life expectancy, difficulty exiting homelessness, and prolonged episodes of homelessness. This study is sampling 750 women drawn from primary care clinics in 10 organizations that are members of the National Health Care for the Homeless (HCH) Practice Based Research Network, located in eight States (California, Illinois, Ohio, Massachusetts, North Carolina, Nebraska, New Hampshire, and Texas). Conducting the study in primary health care settings will result in reaching a broader sample of unstably housed women than using street or shelter population, and is consistent with NIAAA, Health Resources and Services Administration, and Department of Housing and Urban Development priorities to improve understanding and integration of substance abuse and mental health prevention and treatment services in primary health care settings. The study aims are to (1) describe the prevalence and correlates of past-year risky alcohol and drug use and their comorbidity with mental and physical health conditions among homeless women receiving primary health care services in HCH programs; (2) describe access to substance abuse treatment among women in this sample with past-year risky alcohol or drug use, including the rate and correlates of perceived barriers to and motivation to seek substance abuse treatment; and (3) identify potentially innovative approaches to prevent, identify, and treat substance abuse and mental health problems among women who seek primary health care in HCH programs. Findings from this study will provide a platform for future research on interventions that can be brought to population scale to help identify and overcome barriers to treatment for substance use and other mental health disorders among homeless women.

Web-Based Treatment of Heavy Drinking Among Women with a History of Sexual Trauma (Objectives 2.5, 6.1). Heavy drinking and sexual assault are significant public health concerns among college women and are both associated with multiple negative consequences, including academic, physical, and mental health problems. The goal of this mentoring/career development project is to develop and empirically evaluate a Web-based intervention to reduce heavy drinking among college women with a history of sexual assault who display elevated levels of psychological distress. College women with a history of sexual assault often report more heavy drinking and psychological distress than women without a history of assault. Moreover, women with assault histories often have difficulty regulating their emotions and tolerating distress, which can lead to a pattern of drinking to cope with distress. Trauma exposure, negative mood, and poor coping strategies have been associated with poor treatment outcomes and relapse following alcohol treatment. Incorporating distress tolerance and emotion regulation skills with an alcohol intervention may enhance treatment effects among women with a history of sexual assault by decreasing their motivation to drink to cope with depression or anxiety and by building adaptive coping strategies. Therefore, the Web-based intervention will include cognitive behavioral skills for reducing alcohol consumption and incorporate emotion regulation and distress tolerance skills from dialectical behavior therapy. Findings will set the stage for a larger trial to more rigorously test this intervention against active controls in a larger sample. This project thus addresses two key priorities of NIH/ORWH/NIAAA: (1) to reduce heavy drinking among women with a history of sexual and other trauma, and (2) to increase the number of women investigators engaged in research to address the behavioral health needs of women.

Menstrual Cycle, Regulatory Systems, and Alcohol Use in Young Women. Alcohol use disorders (AUD) are the most prevalent mental health disorders in the United States. Although these disorders are traditionally considered a "man's disease," recent epidemiological evidence suggests that the gap in prevalence of alcohol use and dependence between women and men is decreasing. Among moderate drinkers, women are at greater risk for alcohol related health problems such as liver or heart disease compared with men. Given the public health relevance of AUD and the considerable gap in the literature regarding AUD in women,

the present study focuses on vulnerability and protective factors that influence alcohol use in women. In particular, it investigates the relationships among impulsive and executive decision-making systems and dispositional characteristics (e.g., mindfulness) in the context of the naturally occurring stressor (i.e., hormonal variation associated with the menstrual cycle) as they relate to alcohol use in women. This study will further our understanding of the etiological factors that contribute to problematic drinking in an effort to inform prevention and treatment programs for women.

Women, Alcohol, and Other Disorders

Twin Study of Female Alcoholism and Other Disorders (Objective 3.1). Adolescent substance abuse is a powerful predictor of adult adjustment and mental health problems. Yet the mechanisms linking early abuse to later maladjustment are not well understood. Using a unique sample of female twins studied prospectively from ages 11 to 29, this project will examine how adolescent-onset substance abuse affects mental health, social, and neurocognitive functioning in early adulthood. Specifically, a wave of data will be collected from subjects in the Minnesota Twin Family Study (MTFS) as they reach age 29. The resulting data will allow the PI to investigate the developmental processes that link adolescent substance abuse with diverse adult outcomes and explore the mechanisms of substance abuse desistance in early adulthood. The female portion of the MTFS is based on 717 pairs of female twins and their parents drawn from two population-based cohorts. The older twin cohort, originally seen at age 17 and followed up at ages 20 and 24, has completed the age-29 assessment. The younger cohort, originally recruited at age 11 before the initiation of significant substance use, has completed follow-ups at ages 14, 17, 20, and 24 and will be followed through age 29. The age-29 assessment—currently in progress—is focused on outcomes potentially associated with adolescent substance use and risk and protective factors that might influence substance abuse desistance. Data from both cohorts will be combined to examine the developmental trajectories leading to differences in mental health, social, and neurocognitive outcomes at age 29.

Women, Alcohol Use, and Cancer

Alcohol and Breast Cancer (co-funded by ORWH) (Objectives 1.7, 5.2). Alcohol consumption is associated with an increased incidence of breast cancer. The association with alcohol is particularly pronounced in hormone-dependent breast cancers, so cancers that are associated with alcohol consumption are more likely to be estrogen receptor positive. A common hallmark of cancer cells is over-induction of polymerase III (Pol III), which is involved in expression of non-protein coding RNAs such as transfer RNAs. Alcohol induction of Pol III depends on estrogen receptor function, and the combination of estrogen plus alcohol synergistically increases the induction of Pol III activity. ORWH funded earlier foundational work on this topic. More recently, in 2014, ORWH funded a continuation that focuses on signaling changes due to alcohol, in particular at the level of transcription factor modification. Transcription factor Runt-related gene 2 is altered, thereby affecting Pol III gene expression. Understanding the mechanism by which alcohol enhances tumor formation may lead to insights on prevention and therapeutic approaches and may inform women's decisions about drinking alcohol.

Alcohol and Breast Cancer (co-funded by ORWH) (Objectives 1.7, 5.2). The association of alcohol with breast cancer is epidemiologically well-supported, but the mechanisms by which alcohol initiates and promotes breast cancer are poorly understood. This competitive renewal furthers the understanding of the changes in signaling pathways that occur in breast cancer and how alcohol influences them. The work investigates the cellular/molecular mechanisms underlying alcohol-induced tumor promotion and progression. This is important because alcohol consumption not only increases the risk of mammary tumors but also is closely associated with advanced and invasive breast tumors. Specifically, this work will extend the analysis of the erbB pathway by following up on an exciting preliminary observation that the p38gamma isotype (a component of the erbB pathway) is uniquely modified by ethanol. The work explores the downstream molecules activated by p38gamma that may mediate how alcohol enhances the promotion and aggressiveness of breast tumors. Knowledge of this type may provide more focused targets for intervention and help to inform women's decisions about consuming alcohol.

Initiatives

Administrative Supplements for Research on Sex/Gender Differences. NIAAA participated in this ORWH initiative. This FY 2013 Administrative Supplement program is designed to support research that increases understanding of sex and gender differences in health and disease, as part of the implementation of the strategic plan entitled Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research. (PA-13-018)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) (K12). ORWH and co-sponsors, which include NIAAA, issued this request for applications to support junior faculty members, known as BIRCWH scholars, to receive mentored research career development in interdisciplinary research on women's health or on sex/gender differences related to biology, health, or disease. NIAAA provides co-funding for one grant that focuses on understanding the interplay between women's health and addictive behaviors, specifically involving tobacco, alcohol, overeating, and illicit drugs. (RFA-OD-11-002)

Workshop/Symposium

Puberty, Gonadal Hormones, and Sex Differences in Alcohol Abuse and Dependence. Between the ages of 12 and 17, adolescent males and females have similar patterns of alcohol use and similar prevalence of alcohol abuse and dependence. By late adolescence, sex specific patterns begin to emerge, with females exhibiting fewer drinking days in the past month, fewer episodes of heavy drinking, and lower prevalence of alcohol abuse and dependence relative to males. Recent evidence suggests that an increase in gonadal steroids during puberty may influence the structural and functional remodeling of the brain. Thus, hormonal mechanisms, such as activation of reproductive hormones and their effects on neuromaturation, could explain the sex differences in alcohol drinking patterns, sensitivity to alcohol effects, and susceptibility to alcohol abuse and dependence that arise during late adolescence after the onset of puberty. This symposium presented research on the degree to which hormonal changes at puberty may produce sex-specific effects using animal models of alcohol-related behaviors. Preclinical studies are important to determine whether pubertal rises in gonadal hormones may modify brain development to produce sex differences in behaviors that put adolescents at risk for alcohol use and misuse.

[Presented at the Annual Meeting of the Research Society on Alcoholism, Seattle, WA, 2014]

Program Announcements (PAs)

Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence. NIAAA is continuing to participate with the National Institute on Drug Abuse in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence (PA-11-047, PA-11-048, PA-11-049). This initiative, which was recently reissued, encourages research from basic studies of molecular genetics and neurotransmitters to studies of epidemiology, etiology, and prevention/treatment interventions that focus on sex/gender differences. Studies on sex/gender-based interventions related to HIV/AIDS and cross-cutting issues related to stages of the life cycle, health disparities, methodological approaches, and gender-specific recruitment issues are also encouraged.

Effects of In Utero Alcohol Exposure on Adult Health and Disease. The purpose of this funding opportunity announcement (FOA) is to support novel research on how prenatal alcohol exposure may contribute to the etiology of chronic diseases and health conditions later in life.

Central to this theme is the developmental origins of health and disease concept, which suggests that fetal adaptations in response to adverse intrauterine conditions may increase the risk for childhood and adulthood disease (e.g., cardiovascular disease, type 2 diabetes, obesity, select cancers, asthma, behavioral disorders). Studies supported by this FOA will provide fundamental insights into a possible fetal-basis to adult disease that may be influenced by maternal alcohol use. (PA-12-291 and PA-12-292)

Genetic Susceptibility & Variability of Human Structural Birth Defects (R01). NIAAA participated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in this PA designed to study fundamental developmental processes using animal models in conjunction with translational/clinical approaches with the goal of advancing understanding of the etiology of structural birth defects. Alcohol is a known teratogen, capable of causing FASDs, a collection of

birth defects and developmental disabilities that occur in individuals whose mothers drank alcohol during pregnancy. (PA-11-085)

Chronic Fatigue Syndrome (CFS): Pathophysiology and Treatment. NIAAA has a shared interest in two ORWH initiatives on pathophysiology and treatment of CFS, which extend until October 2014. The objective of these program announcements is to encourage research into the etiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the life span; into the environmental and biological risk factors; into the determinants of heterogeneity among patient populations; and into the common mechanisms influencing the multiple body systems that are affected in CFS. Interdisciplinary research is highly encouraged. (PAR-12-032 and PAR-12-033)

National Institute of Allergy and Infectious Diseases

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and other infectious diseases. NIAID also collaborates with other organizations on research initiatives within NIAID's mission areas that aim to improve women's health.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments in research on HIV/AIDS, non-HIV infectious diseases including sexually transmitted infections (STIs), and immunology and immune-mediated diseases. The accomplishments include supporting clinical trials that test antiretroviral (ARV) drugs and topical microbicides to prevent the transmission of HIV to women or their partners as well as a new ARV drug regimen to minimize the risk of mother-to-child transmission of HIV during pregnancy and breastfeeding; epidemiologic studies on the effect of HIV infection on women's risk of cervical cancer or precancer; development and testing of intravaginal rings containing ARV drugs, which women could use to protect against sexually transmitted HIV infection; studies to treat and prevent malaria in children and pregnant women; and basic research that could lead to new treatment approaches to minimize the impact of systemic lupus erythematosus (SLE), Crohn's disease, and other autoimmune diseases that disproportionately affect women; improving the understanding of how the immune system targets central nervous system tissues in multiple sclerosis (MS); and providing insights into complications of human pregnancy. An overview of NIAID activities that address the objectives of the NIH Strategic Plan for Women's Health Research includes a description of the NIAID Women's Health Research Work Group. Additional sections provide overviews of NIAID activities to include women in clinical studies, such as the development of guidance for including pregnant women in vaccine and therapeutics trials; career development activities; research initiatives; conferences and publications; and research on health disparities in women and special populations.

Accomplishments and Activities

HIV/AIDS

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that 35 million people worldwide are infected with HIV. Women face the greatest risk of acquiring HIV because of substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Most women are infected with HIV through sex with men or injection drug use.

According to UNAIDS, in 2014 women accounted for approximately 50 percent of all adults living with HIV worldwide, of which 80 percent reside in sub-Saharan Africa. The Centers for Disease Control and Prevention (CDC) reported that the rate of new HIV diagnoses and deaths in women in the United States declined from 2008 to 2012. However, HIV/AIDS and associated diseases and co-infections continue to cause substantial illness and death in the United States and worldwide. In 2013, WHO reported that HIV/AIDS is the leading cause of death globally for women of reproductive age (15–44 years).

In addition to facing complications associated with HIV/AIDS similar to those that affect men, infected women also suffer gender-specific manifestations of HIV disease, including human papillomavirus (HPV)-related cervical dysplasia (abnormal, precancerous cell growth) and cervical cancer. HIV-infected women have a higher prevalence of HPV infection, a higher risk of progression from infection to disease, and an increased risk of invasive cervical cancer and other HPV-related cancers. Anal cancer is emerging as an important clinical entity in HIV-infected women (as well as in men). An important risk factor for anal cancer in women is advanced cervical dysplasia, while sexual practices and behaviors have not been shown to be associated with anal cancer. (For more information on HPV infection, see Infectious Diseases Other than HIV/AIDS.)

Combination ARV therapy for HIV has not significantly decreased the incidence of HPV-related cancers. Other complications of HIV infection in women, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, and severe herpes infections are reduced in the setting of successful combination ARV therapy. Drug metabolism differs in women compared with men, potentially resulting in differential responses to ARV therapy and an increased incidence of drug toxicities in women.

In many parts of the world, death and illness due to pregnancy and childbirth are frequent occurrences. Thus, use of contraceptives is the most successful intervention to prevent maternal illness and death, and, by preventing pregnancy, to prevent mother-to-child transmission of HIV. Hormonal methods of birth control are most effective but may interact with antiretroviral drugs, which could lead to additional toxicities or treatment failures. Also, and perhaps more important, several recent studies have shown an increased risk of HIV transmission to an uninfected male partner if the woman is using hormonal contraceptives. Forms of contraception that are effective, safe, and do not increase the risk of transmitting HIV to an uninfected partner are urgently needed, as are safe and effective methods to prevent mother-to-child transmission of the virus.

Achieving effective treatment of HIV infection may be more problematic for women than for men because women may have difficulty accessing health care and carry a large burden of caring for children and other family members, including those who also may be HIV-infected. They often lack social and financial resources to cope with HIV and other challenges.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives, including intramural studies; investigator-initiated research; the Women's Interagency HIV Study (WIHS), a long-term cohort study; and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. These clinical trials are being conducted by the Microbicides Trials Network (MTN), AIDS Clinical Trials Group (ACTG), International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), HIV Interdisciplinary Network for Pathogenesis Research in Women, HIV Prevention Trials Network (HPTN), HIV Vaccine Trials Network (HVTN), and International Network for Strategic Initiatives in Global HIV Trials.

Epidemiologic Research

NIAID supports epidemiologic research in the following areas:

- The long-term natural history of HIV infection in women—in particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease throughout a woman's life span;
- The effect of hormonal, endocrine, bacterial, and local factors on the levels of HIV in the plasma and genital tract, and on sexual transmission of the virus;
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ARV therapy, and/or the aging process;
- Characterization of acute clinical events and co-infections and their impact on HIV disease progression; and
- Studies of the female genital tract compartment, including the microenvironment, HIV virology, and immunology of the female genital tract compared with blood.

Scientific Advances

HIV Superinfection Is Less Frequent than Initial Infection in a Cohort of High-Risk Kenyan Women. If an HIV-positive person becomes subsequently infected with a different strain of HIV, they are said to be superinfected. If superinfection occurs, the infected person may progress more rapidly to AIDS and show less sensitivity to therapy. NIAID-funded investigators studied samples from a cohort of more than 100 high-risk women in Kenya to determine if the incidence of superinfection was different from that of initial infection. The rate of superinfection in the cohort was 2.61 per 100 person-years, which is lower than the incidence rate for initial infection of 5.75 per 100 person-years. This is the first rigorously done study to report that HIV infection reduces the risk of reinfection, raising the possibility that immune responses to natural infection are partially protective. Because the superinfection risk changes with time, the researchers suggest that a window of protection may coincide with the maturing of HIV-specific immunity (Ronen et al., 2013).

HIV Superinfection in Female Sex Workers. In contrast to the results above, NIAID intramural researchers demonstrated that HIV superinfection occurred at a high rate and was similar to that of primary HIV infection in Ugandan female sex workers. Regardless of the relationship between rates of superinfection and primary infection, however, the findings suggest that individuals who are participating in higher-risk behavior are most likely at increased risk of both primary HIV infection and superinfection. These findings add to the growing evidence that HIV superinfection occurs at a significant rate throughout the world (Redd et al., 2014).

Women's Interagency HIV Study

WIHS is the largest observational study of HIV-infected women and includes participants living in 10 U.S. metropolitan areas (in FY 2013, WIHS was expanded to include four new research consortia and make it more representative of the U.S. epidemic). The majority of the more than 3,500 women enrolled in the study are African-American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of highly active antiretroviral therapy (HAART). Researchers are investigating factors such as the development of AIDS, drug resistance, co-infections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at http://statepiaps.jhsph.edu/wihs.

Scientific Advances

Life Expectancies of HIV-Infected Individuals in Established NIAID Cohort Studies. Researchers estimated the proportions, timing, and predictors of AIDS-related and non-AIDS-related mortality among HIV-infected and uninfected individuals enrolled in two long-standing NIAID-supported cohort studies. They analyzed data from the Multicenter AIDS Cohort Study (MACS) and WIHS from 1984 to 2008 and 1996 to 2008, respectively, and compared information before and after the HAART era. Once HAART became readily available, the proportion of deaths due to AIDS decreased and the proportion due to non-AIDS causes increased from 6 percent to 53 percent among HIV-positive MACS participants. This change in causes of death was

accompanied by an increase in the median age of non-AIDS death after age 35 from 49 years to 66 years. Despite these advances, life expectancy for HIV-infected persons dying of non-AIDS related causes was still shorter than that of uninfected persons. These results highlight the changing patterns of causes of death between the pre-HAART and HAART eras and emphasize the importance of understanding both death rates and causes of death among those treated for HIV infection (Wada et al., 2013).

International Epidemiology Databases to Evaluate AIDS (IeDEA)

The IeDEA consortium brings together clinical data collected as part of research initiatives and diverse care programs. Seven global regions enroll patients who are representative of the HIV epidemic within their region. The North American AIDS Collaboration of Observational Research Databases includes data from more than 21,000 women living in the United States or Canada. The consortium's size allows for in-depth assessment of clinical outcomes, including rare events and their predictors. Globally, IeDEA represents the severity of the epidemic among women, with more than half of the data coming from women. More information is available at http://www.iedea.org.

Prevention Research—Topical Microbicides

There is an urgent need to develop a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. NIAID-sponsored research focuses on the development of topical microbicides that (1) prevent HIV infection and/or viral replication; (2) are safe and do not irritate vaginal, cervical, urethral, or rectal tissues; and (3) reduce HIV transmission and acquisition, even in the presence of other STIs, which increase the risk of acquiring HIV.

Microbicide Trials Network

In 2006, MTN was formed to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN consists of a strong network of expert scientists and investigators from U.S. and international sites. The network uses a focused research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. More information is available at http://www.mtnstopshiv.org.

Scientific Advances

Social and Cultural Factors Influence Effectiveness of HIV Prevention Strategies in Women. Pre-exposure prophylaxis (PrEP) is an FDA-approved HIV prevention approach for people at high risk of contracting HIV. To prevent infection, healthy individuals take daily doses of antiviral therapy. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, a large, randomized phase IIb clinical trial conducted at multiple sites in South Africa, Uganda, and Zimbabwe, was designed to evaluate the safety and effectiveness of two PrEP approaches: (1) oral tablets containing either the antiretroviral drug tenofovir, or (2) a combination of tenofovir and emtricitabine (known as Truvada), and tenofovir 1-percent vaginal gel. Primary study results released in March 2013 indicated that the three antiretroviral-based strategies intended to prevent HIV infection did not prove effective among study participants because of lack of patient adherence to daily treatment regimens. The VOICE-C substudy examined what social and cultural factors influenced women's daily use of antiviral therapy. The researchers found that these factors included misunderstandings about the trial and the need to take drugs without being infected with HIV, physical side effects, negative attributes of the treatments, and social stigmas associated with being on HIV therapy. These results suggest that social and cultural factors must be considered when designing and implementing future HIV PrEP clinical trials (van der Straten et al., 2014).

Clinical Trials

VOICE-D Trial. The VOICE-D substudy (MTN-003D) was launched after the completion of VOICE to better understand women's actual use of study products and sexual behavior during their participation in VOICE, and to understand why women enrolled and remained in VOICE yet so few adhered to product use. Preliminary results found that the women had fears about the products and side effects that were fueled by peer participants, relatives, and community members' negative attitudes about the products. This information is important given its impact on efficacy. More information is available at http://www.mtnstopshiv.org/news/studies/mtn003.

A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) Trial. Enrollment in this phase III trial (MTN-020) to evaluate the safety and effectiveness of an intravaginal ring (IVR) containing the antiretroviral drug dapivirine was completed in June 2014 with 2,629 women enrolled from South Africa, Zimbabwe, Uganda, and Malawi. This two-arm study comparing the monthly use of a dapivirine-containing IVR to a matched placebo IVR is being conducted in parallel with the Ring Study, a smaller safety and effectiveness study in southern Africa supported by the International Partnership for Microbicides, the sponsor of the dapivirine IVR. These trials are the first to evaluate long-term, sustained delivery of an ARV from an IVR for HIV prevention.

Vaginal Ring Containing Dapivirine in Postmenopausal and Adolescent Females. The first study of a vaginal microbicide in postmenopausal women is underway (MTN-024), testing the safety of the dapivirine ring used monthly for 3 months. In addition, the first study of a microbicide IVR in adolescent females began enrolling in 2014 (MTN-023/IPM 030). This phase IIa, multisite, randomized trial will compare the efficacy of the dapivirine IVR to a placebo IVR in 96 sexually experienced, HIV-uninfected adolescent females.

Rectal Microbicide Safety and Acceptability Study. Researchers are evaluating tenofovir-containing microbicides for rectal use. A multisite domestic and international phase II expanded safety and acceptability study of the reduced glycerine tenofovir 1-percent gel (MTN-017) in men who have sex with men and transgender women was initiated in 2013. Enrollment was completed in 2014.

Vaginal Ring Containing Dapivirine and Maraviroc. An early-phase clinical trial (MTN-013/IPM 026) of an IVR containing two ARV drugs, dapivirine and maraviroc, found the ring to be safe in women who wore it for 28 days. Preliminary results demonstrated the presence of dapivirine in cervical tissue and blood. Laboratory tests of tissue samples showed that dapivirine was able to block HIV infection. The levels of maraviroc were not sufficient to have a similar effect. This was the first clinical study of an IVR with two ARV drugs and with the inclusion of maraviroc.

Programs to Support the HIV Topical Microbicide Preclinical Pipeline

The development of new topical microbicide products continued in 2013–2014 and was supported by programs designed to create a sustainable pipeline of topical microbicide products, strategies, and technologies supporting microbicide safety and efficacy testing. The first program, the Microbicide Innovation Program (MIP) and its successor the Prevention Innovation Program (PIP), is designed to support innovative, high-risk research to develop products, delivery systems, and technologies to populate the early preclinical topical microbicide pipeline. The second program, the Integrated Preclinical/Clinical Program (IPCP) is designed to advance topical microbicides to clinical testing through the support of investigational new drug–enabling studies and first-in human clinical trials. MIP/PIP-supported studies included the development of new single and combination HIV and STI topical microbicides, and topical microbicide sustained-release delivery technologies such as mucosa-penetrating and mucosa-targeted nanoparticles, electrospun nanofiber fabrics, and IVRs. Research to support new prevention strategies incorporating topical microbicides, such as multipurpose prevention technologies, which combine vaginal topical microbicides with hormonal contraceptives, was also initiated. The IPCP continued the advancement of topical microbicide delivery vehicles and products. Products advanced included vaginal films for tenofovir and dapivirine, a gel for use in both the vagina and rectum (DuoGel) in women, and a novel IVR delivering an inactive form of tenofovir that later becomes active in the body. Future clinical testing will be done with plant-produced HIV/HSV (herpes simplex virus) broadly neutralizing antibodies and the HIV entry inhibitor Griffithsin, and IVRs delivering Truvada. Investigators also completed additional clinical studies on the DuoGel and Truvada-delivering IVR, which used a behavioral framework to assess users' perception of good and bad attributes of a product to guide modification of the delivery vehicle and increase potential acceptability/adherence. Finally, the Comprehensive Resources for HIV Topical Microbicides and Biomedical Prevention contract, in collaboration with Merck, enabled clinical testing (MTN-027 and -028) of an IVR, based on the NuvaRing platform to deliver the CCR5 inhibitor vicriviroc and the integrase inhibitor MK2048.

Scientific Advance

Statistical Method Shows Relationships Between Tissue Drug Concentrations and Effectiveness of an Anti-HIV Microbicide. Researchers funded by NIAID created a new statistical model that allowed further analysis of data from an early-phase safety study of the vaginally formulated UC781 gel as a rectal microbicide to prevent HIV acquisition. This new statistical method allowed researchers to determine specific relationships between tissue drug concentrations and the effectiveness of UC781 in a biopsy challenge model, which tests the ability of HIV to infect small samples (biopsies) of rectal tissue from patients. This work provided the first estimate of the concentration of drug in a gel that might be required to prevent HIV transmission and identified the biopsy challenge model as a potential bridge to link drug concentration in tissues with possible efficacy (Richardson-Harman, Mauck, McGowan, & Anton, 2012).

Prevention of Mother-to-Child Transmission of HIV

According to the World Health Organization (WHO), the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most of this mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund and WHO recommend that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe replacement feeding should be exclusively breast-fed for at least 6 months. NIAID is conducting studies for prevention of mother-to-child transmission (PMTCT) in HIV-infected pregnant women. NIAID-sponsored PMTCT research focuses on the following goals:

- Define the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant as well as risks for disease progression within the framework of clinical studies and trials.
- Develop and test additional ARV strategies for PMTCT of HIV infection through clinical trials in the United States and international settings.
- Develop interventions for PMTCT of HIV via breast milk in settings where breastfeeding is the best assurance for infant nutrition.

International Maternal Pediatric Adolescent AIDS Clinical Trials Group

IMPAACT, sponsored by NIAID and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, is a network dedicated to significantly decreasing the mortality and illness associated with HIV disease in children, adolescents, and pregnant women. IMPAACT develops and evaluates safe, cost-effective approaches for interrupting mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treating and preventing co-infections and illnesses associated with HIV; and evaluates vaccines for preventing HIV sexual transmission among adolescents. More information is available at http://impaactnetwork.org.

Scientific Advance

A Protein in Breast Milk Inhibits HIV Transmission from Mothers to Their Infants. To achieve an AIDS-free generation, strategies that prevent the transmission of HIV from mother to child after birth are critical, particularly in developing countries. Surprisingly, more than 90 percent of children breastfed from HIV-infected mothers do not contract HIV. NIAID-funded researchers identified a specific protein in breast milk, called Tenascin-C, which neutralizes HIV. Researchers believe that the anti-HIV properties of Tenascin-C contribute to protecting infants against infection. This knowledge about protective proteins in breast milk could be used to develop new safe and effective treatments to prevent postnatal MTCT and other types of HIV transmission (Fouda et al., 2013).

Clinical Trial

Promoting Maternal-Infant Survival Everywhere (PROMISE) Study. This large, multinational clinical trial, begun in 2010, was designed to determine how best to reduce MTCT during pregnancy and breastfeeding and preserve maternal health during and after pregnancy and breastfeeding. The study is now fully enrolled, and the mothers and infants are in follow-up. Study participants were recruited from as many as 18 countries whose levels of resources range from high to low. One component of the study found that for HIV-infected women in good immune health, taking a three-drug regimen during pregnancy

prevents MTCT more effectively than taking one drug during pregnancy, another during labor, and two more after giving birth. The findings were reported during a scheduled interim review and support the recommendation by the WHO and most countries to provide a three-drug regimen to all pregnant women with HIV infection. The study concluded that there was a significantly lower rate of MTCT among those women who received a three-drug combination. Treatment with a combination containing the drug lamivudine resulted in fewer infant deaths in the first 2 weeks of life and fewer very premature deliveries compared to treatment with another triple-drug combination.

Vaccine Research

Vaccines are the foundation of preventive measures to curtail infectious disease epidemics. NIAID conducts and supports basic research in areas such as infectious diseases, microbiology, and immunology to generate the knowledge essential for developing safe and effective vaccines to prevent HIV infection. The findings from the RV144 HIV vaccine efficacy trial in Thailand, which showed that a candidate vaccine was partially effective at preventing HIV infection, have provided renewed energy in the field. NIAID is building on this achievement through a sustained commitment to pursuing both basic and vaccine discovery research while continuing to advance the most promising HIV vaccine candidates into testing. Even a partially effective HIV vaccine could have a significant positive impact on the health of women, particularly in resource-limited settings.

HIV Vaccine Trials Network

The HVTN is an international collaboration of scientists searching for an effective and safe HIV vaccine. The HVTN's mission is to facilitate the process of testing preventive vaccines against HIV/AIDS, conducting all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. Studies conducted by the HVTN enroll both men and women, and data are analyzed for gender differences with regard to safety, tolerability, and immune responses. More information is available at http://www.hvtn.org.

Other Prevention Research—HIV Prevention Trials Network

Established in 2000, HPTN is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy primarily of non-vaccine interventions designed to prevent the transmission of HIV. The HPTN research agenda focuses on the use of ARV therapy; treatment and prevention of STIs; treatment of substance abuse, particularly injection drug use; behavioral risk reduction interventions; and integrated combination strategies to reduce HIV transmission and acquisition. HPTN studies are conducted in various populations, including women, and in geographical regions that bear a disproportionate burden of HIV infection. More information on HPTN is available at http://www.hptn.org.

Science Advances

Multifaceted Approach Could Help Estimate HIV Incidence. Reliable and cost-effective methods to estimate HIV incidence help monitor the epidemic, identify at-risk populations, and evaluate prevention strategies. NIAID-supported scientists compared three methods for estimating the HIV incidence rate in more than 2,000 women enrolled in the HPTN 064 study. They found that the annual HIV incidence estimate based on acute infection at enrollment was tenfold higher than the incidence estimate based on the time when participants developed an immune response to HIV, or on a new method that uses an algorithm that combines the results of several lab tests. This preliminary evidence suggests that the new approach, which provided a more comprehensive assessment of HIV incidence in the study cohort than an assessment based solely on HIV seroconversion, could be useful in estimating HIV incidence (Eshleman et al., 2013).

Risk Factors for HIV Acquisition Among Women from Selected Areas of the United States. An NIAID-funded study evaluated HIV incidence and described behaviors for up to 12 months among U.S. women living in communities with high HIV prevalence and high poverty rates. Among 2,099 high-risk women aged 18–44 years (85.9 percent Black and 11.7 percent of Hispanic ethnicity), 32 were diagnosed with HIV infection at the time of enrollment. The annual incidence of HIV was 0.32 percent. Older age, substance use, and having an HIV-infected partner were associated with high HIV prevalence. This study enrolled a

cohort of women with a substantially higher HIV incidence rate than the national estimate in the general population of U.S. Black women (Hodder et al., 2013).

Clinical Trials

HPTN 068: Effects of Cash Transfer for the Prevention of HIV in Young South African Women. This phase III, randomized trial will determine whether providing cash transfers to young women and their household, conditional on school attendance, reduces young women's risk of acquiring HIV. More than 2,400 South African HIV-uninfected young women (ages 13–20 years) attending grades 8–11 and living in approximately 24 villages were enrolled. The final interviews are nearly complete. Results are expected in 2015.

HPTN 069: Novel Exploration of Therapeutics for PrEP. NEXT PrEP is a multisite, randomized, double-blind clinical trial of the safety and tolerability of four ARV drug regimens that could be used for PrEP: maraviroc (MVC) alone, MVC and emtricitabine, MVC and tenofovir, and tenofovir and emtricitabine. This study has enrolled approximately 400 HIV-uninfected men who have sex with men (MSM) and 200 HIV-uninfected women who engage in high-risk sexual behaviors. Objectives of the study, which is cofunded by ACTG and includes some ACTG sites, include assessing the pharmacokinetics and tissue penetration of the drugs into rectal, vaginal, and cervical tissues. The study participants are currently in follow-up.

Therapeutics Research

AIDS Clinical Trials Group

Established in 1987, ACTG is a multicenter clinical trials network that conducts translational and therapeutics research in the United States and internationally. Research priorities include translational research and optimizing the clinical management of HIV/AIDS, including HIV-related co-infections and diseases. In collaboration with other clinical trials networks, ACTG also pursues research and development of therapeutic vaccines and research on HIV treatment in pregnant women. More information is available at http://actgnetwork.org.

Scientific Advances

HIV-Infected South African Adults Who Start Antiretroviral Therapy (ART) Early Have Near-Normal Life Expectancies. Few studies exist of the life expectancy of HIV-infected individuals receiving ART in low- and middle-income countries. To address this issue, NIAID-supported investigators used data from South African populations undergoing ART for the first time. The most significant factors determining the life expectancy of treated patients were CD4 count and age at ART initiation, with longer life expectancies for those who started treatment at a younger age. In addition, they found that the average life expectancy of HIV-infected South African women starting therapy between the ages of 20 and 60 was significantly higher than that of the corresponding group of HIV-infected men. This study suggests that HIV-infected individuals in South Africa could have near-normal life spans, provided that they start ART before their CD4 count drops below 200 (Johnson et al., 2013).

Outcomes by Sex Following Treatment Initiation with Atazanavir Plus Ritonavir or Efavirenz with Abacavir/Lamivudine or Tenofovir/Emtricitabine. NIAID-funded researchers evaluated sex differences in treatment responses to initial antiretroviral regimens with atazanavir plus ritonavir (ATV/r) or efavirenz (EFV). They enrolled 1,857 HIV-infected, treatment-naive persons in a randomized trial of open-label ATV/r or EFV combined with the nucleoside reverse transcriptase inhibitors (NRTI) abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC). Women assigned to ATV/r had a higher risk of virologic failure with either NTRI-containing regimen than women assigned to EFV, or men assigned to ATV/r. The effects of ATV/r and EFV on safety and tolerability risk did not differ significantly by sex. With ABC/3TC, women had a significantly higher (32 percent) safety risk compared to men; with TDF/FTC, the safety risk was 20 percent larger for women than for men, but this difference was not statistically significant. Women had slower ATV clearance and higher predose levels of ATV compared with men. Self-reported adherence did not differ significantly by sex. This is the first randomized clinical trial to identify a significantly earlier time to virologic failure in women treated with ATV/r compared with EFV. This finding has important clinical implications given that boosted protease

inhibitors such as ATV/r are often favored over EFV in women of childbearing potential (Smith et al., 2014).

Clinical Trials

Optimizing Treatment for Treatment-Experienced HIV-Infected People. This phase IV study (A5241) was designed to determine whether there is a benefit of adding NRTIs when HIV-infected individuals start on a new anti-HIV drug regimen. Twenty-two percent of study participants were women, which will allow investigators to analyze outcomes specifically in women. All follow-up visits with study participants were completed in FY 2013 and investigators are analyzing the data.

Osteoporosis in HIV-Infected Postmenopausal Women. This ongoing observational study is examining the impact of traditional risk factors for osteoporosis, as well as the impact of HIV infection and ARV therapy, on the prevalence of osteoporosis and the rate of bone loss in HIV-infected postmenopausal African-American and Hispanic women.

Promoting Maternal-Infant Survival Everywhere (PROMISE) Study. (See listing in "Prevention of Mother-to-Child Transmission of HIV" section.) Some of the maternal health components of this study are being conducted in settings where HAART is the standard of care during pregnancy and women do not typically breast-feed. This maternal health component is seeking to determine the best strategy for treating new mothers who have CD4 T-cell counts greater than 400 (that is, have not progressed to AIDS).

The Effect of Vitamin D Repletion on Postmenopausal Women with HIV. This study, which is currently enrolling patients, will examine the effects of vitamin D supplementation on bone turnover, rates of bone loss, and indices of immune function in HIV-infected postmenopausal African-American and Hispanic women. Previous research revealed that low vitamin D levels are common in this population. The study will follow 100 women to determine the change in bone mineral density over 1 year. As other research has suggested that HIV-positive women have higher rates of bone loss than HIV-negative women, vitamin D therapy may help prevent complications of bone loss, particularly bone fractures.

Centers for AIDS Research (CFAR)

The CFAR is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot easily be funded by other mechanisms. There are currently 18 CFARs (16 standard and 2 developmental) located at academic and research institutions throughout the United States. Several of them are actively supporting research activities in women. In 2013–2014, nine CFARs supported 14 women's health pilot projects through the CFAR Developmental Cores.

In addition, the Inter-CFAR Collaboration on HIV Research in Women is a network of CFAR investigators dedicated to promoting cutting-edge HIV research in women. The collaboration develops new strategies for future research to address HIV-related issues unique to women and promotes career development and professional growth among junior investigators interested in this field.

The Lifespan/Tufts/Brown CFAR has an HIV in Women & Underserved Populations Core that encourages and assists CFAR investigators to develop studies related to HIV and women covering a broad range of areas; assists in the submission of developmental grant applications and independent grant applications related to HIV and women; provides resources instrumental in the collection, cataloging, and maintenance of a repository of blood and genital tract secretions; provides training in genital tract collection for virologic and immunologic studies; and assists in the recruitment of women researchers in the area of HIV/AIDS research. More information on the HIV in Women & Underserved Populations Core is available here: http://www.ltbcfar.org/women.html. More information on CFAR is available at http://www3.niaid.nih.gov/research/cfar.

Infectious Diseases Other than HIV/AIDS

Many infectious diseases, including STIs such as HPV, are critical global and national health priorities. These diseases can have a devastating impact on women, with the potential for causing long-term health problems. For example, many diseases can cause pregnancy loss at any stage, problems with the development of the fetus, or complications for the newborn.

Malaria

Pregnancy-associated malaria (PAM), or placental malaria, is associated with low birth weight, maternal anemia, and gestational hypertension, and is a major cause of death and disease for women and their children in sub-Saharan Africa. Both inflammation and the fetal response to infection with the malaria parasite *Plasmodium falciparum* may contribute to these poor outcomes. PAM is caused by infected red blood cells that stick to a type of sugar molecule (chondroitin sulfate A, or CSA) in the placenta, leading to sometimes heavy accumulations of parasites in the placenta. Because women have no immunity to CSA-binding parasites before their first pregnancy, first-time mothers are most susceptible. Although the fetus is not usually infected by the parasite, exposure to PAM in the uterus can increase a child's susceptibility to malaria during early life for reasons that are not yet clear.

Clinical Study

NIAID intramural scientists have created the Pregnancy Malaria Immunology, Pathogenesis, and Vaccine Development initiative. Clinical and laboratory investigations for this project aim to determine factors associated with malaria in pregnant women and young children. These studies are informing intramural scientists' efforts to develop a PAM vaccine.

Scientific Advances

Preventive Treatment Strategy in Pregnant Women Is Associated with Higher Malaria Risk for Their Children. Intermittent treatment with a drug combination called sulfadoxine-pyrimethamine has been used to prevent many harmful consequences of malaria infection during pregnancy. However, it fails to prevent PAM, a common complication of malaria in pregnancy, in areas of the world where resistance to these drugs is widespread. A longitudinal study in Tanzania led by NIAID researchers demonstrated for the first time that this treatment strategy was associated with a higher risk of malaria infection and severe malarial disease in children born to women who had placental malaria. The findings could have important implications for malaria control efforts worldwide (Harrington, Morrison, Fried, & Duffy, 2013).

Narrowing the Field of Anti-Malaria Targets. NIAID intramural investigators recently shed light on acquired immunity to PAM in mothers and their unborn children and infants. Clinical immunity to PAM is attributed to antibodies that recognize the *P. falciparum* protein VAR2CSA on the infected red blood cell surface, but there has been no consensus on which of VAR2CSA's six Duffy binding-like (DBL) domains would be most effective in eliciting immunity if used in a vaccine. These investigators have provided the first evidence that in *P. falciparum*-exposed women who have had multiple pregnancies the DBL2 , DBL3 , and DBL5 domains are targeted by antibody opsonization. This is highly significant as antibody opsonization is the process by which a pathogen is marked for ingestion and destruction by white blood cells called phagocytes. This discovery reveals key information for developing effective preventive and therapeutic approaches for PAM and potentially other infectious diseases (Lambert et al., 2014).

How the Link Between Lupus and Malaria Benefits Women. NIAID intramural scientists have determined that genetic susceptibility to SLE (lupus)-like disease in mice confers a selective advantage for resistance to lethal cerebral malaria (malaria affecting the brain). Their follow-up work in SLE-prone mice showed that genetic susceptibility to lupus is not protective against placental malaria but has a net positive effect on fitness, as it can decrease mortality due to severe malaria and boost reproductive fitness by increasing the total number of fetuses. These results further support the hypothesis that genetic susceptibility to SLE is protective against severe malaria (Waisberg et al., 2013).

Schistosomiasis

Schistosomiasis, also known as bilharzia, is a disease caused by the parasitic worms *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. Although schistosomiasis is not found in the United States, more than 200 million people are infected worldwide. Observational studies suggest that pregnant women infected with schistosomiasis deliver babies with lower birth weight than uninfected women and tend to have poorer pregnancy outcomes.

Clinical Trial

A Randomized Clinical Trial to Evaluate Treatment of Schistosomiasis During Pregnancy. This clinical trial in

the Philippines is assessing whether treating women who have schistosomiasis in the second trimester of pregnancy is safe and whether it increases the birth weight of the newborn.

Chagas Disease

Chagas disease is caused by infection with *Trypanosoma cruzi*, a parasite prevalent in Latin America, which is transmitted by the bite of a type of insect called a triatomine bug. CDC estimates that more than 300,000 people with *T. cruzi* infection, mainly immigrants, live in the United States. About one-third of people infected by the parasite develop serious cardiac or intestinal complications, often decades after the initial infection. Some pregnant women infected with *T. cruzi* transmit the infection to the fetus during pregnancy.

Clinical Trial

Congenital Transmission of *Trypanosoma cruzi*. An NIAID-supported project is enrolling *T. cruzi*-infected pregnant women in Mexico, Honduras, and Argentina to evaluate whether congenital transmission from mother to fetus is influenced by the evolutionary lineage of the infecting parasite. Better understanding of the epidemiology of *T. cruzi* congenital infection is a crucial step toward the potential development of screening and early treatment programs for use in Mexico and Central America, as well as in the United States.

Foodborne Pathogens

Infectious diseases spread through food or beverages are a common, distressing, and sometimes life-threatening problem for millions of people in the United States and around the world. CDC estimates that each year in the United States, one in six Americans (or 48 million people) gets sick, 128,000 are hospitalized, and 3,000 die of foodborne diseases. Pregnant women are at high risk for foodborne infections such as those caused by *Salmonella* or *Listeria* bacteria. These infections can lead to miscarriage, stillbirth, premature delivery, or infection in newborns.

Scientific Advance

New Insights on Vaccination Before Conception for *Listeria monocytogenes*. Pregnant women are unusually vulnerable to infection with the foodborne bacterium *L. monocytogenes* (Lm), with often deadly consequences for the developing fetus. Vaccination of women before conception has been shown to protect pregnant women and their babies from a wide range of infections. This NIAID-funded study examined whether vaccination for Lm before conception protected against subsequent infection by virulent Lm in pregnant mice. The results showed that even though protective Lm-specific immune cells were generated, susceptibility to Lm during pregnancy could not be overcome when researchers mated mice of two different genetic strains. By contrast, vaccination was effective when the parent mice (and thus the mother and fetus) were of the same strain. These findings show that maternal-fetal genetic differences dictate the ineffectiveness of preconception vaccination against fetal complications, and provide new clues on how physiological shifts during pregnancy regulate immune responsiveness (Clark et al., 2014).

Influenza

Each year, seasonal influenza kills between 3,000 and 49,000 Americans and hospitalizes as many as 200,000. Pandemic influenza can produce even greater devastation. NIAID funds basic research on the immune response to influenza vaccination in women and men, and a Maternal Immunization Program to support studies and clinical trials that evaluate the safety and efficacy of vaccines to prevent or treat infectious diseases in women and their babies. Two influenza vaccine studies (described below) are ongoing.

Scientific Advance

Testosterone Suppresses Response to Influenza Vaccination. Females often have more robust immune responses to infection and vaccination than males. However, the exact mechanisms behind these differences in response have not been defined. Using a systems biology approach, NIAID-funded researchers assessed the immune response of a cohort of males and females vaccinated with a seasonal influenza vaccine and found that women produced more neutralizing antibodies and inflammatory cytokines compared with men. These effects could be linked to a cluster of lipid metabolism genes that may be controlled by the male hormone testosterone. Men with high testosterone levels and elevated expression of this gene cluster exhibited a lower immune response to influenza vaccination compared with women, or with men with low testosterone. The

results suggest that male hormones may modulate immune responses to vaccines by altering expression of specific genes (Furman et al., 2014).

Clinical Trials

Post Partum Immunization with Live Attenuated Influenza Vaccine (LAIV) or Trivalent Influenza Vaccine (TIV) in Post Partum Breastfeeding Women. This study (09-0007) evaluated the safety of two different influenza vaccines in breastfeeding mothers and their infants. The study also investigated differences in breast milk antibody immune responses against influenza between the two vaccines. The study was successfully completed during two influenza seasons (2011–2012 and 2012–2013), enrolling 248 pairs of post partum women and their babies. Preliminary safety data suggest that both vaccines are safe to be administered in post partum breastfeeding women. Further outcome information is available at http://www.clinicaltrials.gov/ct2/show/NCT01181323.

A Randomized, Double-Blind Trial on the Safety and Immunogenicity of Seasonal 2010–2011 Inactivated TIV in Pregnant Women (09-0005). This study evaluated safety and antibody production that results from a single intramuscular injection of the 2010–2011 inactivated TIV in women during the second or third trimester of pregnancy. The study was successfully completed, having enrolled 139 pregnant women and 44 nonpregnant women during the 2010–2011 influenza season. Preliminary safety data suggest that the vaccine is safe and produces an immune response in pregnant women. Further outcome information is available at http://www.clinicaltrials.gov/ct2/show/NCT01173211.

Human Papillomavirus

HPV is the most common STI. Persistent infection with certain strains of HPV can lead to cervical cancer, which is one of the most common cancers in women worldwide. Other strains of HPV cause genital warts, benign tumors of the respiratory tract, and cutaneous warts. These lesions can be especially problematic in individuals whose immune systems are compromised by HIV infection or drugs given after organ transplantation. Two vaccines, Gardasil and Cervarix, are licensed for the prevention of genital warts and cervical cancer due to HPV.

Clinical Trials

Clinical Studies of HPV in HIV-Infected Females (A5298). Researchers are evaluating the safety and efficacy of the HPV vaccine to prevent anal HPV infection in HIV-infected women. In addition, the study is comparing two different strategies to prevent advanced cervical cancer in women infected with HIV.

Frequent Detection of HPV in HIV-Infected Women in Uganda. A team led by researchers from NIAID and their colleagues examined the frequency of cervical HPV detection among HIV-infected women in a resource-limited setting in Uganda. The women were followed monthly for 6 months before and after initiation of ART. The researchers did not observe an effect of ART on monthly HPV detection, even if the women's immune systems became healthier or HIV replication was suppressed. They found that only older age and higher pre-ART numbers of CD4 T cells, which are immune cells targeted by HIV, were associated with a significantly lower risk of detecting HPV. The results highlight the importance of continued and consistent screening for HPV, even after starting ART (Rositch et al., 2013).

Herpes Simplex Virus

Herpes simplex virus type 2 (HSV-2) is a common STI and a major cause of genital ulcers worldwide.

Scientific Advances

Development of Genital Ulcers and Reactivation of Herpes Simplex Virus in HIV-Infected Women After Starting Antiretroviral Therapy. To understand the relationship between starting HIV treatment and developing genital ulcers and/or reactivating an inactive herpes infection, NIAID researchers and their colleagues studied two groups of women from Rakai, Uganda, who were co-infected with HIV and HSV-2. After the initiation of ART for HIV, the prevalence of both genital ulcers and reactivation of herpes infection increased significantly among study participants. This may have been due to an inflammatory syndrome that occurs when the immune system overreacts to a microbe following ART. Treatment with the antiviral drug acyclovir reduced genital ulcers and evidence of herpes virus reactivation in the study patients, suggesting that it should be considered as a way to mitigate

these effects following the start of ART in HIV-infected individuals (Tobian et al., 2013).

Experimental Vaccine Strategy Shows Promise Against Genital Herpes. This NIAID-funded study used a mouse model to develop a novel vaccination strategy against HSV-2 that relies on T-cell activation rather than neutralizing antibody production. Known as "prime and pull," the first step is a conventional vaccination to activate T cells throughout the body (prime). This is followed by the application of a small molecule to the genital area, which draws in the activated T cells (pull). These cells establish a niche in the tissue and are ready to provide protection against future infection (Shin & Iwasaki, 2012).

Mycoplasma genitalium

Mycoplasma genitalium is an STI associated with inflammation of the reproductive system. Among women, the worldwide prevalence of *M. genitalium* infection is approximately 1–5 percent. Previous studies have shown that circumcision reduced men's risk of acquiring *M. genitalium*.

Clinical Trial

Male Circumcision Does Not Protect Female Partners from *Mycoplasma genitalium*. NIAID intramural researchers conducted a clinical trial in Uganda to determine whether circumcision would also protect female partners of circumcised men. They found that male circumcision did not protect female partners from *M. genitalium* infection. The researchers suggested that multiple factors may have contributed to the study results. For example, female partners may have engaged in outside relationships, or circumcision may not have affected the infected genital areas of men, such as the urethra (Tobian et al., 2014).

Hepatitis E (HEV)

HEV is a major cause of hepatitis in much of the developing world and is increasingly identified as a cause of hepatitis in industrialized countries. Although most infections go undiagnosed and are self-limited, 10–25 percent fatality rates have been reported among HEV-infected pregnant women, as well as an increased risk of stillbirth and other adverse pregnancy outcomes.

Clinical Trial

Incidence and Natural History of Hepatitis E Virus in Pregnant Bangladeshi Women. This prospective, population-based study aims to determine the disease burden and consequences of infection and to study the immunopathogenesis of HEV in 10,000 pregnant women and their newborn infants in South Asia. This research will establish the foundation for population-level interventions (for example, vaccines) to improve maternal and infant survival in resource-poor settings.

Tuberculosis (TB)

An ancient disease, TB remains one of the major causes of disability and death worldwide. In 2010, an estimated 8.8 million people fell ill with TB, including 1.1 million cases among people living with HIV.

Scientific Advance

Men and Women Regain Weight Differently After Successful Treatment of Tuberculosis. Nutritional changes during and after TB treatment have not been well described. As part of a study conducted through the NIAID-funded Tuberculosis Research Unit, investigators studied how men and women recover weight during and after TB therapy. They evaluated 717 adult patients at 3, 12, and 24 months in a prospective cohort in Uganda to determine changes in body mass index and height-normalized indices of lean tissue and fat mass. The study found that although Ugandan patients with wasting, one of the hallmarks of TB disease, regained weight during treatment, the type of gain differs by gender and patients may remain underweight after the initial phase of therapy (Mupere et al., 2014).

Nontuberculous Mycobacterial Infections

Mycobacteria can cause a lung infection known as pulmonary nontuberculous mycobacterial (PNTM) disease.

Scientific Advance

Insights on the Increased Prevalence of Pulmonary Nontuberculous Mycobacterial Infections in Older Women. PNTM prevalence has risen in recent decades, especially in older women, despite their lack of any apparent immunological problems. Individuals can be predisposed to PNTM, however, if they have conditions that lead to lung damage or to impaired self-clearing mechanisms of the

human respiratory tract. NIAID investigators compared the functioning of the epithelial cells that line and clear airways in PNTM patients and in healthy subjects. They found defective epithelial cell function in PNTM patients but not in healthy individuals. In tissue samples from PNTM patients, the researchers could selectively return these defects to normal using treatments approved for unrelated conditions (e.g., impotence). The results suggest that a therapeutic approach targeting the underlying mechanisms that make people susceptible to PNTM may be readily evaluated clinically (Fowler et al., 2013).

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effects on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune and other immune-mediated diseases, prevent rejection of transplanted organs in women, and prevent the immunologic causes of infertility.

Asthma

Asthma is a severe and chronic disease that causes wheezing, breathlessness, chest tightness, and coughing. It affects more than 230 million people worldwide, including more than 18 million adults and 7 million children in the United States.

Scientific Advances

Sex Hormones and Other Factors that Affect Asthma Prevalence in Adolescent Girls. Development of asthma is influenced by both genetic and environmental factors. The prevalence of asthma in girls increases after puberty, and previous studies have identified an association between asthma and sex hormones—both those produced by the body and those in medications. In this study, NIAID-supported researchers identified a process by which sex hormones lead to modifications of the gene GATA3, which in turn regulates the Th2 immune response associated with asthma. This process was influenced by both oral contraceptive use and a woman's age at first menstrual cycle, revealing a pathway that may explain how sex hormones in women can increase asthma prevalence after puberty (Guthikonda et al., 2014). To determine the genetic factors and processes that influence asthma incidence in adolescent females, this team of investigators analyzed how the process of DNA methylation of genes in the Th2 pathway affects asthma risk in girls 10–18 years of age. DNA methylation alters gene activity while leaving the underlying genetic code unchanged. The results show that interaction between DNA methylation and genetic sequence variations in genes of the Th2 pathway likely contributes to asthma risk in girls. Furthermore, this effect may vary with age, which may influence asthma during the transition from childhood to adulthood (Zhang et al., 2014).

A Genome-Wide Study of Sex-Specific Asthma Risk Genes. Whereas genes on the human sex chromosomes are known to contribute to differences in disease prevalence and risk, the effect of genes from autosomal (non-sex) chromosomes on these differences has not been as well studied. NIAID-funded researchers searched for sex-specific asthma risk genes through a genome-wide scan for interactions between autosomal genes and male or female physiological factors. The researchers studied a group of ethnically diverse individuals of European American, African-American, African-Caribbean, and Latino ancestries. The study identified six sex-specific chromosome regions, or loci, associated with asthma risk, all of which were connected with specific ancestries. One chromosome region, the interferon regulatory factor 1 (*IRF1*) locus, contains a gene that has a known role in immune pathways involved in asthma. These findings, along with prior reports of sex-specific differences in interferon responses, suggest that the *IRF1* locus is a strong candidate for contributing to male-specific asthma risk (Myers et al., 2014).

Maternal Diet May Reduce Childhood Allergy and Asthma. In the United States, food allergy and asthma occur in approximately 5 percent and 8.4 percent of people, respectively. Maternal diet during pregnancy has long been suspected to play a role in the development of childhood allergy and asthma, but previous study results have been conflicting. Unlike previous analyses that focused on late pregnancy, this NIAID-supported study examined the effect of maternal diet during the first two trimesters of pregnancy on the development of childhood asthma and allergy. The results showed that higher maternal intake of peanut, milk, and wheat during early pregnancy was associated with reduced odds of mid-childhood allergy and asthma, suggesting that eating these foods during

pregnancy could help curb the rising incidence of asthma and allergy in the United States (Bunyavanich et al., 2014).

Mucosal Immunology

Immune defense mechanisms and immune regulation at mucosal surfaces including the respiratory, gastrointestinal, and urogenital mucosa are one of the first barriers against infection.

Scientific Advances

Local Immunological Memory in Vaginal Tissue Leads to Improved Protection from STIs. Long-term immunity to infectious diseases relies on the immune system's ability to recognize previously encountered pathogens during reinfections. This immunological memory is facilitated in part by specific components of the immune system called memory T cells. Generated during a prior infection, these cells are ever ready to mount a rapid and powerful response to reinfections. Originally thought to reside only in circulatory systems such as blood, recent studies identified resident memory T cells (Trm) that remain in specific tissues where the infection was first encountered. In this study, vaginal infection of mice with HSV led to the generation of local Trm that provided better protection against HSV than did circulatory memory T cells. These results suggest that alternative vaccine strategies for STIs may result in improved disease prevention in women (Iijima & Iwasaki, 2014).

Insights on the Human Vaginal Immune Response in Health and Disease. The human vaginal mucosa is a major entry site for sexually transmitted pathogens, but the immunological responses within the vagina are poorly understood. NIAID-supported researchers demonstrated that the earliest immune responses in the human vagina can be orchestrated by activation of four different immune cell types. Each cell type then directs the production of different T cells that provide protective immune responses. These results provide insights that may lead to the design and development of effective mucosal vaccines against many STIs (Duluc et al., 2013).

Vaccine Development

Scientific Advance

Modeling Distinct Purine Metabolism to Inform Vaccine Development. This study is using human blood components to model immune responses of male and female newborns and infants to vaccines and adjuvants. Characterizing the impact of sex on vaccine responses will help optimize immunization of both female and male newborns. Although sex-specific differences have not yet been reported, this NIAID-funded study showed that, compared with adults, newborns have elevated blood levels of a natural anti-inflammatory compound called adenosine, which may affect their immunological function. The impaired production of proinflammatory cytokines (proteins that regulate immune function) in response to elevated levels of adenosine may contribute to impaired responses to vaccines and infections in newborns (Pettengill et al., 2013).

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own ("self") organs, tissues, and cells. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, celiac disease, systemic lupus erythematosus, and inflammatory bowel disease. Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women. NIAID supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs.

Scientific Advance

Progesterone Promotes the Stability of Immune Cells With Therapeutic Potential. Regulatory T cells (Tregs) actively suppress activation of the immune system and prevent inflammation. A subset of Tregs, known as induced T-regulatory (iTreg) cells, are difficult to study because they are unstable. Using animal models, NIAID-funded investigators found that progesterone, a female hormone, can generate highly stable iTreg cells that are efficient in suppressing tissue inflammation. These results show

therapeutic promise for autoimmune diseases such as multiple sclerosis and inflammatory bowel disease (Lee, Lydon, & Kim, 2012).

Systemic Lupus Erythematosus

SLE, more commonly known as lupus, is an autoimmune disease. Inflammation caused by lupus can affect many body systems, including the central nervous system, joints, skin, kidneys, blood cells, heart, and lungs. Approximately 322,000 Americans are diagnosed with, or suspected of having, SLE. Ninety percent of people with lupus are women, and generally the age of onset is between 15 years and 45 years. Lupus is more common in Black, Hispanic, Native American, and Asian women than in White women.

Scientific Advances

New Insights on the Control of Autoimmune Antibody Production and Inflammation in Lupus. People with SLE produce abnormal antibodies (autoantibodies) that target DNA and RNA from the body's own cells, contributing to inflammation. Autoantibody production is controlled in part via signals transmitted by two different receptor molecules, TLR7 and TLR9, which are found in various types of immune cells. Through genetic manipulation in mouse models of lupus, NIAID-funded investigators found that TLR7- and TLR9-mediated signaling in immune cells called B cells have opposing effects on inflammation and on the types of autoantibodies produced. These findings stress the critical importance of dysregulated TLR signaling in B cells in the development of SLE (Jackson et al., 2014).

Mitochondrial Receptor Involved in Lupus Pathogenesis. SLE is also marked by abnormalities in immune cells called T cells, including the abnormal processing of signals that trigger cell death. Cellular compartments called mitochondria, which contribute to cell death, are dysfunctional in T cells from people with SLE. A mitochondrial protein known as mTOR is a sensor of mitochondrial dysfunction but its role in autoimmunity, including SLE, remains unclear. To answer this question, NIAID-supported researchers evaluated mitochondrial function and mTOR activity in T cells from healthy individuals and from lupus patients during disease flares and remissions. They found that activation of mTOR causes abnormal cell death and predicts disease flares in people with lupus, pointing to mTOR as a possible target for new SLE therapies (Lai et al., 2013).

Crohn's Disease

Crohn's disease is a form of inflammatory bowel disease that affects women with increased severity and at a higher rate than men.

Scientific Advance

Loss of Estrogen-Mediated Immune Response Makes Females More Susceptible to Crohn's Disease. To investigate possible mechanisms for the gender disparity in Crohn's disease, NIAID-funded researchers studied a strain of mice known as SAMP mice that spontaneously develop chronic intestinal inflammation resembling human Crohn's disease, with a similar disparity between females and males. They found that Treg cells, which are known to modulate immune responses, were reduced in frequency and activity in female mice compared with male mice. Male SAMP mice treated with estrogen responded by increasing Tregs that reduced Crohn's-like symptoms, whereas females were resistant to the effect of estrogen. Further studies showed that estrogen signaling in female mice is disrupted at the receptor level and leads to fewer protective Treg cells. These findings suggest that therapies designed to enhance protective estrogen-mediated signaling in Tregs may be beneficial for treating chronic inflammatory disorders such as Crohn's disease (Goodman et al., 2014).

Multiple Sclerosis (MS)

MS, an inflammatory disease of the central nervous system, is the leading cause of neurologic disability among young adults, causing visual disturbances, muscle weakness, and loss of coordination. Severe, progressive cases can result in partial or complete paralysis. MS affects about 400,000 Americans, and women are affected about twice as frequently than men.

Scientific Advance

Identifying the Cellular Culprits in Multiple Sclerosis. MS occurs when T cells mistakenly attack the myelin sheath that insulates nerve fibers within the brain and spinal cord. However, the specific factors that lead to this T-cell response against nerves remain unclear. NIAID-funded researchers demonstrated that, during disease development

in an animal model of MS, T cells are recruited and can become "activated" in response to specific types of immune cells and other cells in the brain and spinal cord. These activated T cells release chemicals and exert functions that affect the development of MS-like disease. Identifying the cells and pathways controlling T-cell function in MS could help researchers develop treatments and strategies to fight the debilitating effects of this disease (Ji, Castelli, & Goverman, 2013).

Systemic Sclerosis (Scleroderma)

Scleroderma is a group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much of the fibrous protein collagen. Systemic sclerosis is the form of the disease that not only includes the skin but also involves the tissues beneath the skin, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women—especially middle-aged women and African-American women—are affected more than men.

Clinical Trial

The **Scleroderma: Cyclophosphamide or Transplantation** study is comparing the safety and potential usefulness for scleroderma of high doses of drugs to suppress the immune system followed by transplantation of immune system stem cells versus monthly high doses of the immunosuppressive drug cyclophosphamide. The hypothesis is that high-dose immunosuppressive therapy will destroy the malfunctioning immune system and replacement with immature immune cells will permit the development of a healthy immune system, inducing a long-term remission or even eradication of the disease. High doses of cyclophosphamide may reduce symptoms more effectively than the standard low-dose therapy. The enrollment and treatment phases of the trial are complete and follow-up is ongoing. More information is available at http://www.sclerodermatrial.org.

The Microbiome and Autoimmunity

Microbes inhabit just about every part of the human body. Sometimes they cause sickness, but most of the time microorganisms live in harmony with their human hosts, providing vital functions essential for human survival. NIAID participates in the NIH Human Microbiome Project, which is mapping the microbial makeup, or microbiome, of humans to better understand the role of microbes in health and disease. Some NIAID projects study how the microbiome influences immune responses.

Scientific Advance

Microbiota Plays a Role in Autoimmune Disease Gender Differences. It is well established that women are at higher risk than men for developing certain autoimmune diseases. This "gender bias" has largely been attributed to differences in sex hormones, with the commonly accepted view that male hormones have a protective effect. However, studies have also shown that the hormonal influence on gender bias in type 1 diabetes is sensitive to environmental factors, particularly the microbiota—the flora of microbes living in and on a host. An NIAID-supported study of diabetic mice showed that microbiota composition and lineage play a significant role in the hormonal effect on gender bias in diabetes risk. The findings support a model in which signals from hormones, microbes, and the immune system work together to trigger pathways that protect against diabetes (Yurkovetskiy et al., 2013).

NIH Strategic Plan for Women's Health Research

The **Trans-NIAID Women's Health Research Work Group** focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID and provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Heightens awareness across NIAID of the importance and substance of women's health and gender-based research;
- Develops a common framework for identifying and assessing women and gender-based research;
- Encourages trans-NIAID and trans-NIH collaborations on women's health and gender-based research activities; and

- Coordinates structured discussions highlighting issues and advances in women's health research. In FY 2013 and FY 2014, these discussions focused on mucosal immunity in the female genital tract and infectious diseases research in pregnant women.

The research described in the "Immunology and Immune-Mediated Diseases" section above supports ORWH Strategic Plan Objective 1.2. The research described in the "HIV/AIDS" and "Infectious Diseases Other than HIV/AIDS" sections above supports ORWH Strategic Plan Objective 1.6.

Inclusion

NIAID supports many research studies that focus on better understanding gender differences in disease outcomes, as reflected in the "Accomplishments and Activities" section above. NIAID also led a 3-year effort to develop consensus and detailed guidance regarding enrollment of pregnant women in vaccine and therapeutics trials (see "Conferences and Publications," below). Finally, NIAID structured several longitudinal HIV/AIDS studies and programs, described above, to enable the study of sex and gender differences, including the following:

- **WIHS is closely linked to MACS**, a study of MSM, to ensure that data collected in the two studies can be combined and compared whenever appropriate. Studies that compare outcomes for men and women in pharmacology, cardiovascular disease, aging, sleep patterns, metabolic disorders, mental health, and neurologic diseases are ongoing. These projects have demonstrated differences in the pharmacology of antiretroviral drugs and differences in the clinical outcomes between men and women with HIV in the United States.
- The **IeDEA** program combines data from nearly one million people with HIV globally. With these data, researchers can evaluate gender differences in disease outcomes and therapy response.
- **ACTG** has evaluated the differences in response to therapy between the sexes in the context of large randomized clinical trials in clinical trials networks. A study on Optimizing Treatment for Treatment-Experienced HIV-Infected People (A5241) will also examine sex differences.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

NIAID continues to cosponsor the Building Interdisciplinary Research Careers in Women's Health mentored career development awards, which support the development of women's health researchers. This activity supports NIH ORWH Strategic Plan Objective 6.2.

The Inter-CFAR Collaboration on HIV Research in Women develops new strategies for future research to address HIV-related issues unique to women and promotes career development among junior investigators in this field.

NIAID staff participated in the North American Gender Summit in Washington, DC, on November 13–15, 2013, and met with women scientists regarding career development strategies for women in STEM careers. NIAID staff also participated in a variety of other activities, such as the American Society of Microbiology's Committee on the Status of Women Microbiologists.

Research Initiatives

NIAID supports a number of initiatives on research related to women's health, including the following:

Improving Delivery of HIV Prevention and Treatment Through Implementation Science and Translational Research. The purpose of this 2014 funding opportunity announcement (FOA) is to increase the public health impact of HIV/AIDS-related interventions by determining how to deliver them more effectively and efficiently to women in communities and clinics. Intervention strategies could include PrEP, HIV counseling and testing, linkage to care, or treatment adherence (PA-14-129 and PA-14-131).

Integrated Preclinical/Clinical Program for HIV Microbicides and Biomedical Prevention. The goal of this 2014 request for applications (RFA) is to support the development of non-vaccine biomedical prevention for HIV in women, including microbicides, PrEP, and multipurpose prevention technologies. Specifically, this RFA will support the translation of drug delivery system strategies from preclinical to pre-phase I (early-stage) clinical studies (RFA-AI-13-023).

Mucosal Environment and HIV Prevention. NIAID reissued this RFA in 2014 to support the development of non-vaccine biomedical prevention (nBP) strategies for HIV in women, including microbicides, PrEP, and multipurpose prevention technologies. The RFA is intended to support innovative basic research efforts to assess the interaction of genital and gastrointestinal tract mucosal cells with nBP methods to help improve the safety and efficacy of these HIV interventions (RFA-AI-13-012).

Mechanisms of Cellular Immunity in the Female Reproductive Tract. The purpose of this 2013 RFA is to stimulate research to develop vaccines that elicit durable and effective T-cell responses against HIV and other viral pathogens in the female reproductive tract (FRT). Specifically, this RFA will support basic research studies into cellular mechanisms regulating the development of immunity in the FRT (RFA-AI-12-054).

Sexually Transmitted Infections Cooperative Research Centers. NIAID reissued this RFA in 2013 to facilitate collaborations evaluating co-infections of two or more STIs. Specifically, this RFA is intended to stimulate the discovery of new approaches to prevent, diagnose, and treat co-infections, polymicrobial infections, and other clinical outcomes that affect reproductive health (RFA-AI-13-043).

Administrative Supplements for Research on Sex/Gender Differences. This FOA was reissued in 2014 to provide administrative supplements to support research highlighting the impact of sex/gender in human health and illness. The research will address at least one of following objectives: increasing sex differences research in basic science studies; incorporating findings of sex/gender in the design and development of new technologies, medical devices, or therapeutic drugs; or actualizing personalized prevention, diagnostics, and therapeutics for girls and women (PA-14-027 and PA-13-018).

Conferences and Publications

A series of **NIAID conferences on enrolling pregnant women in clinical trials of antimicrobials and vaccines** brought together experts from academia, industry, governmental, and non-governmental agencies to develop a consensus on issues such as inclusion/exclusion criteria, adverse events grading, and biomarkers of health and disease for research studies in pregnant women. This resulted in the publication of an editorial and two guidance papers in September 2013 (Beigi, Goldkind, & Jevaji, 2013; Sheffield et al., 2013; Munoz et al., 2013). Five additional guidance documents were published in a "Clinical Infectious Diseases" supplement funded by the Bill & Melinda Gates Foundation (Beigi et al., 2014; Frew et al., 2014; Sheffield et al., 2014; Rasmussen et al., 2014; Gruber, 2014).

The **CFAR Joint Symposium on HIV Research in Women** met in September 2014 to (1) identify gaps in knowledge in research related to HIV and women and develop strategies that will move the field forward, (2) generate collaborative activity between the different CFARs and with other research networks highlighting cutting-edge science, and (3) promote and emphasize opportunities for young investigators.

NIAID and WHO collaborated to convene a **technical consultation on the development of vaccines against STIs**. The goals were to review and evaluate the needs, progress, and development of new and effective vaccines against "neglected" bacterial and viral STIs, with a focus on HSV, *Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae,* and *Treponema pallidum*. A summary of these discussions was collected in a special issue of the journal *Vaccine* and used to propose a roadmap for future work to accelerate the development and licensure of effective and affordable STI vaccines. (Broutet, Deal, & Fruth, 2014)

Health Disparities

NIAID supports research to understand and eliminate health disparities among women and special populations, including minorities, rural women, lesbians, women of lower socioeconomic status, and women with disabilities. The following scientific advances and ongoing and planned activities are highlighted in this report:

- WIHS;
- ASPIRE;
- MTN-015 and EMBRACE/MTN-016;
- PROMISE Study;
- Studies to Evaluate Approaches for PMTCT;
- Once-Daily Antiretroviral Therapy Combinations for Treatment-Naïve HIV-Infected Patients in Resource-Limited Conditions;

- Sex-Associated Differences in Pre-Antiretroviral Therapy Plasma HIV-1 RNA in Diverse Areas of the World Vary by CD4 T-Cell Count;
- Osteoporosis in HIV-Infected Postmenopausal Women;
- The Effect of Vitamin D Repletion on Postmenopausal Women with HIV;
- A Randomized Clinical Trial to Evaluate Treatment of Schistosomiasis During Pregnancy;
- Congenital Transmission of *Trypanosoma cruzi*;
- Sex Hormones and Post-Puberty Asthma Prevalence in Women;
- Factors that Affect Asthma Risk in Girls May Vary with Age;
- A Genome-Wide Study of Sex-Specific Asthma Risk Genes; and
- Loss of Estrogen-Mediated Immune Response Makes Females More Susceptible to Crohn's Disease.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Executive Summary

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, translational, and clinical research; research training; and information programs on many of the more debilitating diseases affecting Americans. NIAMS funds studies on a number of diseases that affect women disproportionately, including osteoporosis, osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (lupus), scleroderma, and fibromyalgia. NIAMS is committed to uncovering the basis of these sex differences and devising effective strategies to treat or prevent them.

Program Highlights

The anticipated increase in the U.S. elderly population will be accompanied by a larger group of women who are at risk of fragility fractures. New diagnostic methods are being developed to assess bone quality and predict its impact on individuals' health status in order to prevent morbidity from osteoporosis. These approaches include monitoring bone mineral density and bone microstructure. NIAMS also supports an active basic biology portfolio that could inform the development and use of drugs that improve bone quality.

ORWH has been a longstanding contributor to the Osteoarthritis Initiative (OAI), a public-private partnership led by NIAMS and the National Institute on Aging to facilitate development of treatments for people who have knee OA. The OAI, a prospective, natural history cohort, has collected biological specimens (blood, urine, and DNA), images (x-rays and magnetic resonance scans), and clinical data from nearly 5,000 participants ages 45 to 79. In addition to being accessed by almost 3,500 researchers from more than 80 countries and contributing to more than 220 peer-reviewed papers, the OAI is the data source for five NIH-funded research project grants and for the Foundation for NIH Biomarkers Consortium project on OA biomarkers.

Much of the NIAMS budget supports basic research into the biological processes underlying health and disease. Over time, discoveries have led to new treatments for people with a range of debilitating conditions. For example, NIAMS-funded basic research during the 1990s improved the understanding of the molecular mechanisms of inflammation and immune system dysfunction that causes RA. The laboratory results were translated to biologics—drugs in the form of biological molecules that are widely prescribed for millions of patients who have RA. Ongoing NIAMS-funded studies are identifying the factors that contribute to differences in symptoms and severity of chronic pain conditions. These findings are helping to personalize treatments for individual patients.

In FY 2014, NIAMS, the National Institute of Allergy and Infectious Diseases, pharmaceutical companies, and nonprofit organizations established the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus program to develop new models for identifying and validating promising biological targets for new diagnostics and drug development. While the initial research focus is on RA and lupus, the program has the flexibility to expand to related autoimmune diseases contingent on scientific feasibility and availability of resources.

With support from ORWH and other NIH components, NIAMS supports a robust information dissemination and outreach program to distribute research-based information to the public, patients, and health care providers. For example, NIAMS oversees the NIH Osteoporosis and Related Bone Diseases National Resource Center, which is co-funded by the National Institute on Aging, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, ORWH, and the U.S. Department of Health and Human Services Office on Women's Health.

Accomplishments and Activities

Osteoporosis and Fracture Risk

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist. In the United States, more than 40 million people either already have osteoporosis or are at high risk due to low bone mass. Osteoporosis can occur in both men and women and at any age, but it is most common in older women.

Hip fracture is the most devastating consequence of osteoporosis. It leads to short- and long-term functional impairment, loss of independent living ability, and even death. According to the National Center for Health Statistics, there were 258,000 hospital admissions for hip fractures among people age 65 and older in 2010; three-quarters of these fractures occurred in women. The incidence of hip fracture increases with age. Therefore, hip fracture will most likely become an even larger public health problem as the U.S. population ages.

Data Suggests Optimal Screening Intervals. The NIH-funded Study of Osteoporotic Fractures' finding that bone mineral density relates closely to fracture risk contributed to Medicare's decision to pay for numerous older Americans to get their bone mineral density measured. Many started taking bone-preserving drugs due to the results of these tests, and the rate of hip fractures has since dropped nearly 25 percent among female beneficiaries. New, longer-term data from this and other studies are suggesting ways to refine the screening guidance. Women at the highest risk of osteoporosis might benefit from annual exams, while women with the lowest risk could be tested much less frequently, unless other aspects of their health change. Similarly, postmenopausal women age 50 to 64 without osteoporosis on their first bone mineral density test are unlikely to benefit from frequent rescreening before age 65. (Berry et al., 2013; Gourlay et al., 2014; Gourlay et al., 2012)

Treatment May Improve Bone Health in Women with Premenopausal Osteoporosis. By definition, the cause and pathophysiology of idiopathic osteoporosis is unknown; therefore, the optimal clinical strategy is unclear. A recent study of 21 premenopausal women (ages 20–48) who have idiopathic osteoporosis showed that most participants responded favorably to the Food and Drug Administration (FDA)–approved bone building drug teriparatide. A daily dose of 20 micrograms of teriparatide over 18–24 months increased the bone mineral densities of their spines and hips. Moreover, information gleaned from comparing the blood samples provided by the women who did not benefit from the drug with those who did respond provides valuable knowledge of the actions of daily teriparatide and helps to clarify when this agent could be beneficial. (Cohen, Stein, et al., 2013)

Bone Strength Is Reduced in Women with Type 2 Diabetes. There are many risks and complications associated with type 2 diabetes, including bone fractures that cannot be predicted using conventional dual-energy x-ray absorptiometry (DXA) measurements. Researchers tested a relatively noninvasive technique called microindentation and found that the approach detected lower bone material strength in women who have type 2 diabetes compared with those who are nondiabetic, and weaker bone was correlated with higher blood levels of glycosylated hemoglobin (hemoglobin A1c, a biomarker that reflects average blood glucose levels in the past 6–8 weeks) over the last decade. This study not only makes progress toward developing a tool that could be used to predict fracture risk of people who have type 2 diabetes; it also illustrates a relationship between bone strength and blood glucose and suggests that people with more severe (less adequately treated) diabetic disease may be at an even greater risk of bone fractures than those whose diabetes is well controlled. (Farr et al., 2013)

Excess Abdominal Fat Is Associated with Weaker Bone. Although body fat was once thought to protect against osteoporosis, the link between obesity and increased fracture risk is strengthening. A recent study of 40 healthy premenopausal Caucasian women with normal bone mineral density showed that excess abdominal fat is associated with reduced bone quality, bone stiffness, and bone formation rates. Whereas previous research into the connection between obesity and bone has relied on blood chemistry markers and imaging studies, this paper included additional data directly from biopsies taken from the hip. Although these data reinforce the importance of obesity prevention to bone health, the study should be repeated in larger, more diverse groups that include older women,

heavier women, men of all ages and weights, and members of different races and ethnicities before its results can be generalized to the broader population. (Cohen, Dempster, et al., 2013)

3-D Modeling of Bone Structure Predicts Fracture Risk More Accurately than 2-D Images. While fragility fractures are the hallmark of osteoporosis and are associated with severely low bone mineral density, a large percentage of fractures occurs in women with bone mineral density that, while low, does not meet the threshold to be classified as osteoporosis. Using a high resolution imaging technique called HR-pQCT (high resolution peripheral quantitative computed tomography) and mathematical modeling methods to analyze bones in the distal radius of the arm and the distal tibia of the leg of women with low (but not osteoporotic) bone mineral density, researchers determined that women in the fracture group had fewer plate-like structures and fewer connections between rod-like structures in their arm bones, compared with women with similar bone mineral density measurements without a history of fractures. Two-dimensional DXA evaluation is an appropriate screening method for overall fracture risk in the general population. However, women who fracture or have a high risk of fracturing, identified by other means, may need further investigation with a tool like HR-pQCT before deciding on treatment options. (Stein et al., 2014)

Bone Biology

Bone health depends on the balance between two tightly coupled, opposing processes that constitute the bones' constant remodeling activities: bone resorption, in which bone cells called osteoclasts remove old damaged bone; and bone formation, in which bone cells called osteoblasts lay down new bone. Basic NIH-funded research into the mechanisms underlying bone formation and removal and how drugs influence these processes could lead to new treatments for people who are at risk of osteoporotic fractures.

Hormone Produced in Bone Affects Brain Development and Function. Mouse studies into the role of the bone-derived hormone osteocalcin demonstrated that the hormone can cross the blood-brain barrier, where it interacts with neurons to influence brain structure and the animals' behavior. Furthermore, researchers showed that maternal osteocalcin crosses the placenta during pregnancy, where it allows the brain to develop normally before the embryos can synthesize this hormone on their own. Although mice and humans differ in many details of metabolism and physiology, these findings are provocative and provide a context for studies of osteocalcin function in humans. (Oury et al., 2013)

An Alternative Membrane-Bound Thyroid Hormone Receptor Is Important for Bone Formation. Investigators have identified a thyroid hormone receptor variant that is important for bone formation. This alternative receptor, which is shorter than the classical nuclear form, localizes in signaling hubs at the cells' outer membrane instead of the nucleus. The binding of thyroid hormone to the variant receptor triggers a series of events that eventually helps to increase the growth of osteoblasts and protects the osteoblasts and osteocytes from death. The paper also describes how a drug that stimulates the same responses rescues some of the defects observed in the bone-building osteoblasts and osteocytes of mice with low thyroid levels. The drug does not affect the mouse osteoclasts, which are crucial for bone turnover. When combined with what is known about the complex effects of thyroid hormone on bone, these findings suggest that the alternative, membrane-based signaling pathway might have considerable therapeutic potential. (Kalyanaraman et al., 2014)

Estrogen Receptor Activity Varies with Bone Type. Estrogen's bone protective effect is thought to be influenced through interactions between circulating estrogen and a protein called estrogen receptor-α (ERα) on the surface of bone cells. Estrogen inhibits bone resorption when it binds to ERα on bone cells called osteoclasts. However, this activity of estrogen explains only its protective effect on cancellous bone (the inner sponge-like bone), not its effect on cortical bone (which composes the shafts of long bones). Researchers recently demonstrated that ERα enhances cortical bone formation by influencing the behavior of osteoblast progenitors (the cells that give rise to mature bone building cells called osteoblasts) but not on the mature osteoblasts themselves. This helps to shed light on the mechanisms of the protective effects of ERα on bone and may guide the ongoing search for better ways to prevent bone loss associated with age and other pathological conditions. (Almeida et al., 2013)

Adolescent Idiopathic Scoliosis

Adolescent idiopathic scoliosis (AIS) is a curvature of the spine with no clear underlying cause. The condition occurs most often when children are growing rapidly. It affects more girls than boys. In mild cases, monitoring by a physician may be all that is needed. More serious curves can cause pain and disability and may require surgery.

Bracing Successfully Treats Spine Curvature in Adolescents. In 2013, investigators demonstrated that bracing reduces the likelihood that idiopathic scoliosis will progress to the point that surgery is needed. The Bracing in Adolescent Idiopathic Scoliosis Trial compared the risk of curve progression in adolescents with AIS who wore a brace with that of those who did not. The trial was stopped early after finding that bracing significantly reduced the risk of curve progression and the need for surgery and that more hours of brace wear were associated with higher success rates. (Weinstein, Dolan, Wright, & Dobbs, 2013)

Osteoarthritis

OA is the most common form of arthritis. Nearly 27 million Americans, age 25 and older, have OA. Before age 45, more men than women have OA; after age 45, it is more common in women. Healthy cartilage allows bones to glide over one another, and it absorbs energy from the shock of physical movement. In OA, the surface layer of cartilage breaks down and wears away. This allows bones under the cartilage to rub together, causing pain, swelling, and stiffness. Bone spurs develop, permanently changing the joint's shape.

Simple Prescription of Light Activity Keeps Disability at Bay. While numerous studies have shown that moderate-to-vigorous levels of exercise improve pain and function for patients with knee OA, many who have OA cannot engage in even moderately intense physical activities. Using data from the Osteoarthritis Initiative, investigators demonstrated that even light intensity activities can preserve the health of people with knee OA. They found that men or women over age 45 who had or were at risk of developing knee OA were more than 30 percent less likely to develop arthritis-related disabilities if they spent more than 4 hours per day doing light activities such as walking or housework, compared with those who engaged in these or similar activities for less than 3 hours a day. (Dunlop et al., 2014)

Knee Osteoarthritis Does Not Improve with Vitamin D Treatment. Epidemiologic studies have indicated that OA progresses more slowly in people who have higher blood levels of vitamin D. Bone changes are associated with development of knee OA. Knowing that vitamin D is linked to bone health, investigators launched a 2-year randomized, placebo-controlled clinical trial to determine whether supplementation with vitamin D would improve OA symptoms and alter the progression of knee OA. One hundred forty-six people (57 of them women) with moderate to severe knee pain and structural damage were enrolled in the study and randomly assigned to either vitamin D supplementation or placebo treatment. At the end of the study, the two groups reported similar levels of pain and had similar structural changes. In other words, vitamin D does not appear to be a suitable treatment for reducing pain or improving structure or function in patients who have knee OA. (McAlindon et al., 2013)

Anterior Cruciate Ligament Injuries and Post-Traumatic OA

According to the American Academy of Orthopaedic Surgeons, female athletes who participate in jumping and pivoting sports, such as basketball and soccer, are between 2 and 10 times more likely to injure the anterior cruciate ligament (ACL) of the knee than male athletes who participate in the same sports. These types of injuries make it increasingly likely that a person will develop knee OA within one or two decades after the injury.

Imbalanced Muscle Activity Contributes to ACL Injuries. Investigators examining how the muscles of men and women respond during a jumping maneuver that strains the knee have documented a greater imbalance between women's quadriceps and hamstrings (the front and back thigh muscles) than men's during the point in the jump when injury is most likely. Specifically, in the first 40 milliseconds after landing, female participants had a 4.8-fold greater muscle imbalance than male participants. Although people who had previous ACL injuries showed a greater imbalance than their uninjured peers, the difference between the sexes persisted. The increased quadriceps activity relative to the hamstring activity may keep a person's knee in a more extended position, where it is more vulnerable to rotation, which may explain why women are more likely to experience an ACL injury and why both

sexes are at risk for further injury after ACL reconstruction. Researchers postulate that the altered muscle activity in ACL reconstructed knees may be due to a sensory deficit as a result of the original ACL injury, which current surgical techniques cannot repair. These findings underscore the need to better understand the causes of increased quadriceps muscle activity and muscle imbalance in these populations. They also highlight the importance of developing ACL injury prevention programs and rehabilitation strategies that remove or prevent this knee muscle activity imbalance. (Coats-Thomas, Miranda, Badger, & Fleming, 2013)

Age, Sex, and Surgical Approach Predict Outcomes Following ACL Reconstruction. Researchers participating in the Multicenter Orthopaedic Outcomes Network (MOON) study reviewed outcomes data for male and female soccer players who underwent ACL reconstruction and found that in less than 18 months after surgery, 72 percent of the MOON soccer players had returned to competition. Although most were playing at an equal or higher level than their pre-injury activities, older players and women were more likely to have given up the sport. Women also were more likely to suffer a second ACL injury, as were athletes of either sex who had injured the nonkicking leg. Additional data from the MOON cohort revealed that patients who receive a cadaver (allograft) ligament are more likely to need a second surgery within 6 years than those whose ACLs are replaced with tissue from their own body. Allograft tissue is associated with risk of rejection due to immuno-incompatibility and infectious disease transmission, and the identification of another potential complication further emphasizes the importance of discussing the tissue source for ACL reconstruction with patients. Health care providers also now have data that they can refer to when discussing the possibility of needing subsequent surgeries with patients who are planning to return to their previous activities. Moreover, the MOON study findings indicate which patients may benefit from injury prevention programs. (Brophy et al., 2012; Hettrich, Dunn, Reinke, MOON Group, & Spindler, 2013)

Halting Inflammation After Joint Injury May Reduce Risk of OA Later. Injecting an inflammation-blocking medication into a joint area immediately following an injury prevents the onset of post-traumatic OA in mice and may lead to new treatments for patients. The mice that received an injection of anakinra into the joint immediately following injury showed significantly less inflammation and cartilage deterioration, strongly implicating inflammatory cytokine interleukin-1 in the initial inflammatory phase. These results add to the body of evidence that suggests the blockage of inflammation immediately following a joint injury could halt or slow the degenerative changes that lead to OA, thereby preventing or delaying the pain and disability that characterize later stages of the disease. (Furman et al., 2014)

Rheumatoid Arthritis

RA affects an estimated 1.5 million Americans. It is a debilitating autoimmune disease, characterized by chronic joint inflammation, in which the body's natural defense system attacks its own tissues. RA occurs in all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it. Like some other forms of arthritis, RA occurs much more frequently in women than in men. About two to three times as many women as men have the disease.

Common Therapy for RA Reduces Risk of Death. Taking methotrexate, a commonly prescribed anti-inflammatory medication, may reduce the risk of death among patients with RA. Investigators examined the medical records of more than 5,500 RA patients, 75 percent of whom were women. After adjusting for patient characteristics that might affect survival, such as coexisting conditions, methotrexate use was associated with an improvement of up to 70 percent compared with those not taking the drug. The protective effect kicked in after taking methotrexate for more than 1 year, but it did not increase with longer duration of use. This finding suggests that the drug's benefits are not cumulative over the long term. Rather, methotrexate likely needs to be taken continuously to maintain its therapeutic value. (Wasko, Dasgupta, Hubert, Fries, & Ward, 2013)

Age of RA Patients Influences Physician Prescribing Practices. A study by NIAMS-funded researchers suggests that physicians should focus more on a patient's comorbidities and less on a patient's age when deciding the best treatment for RA. The researchers analyzed data on a subset of patients participating in the Consortium of Rheumatology Researchers of North America study,

70 percent to 80 percent of whom were women, to assess whether older RA patients and patients with more than one comorbidity had worse outcomes after starting treatment with a disease-modifying antirheumatic drug or biologic agent than younger patients and patients without comorbidities. Patients with more comorbidities improved less than patients with fewer coexisting diseases. Results also suggested that patients with fewer comorbidities, those who had spent a shorter period living with the RA, and those who had the lowest levels of disease at the beginning of the study were more likely than other patients to achieve disease remission. While physicians' treatment decisions are not influenced by the number of patient comorbidities, they may be influenced by a patient's age; physicians were more likely to prescribe new biologics for patients less than 45 years of age than they were for older patients, perhaps fearing that patients age 65 and older would not respond. The findings do not support the view that all older patients are poor candidates for biologics; older patients with fewer comorbidities are as likely, if not more so, to respond to newly prescribed biologic therapies than younger patients with more comorbidities. The authors of the study theorize that physicians should consider the number of coexisting diseases or conditions rather than age when selecting a therapy to treat RA. (Ranganath et al., 2103)

Lack of Sleep May Trigger Pain in RA. It has long been thought that RA pain originated in the affected joints as a result of inflammation. However, emerging evidence indicates that the pain stimulus may originate in the brain or another part of the central nervous system, and not just from the joint. One of the first studies to examine how sleep and other factors may influence an RA patient's pain experience revealed that women who have RA have significantly higher blood levels of factors associated with inflammation than women without RA. They are also more likely to experience anxiety; depression; sleep disruption; and "catastrophizing," or thinking a situation is worse than it really is. Moreover, the RA patients were more sensitive to pain, and this sensitivity was magnified when sleep problems occurred. This study challenges conventional thoughts about the origin of RA pain and could influence how health care providers treat their patients. (Lee et al., 2013)

RA Research Provides Another Reason for Younger Women to Maintain a Healthy Weight. Data from the Nurses' Health Study and the Nurses' Health Study II support an association between overweight and obesity and RA. While other research has yielded similar conclusions, these two cohorts also provided information about the relationship between body mass index and RA diagnosis at different ages. Being overweight or obese at 18 years of age was associated with a 35 percent increased risk of developing RA and an almost 50 percent increased risk of developing seropositive RA, but the association disappeared for women who were diagnosed with RA after 55 years of age. When combined with other work into how body fat contributes to the pathophysiology of RA, these results suggest differences in the molecular mechanisms underlying RA diagnosed at younger ages versus RA diagnosed at older ages. Moreover, the data continue to support the prevailing public health message regarding the importance of maintaining a healthy weight, especially for women who have other RA risk factors. (Bing et al., 2014)

Gut Microbes Linked to RA. Research suggests that the microbes living in and on our bodies play an important role in RA. Researchers compared the gut microbiome of people with new-onset, untreated RA to that of healthy controls, patients with RA who were receiving treatment, and patients with psoriatic arthritis. They found that the bacterium *Prevotella copri* was more abundant in patients with new-onset, untreated RA than in the other groups, suggesting that the bacterium contributes to the development of the disease. More extensive studies are needed to determine whether *P. copri* can cause RA, but if so, therapies that target the bacterium could help to prevent the disease or delay its onset. This work was partially supported by American Recovery and Reinvestment Act of 2009 funding through NIAMS and the NIH Office of the Director. (Scher et al., 2013)

New Genetic Risk Variants Discovered in RA. When an international research team leveraged genomic data collected through the North American RA Consortium (NARAC) and other large data sets, they identified 42 areas in the human genome associated with RA. The majority of the newly identified loci appear to contain genes strongly linked to immune functions. Since many are the targets of drugs for other conditions, the findings hint at approaches for RA treatments. The data also may explain why more women than men develop RA. One of the new loci (IRAK1) was found on the X chromosome. This site has previously been associated with systemic lupus

erythematosus, another autoimmune disease that affects more women than men. The NARAC Genetics of RA grant R01-AR044422 referenced in this publication was co-funded by NIAMS and ORWH. (Eyre et al., 2012)

Lupus

Lupus is a chronic autoimmune disease that, for unknown reasons, causes the immune system to mistakenly attack the body's own healthy cells and tissues. An estimated 90 percent of people diagnosed with lupus are women. Lupus is more prevalent in African-Americans, Hispanics, Latinos, and Asians. African-American women are three times more likely to get lupus than Caucasian women. African-Americans, Hispanics, and Latinas tend to develop lupus at a younger age and have more symptoms at diagnosis, including kidney problems.

Biomarkers May Predict Lupus Flares in Women. A team of researchers has identified a pattern of biological molecules in the blood of people with systemic lupus erythematosus that signals the onset of a disease flare. Investigators compared 52 molecules in blood samples from women with lupus whose disease flared during the study, from female patients who did not flare, and from healthy female volunteers. Compared with clinically stable women, patients with impending flares had higher levels of pro-inflammatory cytokines and lower levels of regulatory mediators, suggesting that the balance between inflammatory and regulatory factors is altered before a lupus flare. The molecular pattern they have found may help doctors to predict oncoming flares and enable them to treat patients aggressively before symptoms become full blown. They should also help optimize therapy for all patients by differentiating those with stable disease from those who might benefit from additional, more aggressive therapies. (Munroe et al., 2014)

Novel Drug Delivery System Shows Early Promise for Treating Lupus in Mice. A drug delivery system using nanoparticle technology that allows for better targeting of specific immune cells can potentially improve treatment approaches for lupus. Existing therapies globally suppress the patient's immune system, which leads to various complications. To test the theory that a localized drug delivery should alleviate some of these challenges, investigators designed a nanogel formulation that could deliver the immunosuppressive drug mycophenolic acid to specific immune cells. When investigators injected the nanogels into female mice that were susceptible to lupus, the drug preferentially accumulated in cells that are involved in the immune dysfunction, inflammation, and organ damage that characterize the disease. The drug delivered by this new method improved the survival by 3 months when given prophylactically to the animals before they developed symptoms and by 2 months when given to mice that already had serious kidney damage. While further studies are needed before this nanogel strategy can be tested in people, this research provides a promising starting point for lupus treatments and could be applied more broadly to other autoimmune conditions. (Look et al., 2013)

Oxidized Proteins Increase Cardiovascular Risk in Systemic Lupus Erythematosus. Although high-density lipoprotein (HDL) cholesterol typically protects against atherosclerosis by removing the atherosclerotic low-density lipoprotein cholesterol, HDL can burrow into artery walls and begin the atherosclerotic process when it becomes oxidized. Researchers in the NIAMS Intramural Research Program showed that patients with lupus have high levels of oxidized HDL, impaired function of this lipoprotein, and high levels of structures called neutrophil extracellular traps (NETs) that contain oxidizing enzymes. Ninety percent of study participants were women. Antimalarial drugs commonly used to treat lupus significantly decreased NET formation and consequently decreased the capacity of their enzymes to oxidize HDL in blood collected from female mice. The results from this study could lead to new methods and therapeutics for preventing and treating early atherosclerosis in people with lupus and other autoimmune diseases. (Smith et al., 2014)

Mouse Model Reveals Surprising Protective Role of Neutrophil Cell Death in Lupus. Instead of initiating lupus, a form of neutrophil cell death called NETosis may inhibit the disease. When researchers created a mouse model that lacked the gene for NADPH oxidase (Nox2), a key component necessary for NETosis to occur, they expected the animals to be protected against lupus. Instead, the animals showed exacerbated signs of the disease. This held true for male and female mice that could not produce Nox2 and for female mice that had only one copy of the Nox2 gene. Interestingly, these observations are consistent with studies that link Nox2 deficiency to

lupus symptoms in humans. Eventually, these findings could have clinical implications, helping to predict the risk of lupus development in an individual, as well as perhaps therapeutically promoting the activity of Nox2 to protect against or treat disease. (Campbell, Kashgarian, & Shlomchik, 2012)

Scleroderma

Scleroderma is a rare, severe, and heterogeneous autoimmune disease that involves progressive hardening of the skin and of internal organs. The characteristic hardening is due to fibrosis. Systemic sclerosis is one form of scleroderma and involves many parts of the body, such as skin, internal organs, and blood vessels. This form of the disease affects more women of African descent than women of European descent.

Pathways to Lung Fibrosis in Systemic Sclerosis. In recent decades, pulmonary complications have emerged as the major disease-related cause of death in patients with scleroderma. To better understand the factors that contribute to progression of lung disease in scleroderma patients, investigators analyzed the gene expression of lung tissue in 28 women with scleroderma-related pulmonary fibrosis. In contrast to gene analysis of end-stage lung tissue obtained at the time of transplantation, this study examined gene expression during early stage fibrotic disease. Expression of certain genes correlated with changes detected by pulmonary tests routinely used by clinicians to monitor lung disease. The results could help clinicians determine which scleroderma patients with lung problems are most likely to develop severe restrictive pulmonary disease and point to pathways that could be targets for the development of therapies that slow or halt disease progression. (Christmann et al., 2014)

Fibromyalgia

Fibromyalgia syndrome is a chronic disorder characterized by widespread musculoskeletal pain and tenderness. It is frequently accompanied by other symptoms, such as fatigue, insomnia, depression, and anxiety. Researchers at the Centers for Disease Control and Prevention estimate that fibromyalgia affects 5 million Americans ages 18 and older. Between 80 percent and 90 percent of those diagnosed with fibromyalgia are women, and the reason for this difference is unknown. The precise cause of fibromyalgia also is not known, but research suggests that it is related to a problem with the central nervous system's processing of pain. In addition to medications, cognitive behavioral therapy (CBT) is a commonly recommended treatment for fibromyalgia.

Two Therapies May Be Better than One for Fibromyalgia Patients. Researchers successfully completed a 21-week randomized, double-blind, placebo-controlled pilot study examining the feasibility of conducting a larger clinical trial to examine the effects of combining CBT and the drug milnacipran for the treatment of moderately severe fibromyalgia. The data from 58 participants, 93 percent of whom are women, suggest that using both therapies together improves physical function and reduces pain when compared with the drug alone. They also demonstrate that the study approach is feasible, and they provide guidance regarding the design of a larger comparative effectiveness trial. (Ang et al., 2013)

Standard Cognitive Behavior Therapy Regimen Fails to Increase Activity of Teens with Juvenile Fibromyalgia. Although patients with fibromyalgia are told to engage in moderate aerobic exercise three or four times per week, most patients with the condition are sedentary. When researchers conducted one of the first behavioral studies in juvenile fibromyalgia to quantify the effects of CBT on physical activity, they determined that CBT did not increase the teens' activity levels despite improving their daily functioning and social involvement. Unlike previously published work, this study examined actual physical activity levels of the adolescents (64 girls and four boys) by using objective actigraphy measurements. Researchers postulate that a CBT curriculum specifically designed to increase physical activity could encourage patients to become more active. (Kashikar-Zuck et al., 2013)

Researchers Document Relation Between Activity and Pain Intensity in Adults Experiencing Chronic Pain. Previous research has demonstrated the benefits of exercise in people who have chronic widespread pain conditions, such as fibromyalgia, while documenting that these individuals are also hesitant to participate in the recommended amounts of daily physical activity. Now investigators are using data from the National Health and Nutrition Examination Survey to quantify the activity trends for people with chronic pain. Their goal is to identify

people who would benefit from innovative physical activity regimens to increase their amount and intensity of activity. Investigators hypothesized that individuals with regional or widespread pain would have decreased physical activity compared to adults without chronic pain, but data from 3,952 participants (1,921 men and 2,031 women) revealed no significant association between pain status and time spent in sedentary and light physical activity. However, time spent performing moderate to vigorous physical activity was significantly lower for those experiencing widespread pain compared to those with no chronic pain. This underscores the need for clinicians to emphasize the importance of increasing physical activity in chronic pain patients, even if the patients regularly engage in slow walking or "light" household activities. (Dansie, Turk, Martin, Van Domelen, & Patel, 2014)

Skin Health

The increasing incidence of skin cancer among young women has coincided with the rising popularity of indoor tanning. There has been considerable recent interest in the link between indoor tanning (as a source of ultraviolet [UV] radiation) and skin cancer. While indoor tanning has been shown to significantly increase the risk of melanoma, a lethal form of skin cancer, its other health effects and public health strategies to mitigate its negative impacts are less clear.

Indoor Tanning Significantly Increases the Risk of Non-Melanoma Skin Cancer (NMSC). While formerly observed most frequently in older men, the incidence of NMSC (i.e., squamous cell carcinoma and basal cell cancer) has increased dramatically in younger adults (aged 18–40 years) and women in the last 25 years. Investigators combined the data from 12 studies on indoor tanning and NMSC and concluded that indoor tanning increases the risk of squamous cell cancer by 67 percent and basal cell cancer by 29 percent, compared with people who have never used indoor tanning. More frequent use of indoor tanning was associated with an even greater increase in risk, as was exposure to indoor tanning before the age of 25. The authors conclude that, overall, an estimated 170,652 cases of NMSC per year can be attributed to the use of indoor tanning in the United States. (Wehner et al., 2012)

Chronic UV Exposure Induces Opioid Response that Is Associated with Tanning Addiction. Skin cancer incidence is still on the rise, despite the fact that the link between skin cancer risk and chronic UV exposure is well known. A 2014 publication sheds light on the biological basis of tanning addiction and may lead to new prevention strategies and ultimately reduce skin cancer incidence. Mouse studies showed daily UV exposure at doses sufficient to cause sunburn triggers keratinocytes to release β-endorphin, an endogenous opioid that addicts the mice to UV light. The UV-treated mice showed a higher threshold for pain than untreated mice, as well as signs of addiction, such as opioid tolerance and dependence. (Fell, Robinson, Mao, Woolf, & Fisher, 2014)

NIH Strategic Plan for Women's Health Research

While all of the accomplishments and activities described in this document relate to the goals and objectives outlined in the NIH Strategic Plan for Women's Health Research, the following two efforts are particularly noteworthy. Both are examples of NIAMS-led strategic alliances and partnerships to maximize the domestic and global impact of women's health research (Goal 4).

Accelerating Medicines Partnership in RA and Lupus (AMP RA/Lupus)

The 5-year, $41 million AMP RA/Lupus program described under "Funding Initiatives, Workshops, and Conferences" relates directly to Objective 4.2, "Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry." During the program's launch, NIAMS leadership participated in several Capitol Hill briefings and met with professional societies and advocacy groups. These activities make the AMP RA/Lupus also relevant to Objective 4.4, "Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups."

Update of the 2007 Future Directions of Lupus Research Report

In 2007, NIH developed the Future Directions of Lupus Research report in response to FY 2005 House Appropriations Committee Report Language. In July 2014, the Congressional Lupus Caucus sent a letter requesting that NIAMS, as convener of the Lupus Federal Working Group, evaluate progress made toward achieving the priorities and goals set forth in the 2007 report and develop a coordinated lupus research action plan. NIAMS is gathering input from other NIH ICs through an internal process and from the public and researchers through a Request for Information (NOT-AR-15-007). Once the Institute has developed a draft action plan, NIAMS will hold a webinar with researchers and issue a second Request for Information to get feedback from the public on the draft. This activity ties directly to Objective 4.2, "Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry," and Objective 4.3, "Promote an environment that uses multiple avenues and technologies to facilitate continuing input from partners committed to improving women's health and promoting research."

Inclusion

NIAMS Supports 2014 Research Symposium on Musculoskeletal Sex Differences Throughout the Lifespan

In FY 2014, NIAMS issued a Conference Grant (R13AR066518) for a workshop titled Musculoskeletal Sex Differences Throughout the Lifespan Research Symposium, which was organized and sponsored by the American Academy of Orthopaedic Surgeons; the journal *Clinical Orthopaedics and Related Research*; the Orthopaedic Research Society; the Center for Musculoskeletal Health–University of California, Davis; and the Society for Women's Health Research. The program included a question and answer session with Dr. Joan McGowan, director of the NIAMS Division of Musculoskeletal Diseases, who provided an overview of NIH's plans to require appropriate sex and gender inclusion in preclinical research.

NIAMS Videos Feature Lupus Patients

In FY 2014, NIAMS began developing a series of videos featuring patients who have participated in studies at the NIH Clinical Center. The first two focus on Shirley and Liliana, who describe their experiences with being diagnosed with lupus and their subsequent involvement in clinical research. Both videos are available through the NIAMS Web site and the NIAMS YouTube channel.

Information Dissemination

Disseminating information about research progress continues to be an essential component of the NIAMS mission. ORWH has a long history of supporting the NIAMS-led NIH Osteoporosis and Related Bone Diseases National Resource Center, which links bone health resources with health professionals, patients, and the public.

NIAMS is committed to communicating research advances to all segments of the public. As part of an effort to distribute culturally appropriate health messages for underserved populations, NIAMS released a series of 2013 and 2014 health planners tailored for African-Americans, American Indians/Alaska Natives/Native Hawaiians, Asian Americans/Pacific Islanders, and Hispanics/Latinos. This activity, which has reached all 50 States and five U.S. Territories, is continuing in 2015. NIAMS also adapted some publications for Spanish, Chinese, Korean, and Vietnamese speakers and contributed materials to the National Institute on Aging's NIH Senior Health Web site.

In FYs 2013 and 2014, NIAMS updated 90 of its publications, many of which are focused on diseases or conditions that disproportionately affect women. New or revised materials that may be of particular interest to women follow.

Bone Health

- Bone Health for Life: Health Information Basics for You and Your Family (English and Spanish)
  - http://www.bones.nih.gov
- Osteoporosis module on the NIH Senior Health Web site
  - http://nihseniorhealth.gov/osteoporosis/whatisosteoporosis/01.html

Osteoarthritis and Total Joint Replacement

- Living with Arthritis: Health Information Basics for You and Your Family (English and Spanish)
  - http://www.niams.nih.gov/Health_Info/Arthritis/default.asp
  - http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Artritis/default.asp
- Osteoarthritis module on the NIH Senior Health Web site
  - http://nihseniorhealth.gov/osteoarthritis/whatisosteoarthritis/01.html
- Joint Replacement Surgery: Health Information Basics for You and Your Family (English and Spanish)
  - http://www.niams.nih.gov/Health_Info/Joint_Replacement/default.asp
  - http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Cirugia_de_reemplazo_articular/default.asp

Autoimmune and Rheumatic Diseases

- Living with Arthritis: Health Information Basics for You and Your Family (English and Spanish)
  - http://www.niams.nih.gov/Health_Info/Arthritis/default.asp
  - http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Artritis/default.asp
- Living With Lupus: Health Information Basics for You and Your Family (English and Spanish)
  - http://www.niams.nih.gov/Health_Info/Lupus/living_with_lupus.asp
  - http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Lupus/vivir_con_lupus.asp
- Rheumatoid Arthritis handout on health
  - http://www.niams.nih.gov/Health_Info/Rheumatic_Disease/default.asp
- Systemic Lupus Erythematosus handout on health
  - http://www.niams.nih.gov/Health_Info/Lupus/default.asp
- Understanding Autoimmune Diseases
  - http://www.niams.nih.gov/Health_Info/Autoimmune/default.asp

Funding Initiatives, Workshops, and Conferences

Accelerating Medicines Partnership in RA and Lupus

In September 2014, NIAMS, the National Institute of Allergy and Infectious Diseases, and partner organizations established the AMP RA/Lupus Program. AMP RA/Lupus supports an initial milestone-driven exploratory funding period for 11 research groups across the United States, with possibility of receiving funds for a large validation project to analyze the interplay among biological pathways in tissues of patients with RA and lupus. This 5-year, $41 million effort's goal is to integrate data from genome-wide analytic approaches to generate a comprehensive understanding of the mechanisms of tissue damage in RA and lupus. Partner organizations include the Rheumatology Research Foundation, the Foundation for NIH (FNIH), the Lupus Foundation of America, the Lupus Research Institute/Alliance for Lupus Research, the Arthritis Foundation, AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Sanofi, and Takeda.

Bone Quality Initiative

In December 2013, the FNIH Biomarkers Consortium launched a 3-year study to track the progression of osteoporosis more precisely and pave the way for better treatments. Investigators will leverage data from existing studies to assess the validity of specific imaging and biochemical markers for bone health, with the goal of conclusively establishing these measurements' value for drug development and clinical use. The Bone Quality Project involves osteoporosis experts from NIH, FDA, academic institutions, the pharmaceutical industry, and the nonprofit sector.

NIAMS Establishes a Systemic Autoimmunity Research Program in Bethesda, MD

In FY 2013, NIAMS recruited Dr. Mariana Kaplan as the Chief of its newly established Systemic Autoimmunity Branch in the Institute's Intramural Research Program. Dr. Kaplan's research focuses on the mechanisms by which cardiovascular disease is accelerated in people with lupus, the role of innate immunity in the development of lupus-related organ damage, and strategies to curtail tissue damage in lupus patients. Now at NIH, her projects are expanding to combine natural history and clinical studies with basic research into the etiology and pathophysiology of rheumatic diseases, with an emphasis on lupus and other systemic autoimmune diseases affecting adults.

STOP Lupus (Safety and Tolerability of Omalizumab in Patients with Lupus)

In FY 2013, the NIAMS Intramural Research Program began recruiting patients for a study to test whether omalizumab, an antibody-based drug that originally was used to treat severe allergic asthma, is safe and effective for people with lupus. The study builds on preclinical work conducted by NIAMS investigators and others that demonstrated that the molecules targeted by omalizumab in asthma also contribute to the kidney damage experienced by some lupus patients.
(ClinicalTrials.gov Identifier: NCT01716312)

Partnerships to Advance Therapies for Rheumatic Diseases in Children and Adults

In March 2013, NIAMS arranged for members of the private sector, academic researchers, and regulatory agencies to discuss strategies for meeting shared goals in the treatment and prevention of rheumatic diseases. Validation of RA biomarkers through the NIAMS-funded Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository (TETRAD) and evaluation of treatment safety in pediatric rheumatic diseases, as being pursued through the Childhood Arthritis and Rheumatology Research Alliance, were featured as valuable opportunities. The following year, the FNIH Biomarkers Consortium steering committee announced that it was moving forward with a project that is based on TETRAD data and samples.

The Role of Inflammation in OA

In 2013, NIAMS hosted a roundtable discussion on strategies to combine findings from basic, translational and clinical OA research with recent advances in inflammation research to enhance understanding of the early processes involved in the initiation and onset of disease. Part of the Institute's scientific planning process, the full-day meeting with grantees, clinicians, and patients explored the evidence for inflammation in the development of OA and the relationship of inflammation to pain and other pathogenic pathways in the disease. The group also discussed how interventions during the initial injury of a joint and the healing process might influence later OA development.

Participation in ORWH Funding Opportunity Announcements

In addition to the Administrative Supplements for Research on Sex/Gender Differences funding opportunity announcements (PA-13-018 and PA-14-027), NIAMS participated the following the ORWH-led Funding Opportunity Announcements:

- *Advancing Novel Science in Women's Health Research* (PAS-10-226), which solicited applications for pilot projects or small, self-contained projects that promoted innovative, interdisciplinary research to advance new concepts in women's health research and research on sex/gender difference. In FYs 2013 and 2014, NIAMS

co-funded two projects under this initiative: Sex-specific Movement Differences in Young Adults with and without Hip Pain (R21AR061690) and Magnetic Resonance Imaging of Bound and Free Water in Cortical Bone (R21AR063894).

- *Building Interdisciplinary Research Careers in Women's Health (BIRCWH) (K12) (RFA-OD-11-002)*, which supports mentored research career development of junior faculty members, known as BIRCWH Scholars, who have recently completed clinical training or postdoctoral fellowships and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, or health services research relevant to women's health or sex differences research.

Health Disparities

Several of the diseases mentioned above disproportionately affect women from underserved or underrepresented minority groups. NIAMS is committed to exploring genetic, biological, and environmental risk factors among different populations; conducting behavioral research into cultural issues that can influence disease management and outcomes (e.g., risk behaviors, medical compliance); investigating problems concerning access to care and exploring the impact of language barriers and cultural health literacy on health care delivery; and incorporating findings from these efforts into patient education strategies to promote healthy behaviors and improve lives.

Living in a Disadvantaged Neighborhood Worsens Musculoskeletal Pain Outcomes After Trauma

Individuals living in less affluent neighborhoods have worse musculoskeletal pain and recover less quickly after stressful events such as motor vehicle collision than individuals who live in higher socioeconomic status neighborhoods. The findings persisted after researchers accounted for individual characteristics such as age, sex, income, education, and employment status. Biomarkers associated with people's stress response ("fight or flight") system suggest that increased stress of living in a disadvantaged neighborhood affects biological systems in ways that increase pain and worsen pain outcomes. The results from this study of 948 people, 61 percent of whom were women, also add to the body of evidence that stress response systems are involved in the development of chronic pain. (Ulirsch et al., 2014)

NIAMS Hosts Bilingual Twitter Chat to Educate People About Lupus

As part of the Institute's efforts to reach multicultural communities with health information and resources, NIAMS hosted a Twitter chat in English and Spanish in September 2014. The social media event was held in recognition of Hispanic Heritage Month. It focused on lupus because the disease disproportionately affects Hispanic women. Tweets from NIAMS were posted in both languages, and questions were answered in the language in which they were received. The hour-long chat generated almost 600 tweets from more than 100 contributors and involved other ICs, the HHS Office on Women's Health, and NIH-funded investigators. Participants asked questions about diagnosing lupus, differences among the various types of lupus, its impact on people's lives, and what research is being conducted at NIH. Patients also posted messages about their personal experiences living with the disease.

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National Institute of Biomedical Imaging and Bioengineering

Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established by law in December 2000 and received its first appropriation and grant funding authority in FY 2002. As NIBIB continues to mature and establish programs, funding opportunities have been developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

NIBIB serves as the hub within NIH for coordination of biomedical imaging and bioengineering efforts. NIBIB (1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; (2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; (3) formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering; and (4) sponsors scientific meetings and symposia, collaborates with industry and

academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FY 2013 and FY 2014, NIBIB funded grants that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to tissue engineering activities designed specifically for women's diseases such as breast cancer, diseases with profound consequences for women such as sexually transmitted diseases, and conditions that predominate in women.

During FY 2013 and FY 2014, NIBIB supported research on women's health in the following disease areas: factors that influence careers of women in science and engineering, technologies to reduce health disparities, aging, breast cancer, solid tumors, sexually transmitted infections, and reproduction and fetal health conditions.

In December 2004, Dr. Anthony Demsey joined NIBIB as the Director of the Office of Extramural Policy and subsequently of the Office of Research Administration. Until his retirement from the government in mid-2014, Dr. Demsey had the overall responsibility of managing and monitoring all NIBIB activities that specifically focus on women's health research. Dr. Karen Peterson now serves in this capacity, and also has direct day-to-day responsibility for women's health research oversight. Drs. Demsey and Peterson have served as NIBIB's representatives to the Coordinating Committee on Research on Women's Health.

Accomplishments and Activities

NIBIB is continuing to develop and support a research portfolio that pursues cutting-edge science in the area of women's health research. NIBIB increased its commitment to women's health research from $16.3 million in 2013 to $17 million in 2014.

Highlighted below are significant NIBIB research accomplishments related to women's health.

Breast Cancer

Multilayered Redox-Responsive Nanoparticles for Delivery of Drug-siRNA Combination. Metastasis is the main cause of cancer mortality and morbidity, resulting in several million deaths annually, and existing therapeutic approaches rarely reverse or stop metastatic progression. However, novel therapies relying on the combination of small interfering RNA (siRNA) with traditional small-molecule drugs have the potential to greatly enhance the treatment repertoire and efficacy for many types of cancers. The goal of this grant is to allow for delivery of both small molecule chemotherapeutics and siRNA within a single silica nanoparticle formulation, and to silence genes that allow for cancer progression while also delivering the small molecule therapy. This application is focused on treating primary tumors and lung metastases of breast cancer.

Evaluation of Digital Breast Tomosynthesis as a Method for Routine Breast Cancer Screening. Digital breast tomosynthesis (DBT) is considered a very promising development in breast cancer imaging as clinical pilot studies have demonstrated that DBT yields higher sensitivity and specificity than projection mammography, the current breast cancer screening tool of choice. However, there is concern regarding the use of DBT for routine breast cancer screening because DBT generates approximately 50 times more images than projection mammography, and, therefore requires extensive review time for the radiologist. One investigator funded by NIBIB is using time-controlled viewing experiments to gain insight into the likely success of DBT as the population breast cancer screening modality of choice. The study compares the performance of radiologists in detecting breast cancer when interpreting DBT cross-sectional images with their performance in interpreting digital mammography images.

High-Resolution Whole-Breast MRI at 3.0T. The applicants proposed to develop, implement, and validate breast magnetic resonance imaging (MRI) methods with very high spatial-resolution at 3T. Although breast MRI has recently been shown to be cost-effective in screening high-risk patients or patients with a contralateral breast cancer, its sensitivity to ductal carcinoma in situ, ability to assess small lesions, and positive predictive value limit increased use. Higher resolution MRI can address all of these limitations, providing a more accurate tool for assessment of breast cancer. Improved specificity may reduce the rate of unnecessary biopsy while also making MRI effective for screening lower risk patients. Increased sensitivity for small

lesions will allow for earlier detection of cancer and result in increased survival rates and a reduced screening frequency.

Thermally Targeted Drug Delivery by Elastin Biopolymers. Cancer describes a collection of diseases caused by multiple genetic mutations arising from environmental insults, somatic DNA replication error, and inherited genetic defects. The modern treatment of cancer typically includes various combinations of radiation, chemotherapy, surgery, or drug-based therapies. Moreover, a critical failure in such therapies/treatments can ultimately lead to metastases. A team of investigators is developing a new combination strategy to treat cancer (including breast cancer) using a novel drug delivery approach. The dual-targeting delivery strategy described in this proposal attacks both the tumor vasculature and the cancer cells directly when applying a localized hyperthermia approach. Here, scientists have developed elastin-like polypeptide nanoparticles (ELPs) that undergo a transition from a solid to a liquid when heated. This causes the delivery vehicles to aggregate in targeted regions of tumors. In the first stage of therapy, the tumor vasculature is ablated by irradiating the aggregated ELPs that are formed, and in the second stage the doxorubicin is released to kill the remaining cancer cells. Studies thus far have shown that these thermally triggered ELPs result in increased tumor accumulation and better distribution in tumors to improve overall therapeutic efficacy compared with conventional therapeutic approaches such as a single-drug delivery modality or non-thermally targeted systems. Additionally, they have found that effects of hyperthermia, rather than the phase transition itself, lead to increased concentrations of drug at the tumor site. The temperature cycling appears to create temperature gradients that drive the drug into the tumor by diffusion. Most studies are currently using a colon cancer model, but they are being extended to a breast cancer model.

Development of Practical Mid-Infrared Spectroscopic Imaging Technology for Cancer. This project proposes to develop a new chemical imaging instrument to image biopsy tissues in order to achieve earlier decisions and more accurate diagnoses. The goal is to develop techniques for processing breast and prostate cancer biopsy samples. Using imaging technology, the investigators aim to accomplish these goals without using dyes, stains, or human supervision, which could transform standard practices used for histological assessment.

Time-Resolved Breast Imaging Using a Combined MRI and Optical Tomography Approach. A breast cancer patient's response to primary systemic therapy is important in deciding whether to switch to a different treatment regime or to progress to surgery immediately. The overall goal of this proposal is to combine MRI and near-infrared spectroscopy and tomography to characterize the predictive value of compression-enabled measurements of tissue hemodynamics, blood flow, and oxygen consumption as new biomarkers that are sensitive to therapy progress, and to quantify their relationship to final pathological outcome. The investigators use fast optical tomography during breast compression to investigate biomechanical and metabolic characteristics of normal and lesion tissues, with the goal of improving specificity for cancer diagnosis and non-invasively monitoring chemotherapy progress.

Magnetic Resonance Elastography. The goal of this research is to develop, validate, explore, and identify high-impact applications of a new diagnostic imaging technology for quantitatively assessing the mechanical properties of tissues: magnetic resonance elastography. Mechanical waves are generated in tissue, and a remarkably sensitive phase-contrast MRI technique using synchronous motion-sensitizing gradients is used to directly image the pattern of wave propagation. Specially developed mathematical algorithms are used to analyze the wave images and to generate quantitative images depicting the stiffness and other mechanical properties of tissue. Using magnetic resonance to palpate tissues will allow clinicians to identify breast lesions and will distinguish benign lesions from malignant ones.

Near-Infrared Diffused Light Imaging with Ultrasound Guidance. The goal of this project is to explore the utility of a novel hybrid ultrasound/optical imaging technique for (1) accurate diagnosis of breast lesions that could result in the reduction of benign biopsies and (2) assessing chemotherapy response and evaluating treatment efficacy. Investigators have developed a novel hybrid ultrasound/optical imaging system that uses simultaneous optical (infrared) and ultrasound sensors in a hand-held probe. This method provides accurate detection of tumor angiogenesis (i.e., formation of new blood vessels), and the distribution of these new blood vessels, which helps distinguish benign lesions from early-stage cancers. This method will be tested in a large number of patients who will also receive ultrasound-guided biopsy. Early results

indicate that this may be a promising method as an adjunct to mammography and may help to reduce the number of benign breast biopsies, compared with methods that have been in use for more than 20 years.

Robotic Haptic Feedback System for Breast Biopsy (Bx)/Radiofrequency Ablation (RFA) of Breast Tumor Under Continuous MRI. This project proposes to develop an image-guided robotic system that will be able to perform Bx and deliver RFA at the site of the breast tumor. The investigators will incorporate continuous MRI during the procedure so that sampling errors will be minimized during the biopsy. Furthermore, the haptics in the teleoperated robotic system will provide force feedback to the clinicians to guide the biopsy and RFA needle with wider areas of access to various regions of the breast.

Micellar Nanocarriers with Controlled Multivalent Ligand Presentation. The aims of this project relate to the development of a novel 3-helix micellar nanoparticle as an active targeting drug delivery platform. The investigators have designed and synthesized 3-helix micelles that are uniform in size from 10 nm to 20 nm, based on amphiphilic 3-helix peptide-polyethylene glycol conjugates. The group will synthesize targeted micelles, study their internalization in in vitro studies, conduct in vivo studies in models of breast and prostate cancer, and examine the micelles' pharmacokinetics and biodistribution.

Cerenkov-Specific Contrast Agents. The aim of this project is to develop novel contrast agents that are functionally specific to Cerenkov imaging. Cerenkov light emission occurs when beta particles emitted during radioactive decay exceed the speed of light in a dielectric medium. The successful development of the proposed could create contrast agents for dual Cerenkov-PET imaging to improve tumor detection. Currently, the team is working on the synthesis and optimization of pH-sensitive dyes for in vivo detection of tumor pH. The team will next test these in a mouse breast tumor model. This project is important because this group is generating a novel class of functional imaging agents that could enhance the classification and treatment guidance of a number of cancers, including breast cancer.

Functional Proton-Electron Double-Resonance Imaging: Development and Application. The overall goal of this project is to advance the new technique of proton-electron double-resonance imaging to a level of development that would allow the functional mapping of cellular parameters, such as pH, oxygen level, and redox and intracellular glutathione, in animals. If successful, the ultimate goal is the development of a novel technique for the interrogation of critical intracellular and extracellular metabolic variables in and around tumors. Initially these studies will be carried out in breast cancer models, but the technique should have wider applicability to other cancers.

Digital Specimen Tomosynthesis for Volumetric Imaging of Lumpectomy Specimens. The objective of this project is to develop a digital specimen tomosynthesis (DST) system, based upon the currently used clinical specimen radiography (SR) system for performing rapid, volumetric imaging of breast lumpectomy specimens in or near a surgical suite. Even though SR is used currently for surgical positive-margin evaluation and pathological examination guidance, its utility is limited by a lack of volumetric information about specimens in SR images, and the resulting uncertainty adds to the number of positive margins identified and subsequent re-excisions. The DST to be developed in this project, if successful, would yield the sophisticated imaging task within 1–2 minutes, which is acceptable clinical time for a rapid and accurate evaluation of the specimen in identifying positive margins. This project could have a high impact in reducing the post-surgical morbidity and recovery time, enhancing subsequent quality of life; and potentially also recurrences, to the extent that disease-free margins are rapidly and accurately identified. To date, the team has had extensive consultations with breast surgeons, radiologists, and pathologists, and has incorporated extensive additional clinical and workflow details for lumpectomy surgery and associated pathology, image analysis, and pathology sectioning—all in order to refine the system design toward accuracy and clinical acceptance.

A Novel Optical Spectral Imaging System for Rapid Imaging of Breast Tumor Margins. Of women undergoing breast conserving surgery (BCS), such as lumpectomy or partial mastectomy for breast cancer, approximately 20 percent to 70 percent return for repeat surgery due to incomplete removal of the cancer at the first BCS. The goal of this project is to develop and validate a miniature optical spectral imaging tool for intraoperative assessment of tumor margins in patients undergoing BCS. Utilizing ex vivo breast cancer specimens, the team optimized an 8-wavelength system for optical

characterization of hemoglobin, β-carotene, and scattering to distinguish between normal and malignant tissue.

Biomaterial-Based Breast Cancer Vaccine. Cancer cells are generally ignored by the immune system. This is because—for the most part—they more closely resemble cells that belong in the body than pathogens, such as bacterial cells or viruses. The goal of cancer vaccines is to provoke the immune system to recognize cancer cells as foreign and attack them. This application proposes a new approach to cancer vaccines, in which biomaterials that can be introduced into the body in a minimally invasive manner (via injection) are used to program, in situ, host dendritic cells to generate a potent cytotoxic T lymphocyte response. Recent data in a mouse model suggests that the biomaterial vaccine is able to recruit dendritic cells, program them with a danger signal while loading them with antigen, and enhance their trafficking to the lymph node to present processed antigen to other immune cells. This ultimately leads to an increased immune response, compared with bolus vaccine, and a reduction in tumor volume in mice.

Other Cancers

Quantitative Endoscopic Imaging for Ovarian Cancer. Advanced ovarian cancer is an extremely lethal gynecologic malignancy with metastasis to organs and the lining of the pelvis and abdomen. A therapeutic challenge relates to difficulties in identifying and completely removing disease from the abdominal and pelvic cavity including microscopic metastatic tumor nodules. The principal investigator who is in the first year of this grant is developing an illumination and drug release system to detect and treat these micronodules while sparing normal surrounding tissues. The dual-channel endoscopic system will incorporate fluorescence imaging to identify tumor deposits and adaptive beam-shaping for light-induced porphyrin-based liposomal drug delivery.

Joint Segmentation of MR and CT Scans for Gynecologic Cancer Brachytherapy. In gynecologic brachytherapy, radioactive isotopes are placed directly into a cancer of the uterus, cervix, or vagina in order to eradicate the cancer. This is usually done with the insertion of a hollow applicator into the tumor and a three-dimensional computerized-tomography (CT) volume is used to guide subsequent radiation planning. Since an MRI provides a clearer delineation of the target volume that should receive the highest dose of radiation, current practice is for patients with large tumors to undergo both a CT scan and MRI exam. Usually, these datasets are aligned and treatment regions are outlined in a fairly complex process requiring input from the radiation oncologist and physicist, while the patient is under anesthesia and awaiting treatment. The funded project plans to improve the efficiency of this workflow by using advanced image analysis methods. In this process, using Bayesian segmentation techniques, the team plans to develop tools that can simultaneously register the magnetic resonance (MR) and CT images for the radiation treatment planning.

Reproductive Health

Center for Point-of-Care Tests for Sexually Transmitted Diseases. The Center for Point-of-Care (POC) Tests for Sexually Transmitted Diseases creates and tests unique methods for the diagnosis of sexually transmitted diseases (STDs). The goals of this project are (1) to address the epidemics of STDs and HIV in the United States and in resource-poor settings by the development and better use of POC tests, (2) to address health inequity, and (3) to improve the sexual health of individuals. The STD area is optimal for development of POC tests given the stigma, privacy, and confidentiality issues that limit the effectiveness of current approaches to testing and follow-up treatment. Many STDs have serious long-term consequences for women because many, if not most, STD infections are asymptomatic. The Center is developing a range of technologies for detection of *Chlamydia trachomatis,* including immunoassay and molecular diagnostic approaches, and assessing the acceptability of sample collection by patients as well as the ability of patients to obtain accurate results when compared with testing by trained health care professionals.

Perfused 3-D Tissue Surrogates for Complex Cell-Cell Communication Systems. This group is tackling complex problems in the communications between cells and their immediate environment—the extracellular matrix—from a modeling and engineering perspective. One aspect of this large effort focuses on the initiating events that lead to chronic inflammation and fibrosis, using pairs of communicating cells: a cell type serving as an immediate responder to an inflammatory cue (e.g., macrophage), and

a cell type serving as a second responder (e.g., an epithelial cell of liver or endometrial origin). This project proceeds in a sequential fashion, learning rules for communication in autocrine fashion (one cell type communicating with itself), and then adding in a second layer of complexity. This approach has already led to an important clinical finding in an improved, evidence-based system for diagnosis of endometriosis.

Steroid-Based Contrast Agents for Magnetic Resonance Imaging of Endocrine Disease. Steroid hormone receptors play a crucial role in an array of biological processes including puberty, reproduction, menopause, and cancer. The clinical decision based on the expression of steroid hormone receptors relies on invasive needle biopsy. Developing specific and sensitive imaging probes to target these receptors may lead to a noninvasive screening method for sex-specific diseases including breast, ovarian, and endometrial cancers. The proposed project aims to design and develop steroid hormone receptor-targeted MRI probes to be used as diagnostic and monitoring tools for the receptor status of diseases in women.

Development of Advanced Techniques for MR of the Newborn Brain. This project is focused on developing both imaging and metabolic assessment techniques through MRI and spectroscopy in neonates. With the extraordinarily high premature birth rate—more than 540,000 per year in the United States—and its extremely high human and economic costs, neonatal MRI is a critically important advance in radiological care. These investigators propose to develop and translate new specialized 3T MRI tools for the noninvasive characterization of brain maturation and injury in premature and term newborns.

Advanced Fetal Imaging. The fetal period is a time of unparalleled brain growth and development and is arguably the most important time for defining future cognitive potential. Therefore, when fetal brain development is impaired, as it is in many disorders including congenital heart disease, abnormalities emerge in utero and contribute to lifelong cognitive impairment that cannot be corrected even with optimal postnatal care. This has led to an overwhelming public health need for methods that detect early in utero anatomical and physiological abnormalities to better counsel parents and to better guide development and optimization of fetal interventions (surgical or medical) to prevent or mitigate such long-term consequences. Although there has been ongoing optimism that fetal MRI could fulfill this role, it still remains severely limited by the unique anatomy of the gravid abdomen, the small size of the fetus and, most importantly, fetal motion. As a result, fetal brain MRI lags far behind postnatal brain imaging. This project is focused on advancing fetal MRI using an integrated approach that addresses the entire imaging acquisition process.

Molecular and Cellular Transport in Mucus. STDs and unwanted pregnancy create tremendous burdens on individuals, on U.S. society, and on the national health care costs. The goal of this project is to understand the biological barriers to protein and DNA transport at mucosal surfaces and to produce new polymeric delivery systems to enhance immune protection within the female reproductive tract. The team has designed and synthesized biodegradable nanoparticles that can cross the human cervical mucus layer, enter specific cells, and release complex agents such as siRNA and DNA to treat or protect against infectious diseases, such as genital herpes, and specific pathogens. The team is also expanding into investigating new delivery systems for treatment of simian immunodeficiency virus infection in rhesus macaques, the premier model of HIV infection in humans.

MRI of Fetal Ventriculomegaly: Morphology and Outcome. Ultrasound is the imaging modality of choice for fetal evaluation. However, there are many cases in which ultrasound is non-specific, and further development of ultrasound techniques is needed, especially for fetuses with ventriculomegaly (VM). Fetuses with VM are a heterogeneous population, and it is likely that using additional MRI data will facilitate improved counseling and management of these patients. This research is based on the hypothesis that the additional use of MRI with ultrasound will improve the diagnostic utility for patients with VM and the ability to predict outcomes, when compared with ultrasound data alone.

Point-of-Care Ultrasound for Maternal Health. Ultrasound has become an integral part of prenatal care. However, many patients in rural or underserved areas do not have access to this diagnostic equipment. System costs and the need for trained operators limit the use of ultrasound to hospitals, clinics, and doctors' offices. Researchers at General Electric Global Research in Niskayuna, NY, are tackling both challenges. First,

they developed a low-cost method to fabricate ultrasound transducers—the probes that generate and receive sound waves—and now they are developing software that automatically adjusts image quality, thereby reducing the need for specialized operator training.

Development of Spatial-Temporal Analysis Tools for Uterine Biomagnetic Signals. This study was designed to record the magnetic field corresponding to the electrical activity of uterine contraction and provide requisite spatial-temporal information. To take advantage of the spatial-temporal resolution in uterine magnetomyographic signals, the investigators further enhanced the computational and analysis tools and developed this system as a clinical device to predict the onset of labor in the case of term and preterm patients. The goal is to develop techniques to improve the extraction, recognition, and validation process of uterine signals of the term patient and especially for the management of patients at high risk for premature delivery.

Development of Analysis Tools to Enhance Fetal Neurological Assessment. The ultimate goal of this project is to develop a clinical neurological assessment tool for the developing fetus. The investigators have shown that the fetal spontaneous brain signals can be extracted from biomagnetic recordings with sufficient signal-to-noise ratio. Further, they have shown its applicability in tracking the neurological activity of growth-restricted fetuses. The success of these studies was largely dependent on the development of appropriate analysis tools. The investigators have moved on to the next stage of the project to further improve the analysis methods to account for spontaneous fetal data that occur over long duration data sets, and to develop clinically relevant indices to track fetal neurological maturation. The investigators also plan to extend their studies to the other high-risk subgroups such as chronic and pregnancy-induced hypertensive mothers.

A Low-Cost Cardiac Annunciator to Reduce Stillbirths and Neonatal Deaths. Some of the 3.7 million neonatal and 2.6 million stillbirths that occur in the world each year could be avoided if the birth attendants are made aware of the fact that some of the unresponsive neonates at birth are alive and can be resuscitated. The ultimate goal of this project (funded through an Indo-U.S. collaborative program for low-cost medical devices) is to develop and evaluate a simple cardiac annunciator, which can be placed on the chest of the newborn infant to detect the electrocardiogram and produce a sound and light flash for each detected heartbeat. The device development will be done in the United States, and the device will be tested in clinical facilities domestically and in India. A prototype device has been built and preliminary laboratory tests have been undertaken. It has been evaluated on a small number of subjects (n = 6) and has worked reliably. An initial evaluation at a local community hospital in India is currently under way. The plan is to build a sufficient number of these devices to provide to co-investigators in India to perform clinical studies.

Cell Phone-Based Protocols for Diagnosis and Management of Childhood Pneumonia. While pneumonia is the leading cause of death in children worldwide, the current approach—using paper-based protocols and relying on a clinician's ability to manually count the respiratory rate—has proven inadequate for diagnosing pneumonia in a timely manner and affecting effective treatment options. The proposed work (funded through an Indo-U.S. collaborative program for low-cost medical devices) plans to develop, design, and test an Android smartphone-based device, incorporating a user-friendly digital version of local Integrated Management of Neonatal and Childhood Illness protocols and tools for assessing respiratory rate and oxygen saturation. This device will be used to provide appropriate treatment algorithms and instructions on managing childhood pneumonia. The first version of the mobile application technology (mPneumonia) has undergone initial beta testing. The team is currently developing and localizing the content of the mPneumonia application and plans to perform a pilot field evaluation assessing its feasibility, usability and acceptability among three tiers of public-sector health workers (physicians, accredited social health activists, and auxiliary nurse midwives) and caregivers of children under 5 years of age.

The National Physicians Cooperative (NPC) Preserves Fertility for Female Cancer Patients. This cooperative includes 5 core institutions and 15 allied centers throughout the United States. The primary goals of this cooperative are to (1) collect adult human ovaries from women with cancer and distribute them for basic science research; (2) educate providers, patients, and the community through the allied centers about fertility options for women with cancer; and (3) disseminate the technical knowledge of follicle maturation and cryopreservation to the allied centers.

Active research into fertility preservation and germinal tissue preservation could provide opportunities for restoring fertility and other ovarian functions after cancer treatment to improve post-treatment quality of life. Subjects can enroll under one of two separate institutional review board-approved protocols. In the ovarian tissue cryopreservation for fertility preservation protocol, 80 percent of tissue is for the subjects' own use and 20 percent is for the research repository. The Scaffold protocol is for women whose ovaries have been removed for medical indications; they do not want fertility preservation but will donate tissue for research only. Virtual grand rounds are conducted quarterly and preserved on NPC's oncofertility Web site. NPC also has a national fertility hotline and Web site and are approached via these avenues approximately 10 times per week by providers and patients. The cooperative has experienced a 220 percent increase in providing fresh tissue in the year reported in the latest progress report.

Minimizing the Role of Cryoprotectant Toxicity for Cryopreservation. One way to preserve a woman's fertility after radio- or chemotherapy is to harvest and freeze her oocytes. Yet ova are notoriously delicate and recovery after thawing is generally very poor. Using computational models to inform experimental techniques, NIBIB investigators are making great headway in addressing this problem by designing optimized cryoprotective agents.

NIH Strategic Plan for Women's Health Research

Most NIBIB-funded projects in women's health align strongly with Goal 2 of the ORWH Strategic Plan: "Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs." In particular, many projects align with Objective 2.6, "Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery." An example of such a project is a study of the high-resolution whole-breast MRI at 3.0T, which looks at optimizing imaging of the breast using MRI. Many other projects funded by NIBIB align with Objective 2.7, "Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls." An example of a project that aligns with this objective is the biomaterial-based breast cancer vaccine, which aims to develop a novel type of vaccine to prevent breast cancer from occurring.

Inclusion

Given that the focus of the NIBIB research is early-stage technology development, NIBIB usually does not support projects through the phase II or phase III clinical trial stages. Instead, as a project matures, its support might be transferred to one of the organ- or system-specific ICs for further development, including phase II and phase III trials. Therefore, we have no major activities or clinical trials to report.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

NIBIB is committed to increasing the participation and success of minorities and underrepresented populations in science and engineering. To this end, NIBIB has recently awarded contracts to the University of Maryland, Baltimore County, and Savannah State University. These contracts will allow the institutions to test the effectiveness of a concerted program combining intensive recruitment and outreach efforts; strong faculty and peer-to-peer mentoring; exposure to academic and industrial research experiences; professional development counseling; and social networking in increasing the number of underrepresented students in STEM fields. We envision that outcomes and best practices developed by these institutions will inform future programs to further increase the STEM diversity pipeline.

Funding Initiatives, Workshops, and Conferences

In FY 2013–FY 2014, NIBIB led and participated in several initiatives that addressed areas relevant to women's health.

NIBIB-Led Initiatives

PAR-11-044—Indo-U.S. Collaborative Program on Low-Cost Medical Devices (R03)

NIBIB continued a funding program to encourage collaborative research and/or technology development between scientists and engineers in the United States and India to develop new, low-cost, and appropriate diagnostic and therapeutic medical technologies for low-resource settings and underserved populations within the United States and/or India. The PAR supports a wide range of research, including maternal/neonatal/infant health, cardiovascular diseases, cancer screening, and translational research, among others.

RFA-EB-13-001—Blood Pressure Measurement Technologies for Low-Resource Settings in the United States and India (U01)

NIBIB initiated a new partnership with India's Department of Science and Technology to develop new methods of measuring blood pressure. Technologies developed under this initiative should be mobile and usable at the point of care, and they should be affordable and appropriate for use in low-resource settings. The technologies developed under this RFA have wide applicability, including use in management of hypertension in women.

Joint Initiatives

PA-14-358—Biology of the Temporomandibular Joint in Health and Disease (R01)

The National Institute of Dental and Craniofacial Research and NIBIB released this funding opportunity to continue encouraging research to advance our understanding of the temporomandibular joint in health and disease and to stimulate research that complements previous efforts in this area. A companion funding opportunity announcement was released for the R21 mechanism as well (PA-14-359 [R21]).

Health Disparities

NIBIB participates in the program announcement "Research Supplements To Promote Diversity in Health-Related Research (Administrative Supplement)" (PA-12-149).

In addition, NIBIB leads RFA-EB-10-002, "Development and Translation of Medical Technologies that Reduce Health Disparities (SBIR [R43/R44])." This initiative was reissued in 2014 as RFA-EB-14-001.

NIBIB sponsored a funding opportunity focused on reducing health disparities through the development and translation of appropriate medical technologies, new or existing, that can have a significant impact on health care access and health outcomes for health disparities in populations. The RFA supports a wide range of research aimed at the development of innovative diagnostics, treatments, and preventative strategies to reduce, and eventually eliminate, health disparities.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Executive Summary

The mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is to ensure that every child is born healthy and wanted; that women suffer no harmful effects from reproductive processes; that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and to ensure the health, productivity, independence and well-being of all people through optimal rehabilitation. Within this mission, NICHD supports essential research that plays a unique role in women's health, aiming to overcome many of the complex challenges that women encounter over their lifetimes. NICHD is home to much of the nation's leading science related to women's overall health, gynecological health, pregnancy, and childbirth, as well as studies of sex differences in diseases and conditions related to child health and medical rehabilitation.

NICHD supports a wide-ranging research portfolio in women's health. Among the Institute's major research areas are preconception care and pregnancy (including such complications as preterm birth and preeclampsia); gynecological conditions (including vulvodynia, pelvic floor disorders, impaired fertility, uterine fibroids, and endometriosis); HIV and its associated co-infections as they affect women; and other critical aspects of women's health, including sex and gender as biological variables. A related Institute priority is training the next generation of researchers in women's health, with a special emphasis on career building for women scientists. Furthermore, the Institute maintains multiple, diverse outreach and dissemination activities to share research results and health information with the general public. NICHD research and research training are located primarily in the following seven major Institute programs, although interests in women's health extend across the Institute.

The Gynecologic Health and Disease Branch (GHDB). Established in 2013, GHDB focuses on basic science, translational and clinical research, and research training programs related to gynecologic health in women and adolescent girls. The Branch portfolio emphasizes studies of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, pelvic floor disorders, and menopause transition/perimenopause, as well as studies of the mechanisms underlying chronic pelvic pain, vulvodynia, and dysmenorrhea. The Branch also supports research training and career development programs of investigators interested in women's reproductive health. (http://www.nichd.nih.gov/about/org/der/branches/ghdb/Pages/overview.aspx)

The Contraceptive Discovery and Development Branch (CDDB). CDDB develops and supports research and research training programs in contraceptive development. Major research areas include studies of new contraceptive methods (female and male); mechanisms of action and effects of contraceptive and reproductive hormones, drugs, devices; and procedures as well as optimal formulations and dosages of contraceptive agents and spermicidal microbicides. (http://www.nichd.nih.gov/about/org/der/branches/cddb/Pages/overview.aspx)

The Fertility and Infertility Branch (FI). FI supports scientific research aimed at alleviating human infertility, uncovering new possible pathways to control fertility, and expanding fundamental knowledge of processes that underlie human reproduction. To this end, the FI Branch provides funds for basic, clinical, and translational studies that will enhance our understanding of normal reproduction and reproductive pathophysiology and enable the development of more effective strategies for the diagnosis, management, and prevention of conditions that compromise fertility, with the ultimate goal of promoting a better quality of life for all individuals. (http://www.nichd.nih.gov/about/org/der/branches/fi/Pages/overview.aspx)

The Maternal and Pediatric Infectious Disease Branch (MPIDB). MPIDB develops and supports a wide range of domestic and international research related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and associated co-infections (such

as tuberculosis, malaria, and hepatitis), as well as noninfectious complications of HIV in pregnant and nonpregnant women, infants, children, adolescents, and the family unit as a whole. (http://www.nichd.nih.gov/about/org/der/branches/mpidb/Pages/overview.aspx)

The Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB). OPPTB promotes basic, translational, and clinical research to improve the safety and efficacy of pharmaceuticals and to ensure centralization and coordination of research, clinical trials, and drug development activities for obstetric and pediatric populations. The Branch is responsible for developing and supporting a comprehensive national effort to increase the knowledge base for understanding how to treat disease appropriately during pregnancy, as well as infancy and childhood, using pharmaceuticals carefully tested for safety and efficacy in their target populations. (http://www.nichd.nih.gov/about/org/der/branches/opptb/Pages/overview.aspx)

The Pregnancy and Perinatology Branch (PPB). PPB seeks to improve the health of mothers and children by supporting research in maternal health, pregnancy, fetal well-being, labor and delivery, neonatal and infant health and well-being, and the long-term health outcomes associated with pregnancy and with fetal and infant development. (http://www.nichd.nih.gov/about/org/der/branches/ppb/Pages/overview.aspx)

Additionally, the NICHD Division of Intramural Research conducts interdisciplinary research in both basic and translational science to enhance the understanding of the biology of development and reproduction to ensure the health of infants who develop into adulthood and to optimize the health of women. The division strives to understand the basics of science through research in cell biology and metabolism, molecular medicine, genomics, and developmental endocrinology. For example, the intramural Program in Perinatal Research and Obstetrics (PPRO) studies pregnancy and pregnancy complications. The PPRO provides state-of-the-art prenatal care to women enrolled in NICHD protocols and has made major contributions to understanding the mechanisms of disease in premature labor and delivery and preeclampsia. (http://www.nichd.nih.gov/about/org/dir/Pages/index.aspx)

Accomplishments and Activities

NIH Strategic Plan for Women's Health Research

NICHD Highlights: Research on Women's Health and Research on Sex Differences

The NICHD Human Placenta Project is responsive to Strategic Plan Objective 2.5, "Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions in women and girls." Despite growing evidence that the development and function of the placenta as the fetus grows and develops within it is critically important for enhancing the lifelong health of women and their offspring, the placenta is the least understood human organ. The reason is that scientists lack the technology and techniques to study the placenta throughout a pregnancy, when the earliest signs of risk for the pregnant woman and/or the fetus may emerge. Such placenta research as exists is limited to the placenta after birth. The initial goals of the Human Placenta Project include improving current methods and developing new noninvasive or minimally invasive technologies for real-time, in vivo assessment of placental development and evaluating markers for prediction of adverse pregnancy outcomes. These goals also include understanding the contributions of placental development to the long-term health or diseases of women and their offspring and to develop interventions to prevent abnormal placental development and mitigate the risks to women of, lifelong cardiovascular disease associated with preeclampsia in pregnancy. (https://www.nichd.nih.gov/research/HPP/Pages/default.aspx) (Guttmacher, Maddox, & Spong, 2014)

The MyPregnancy Initiative is expected to yield unique new data resources that will support the Strategic Plan Objective 2.3, "Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls," and Objective 3.4, "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring." As planned in FY 2013–2014, the initiative leverages social media as a unique, national registry allowing researchers, with appropriate confidentiality and consent policies, to hear directly from women about their experiences during

pregnancy, including preterm and term births. Using a longitudinal, crowd-sourcing approach, the initiative will ask pregnant women about what is going on in their pregnancies. Participants will enter information throughout gestation into online surveys and trackers via a Web site or mobile applications. In exchange, participants will be able to track their pregnancy data over time, print out reports to share with their health care team, and see how they compare to other women in the initiative's data base. MyPregnancy will provide participants with links to trusted, evidence-based information from partner organizations about healthy pregnancy and pregnancy complications. After a critical mass of data is collected, de-identified data will be available to researchers for analysis. In June 2014, the Institute hosted the Pregnancy Registry Strategy Meeting to enable potential stakeholders to provide input on the structure and organization of the project and to garner their support.

NICHD National Maternal and Child Health Program. NICHD activities in this area are responsive to Objective 5.1, "Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues." NICHD created this program together with more than 30 of the nation's most prominent maternal and child health care provider associations, Federal agencies, and other partners. The program's objectives are to identify key challenges in maternal and child health, review relevant research gaps, initiate activities, and propose solutions to advance the field. Program activities focusing on preterm birth have produced online public information about the importance to the health of the mother and the baby to wait until at least 39 weeks of pregnancy to deliver if the mother's or child's health is not in danger. A new program effort is to increase awareness of postpartum depression among women and their families, with an emphasis on presenting to a health care provider for diagnosis and treatment. Minority women will be a special target group due to the stigma of mental illness that is very prevalent in this population.

Research on Disorders or Differences of Sex Development. NICHD research in this area is responsive in part to Strategic Plan Objective 1.1, "Encourage genetic and epigenetic studies to identify sex differences in gene expression," and in part to Objective 1.7, "Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues and organs…." Disorders or differences of sex development (DSD), sometimes referred to as "intersex" conditions, are approximately 40 rare genetic disorders in which the development of chromosomal, gonadal, or anatomic sex is atypical and variable in type and severity among DSD. Symptoms may include significant endocrine disorders; atypical appearance of genitalia or such anomalies as mixed ovo-testicular gonads; absence of a uterus; and, in rare instances, XY (male) genes in women and girls whose gender identity and physical characteristics are female. While the primary focus of NICHD-supported research in this area is to improve the diagnosis and care of children and adolescents with DSD, studies of atypical developmental processes of sex determination and sex differentiation may also expand understanding of typical pathways in such processes. NICHD-supported research in this area includes the multisite Disorders of Sex Development Translational Research Network (R01HD068138-4). A major component of this project is whole-genome sequencing to tease out the genetic signatures of DSD in infants and children, who also receive multidisciplinary care and are followed over time. NICHD research also addresses adult treatment of congenital adrenal hyperplasia (CAH). An NICHD intramural clinical trial comparing a cortisol pump with standard treatment for CAH to maintain adequate hormonal balances was under way in FY 2014. (https://clinicaltrials.gov/ct2/show/NCT01859312?term=Congenital+Adrenal+Hyperplasia+AND+Bethesda&rank=1)

Research on the Health of Sexual and Gender Minority (Formerly LGBTI) Populations. Research in this area is responsive in part to Strategic Plan Objective 1.8, "Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being." The research focuses on behavioral, social, biological, and clinical processes that affect health and development among lesbian, bisexual, and transgender women as well as other sexual and gender minority populations. The goal of this project is to focus on developing effective supportive, preventive, and treatment interventions and health service delivery methods that will enhance the health and mitigate or prevent health risk factors for sexual and gender minority populations. Funding opportunity announcements (FOAs) for this program were first published, by multiple collaborating ICs,

in FY 2000 and re-issued, most recently in FY 2012 (PA-12-111, PA-12-112, PA 12-113). In FY 2014, the Institute decided to reissue the FOA with the more inclusive title "The Health of Sexual and Gender Minority Populations."

NICHD Accomplishments: Scientific Research Advances in Women's Health

Contraception

(See also Health Disparities, below)

Long-Acting Reversible Contraception (LARC) Can Dramatically Reduce Teen Pregnancy Rates. Young, sexually active women, the group with the highest rates of unintended pregnancies and abortions, tend to use less reliable reversible contraceptive methods (e.g., hormone pills, condoms) rather than far more reliable LARC methods (e.g., intrauterine devices [IUDs], implants). A recent study tested the hypothesis that the costs of LARC or lack of adequate information may explain low rates of use by this age group. The study, known as the Contraceptive Choice Project, provided accurate, detailed information about reversible contraceptive options to more than 1,400 women aged 15–19 years and gave each participant her contraceptive of choice without cost. Nearly three-quarters (72 percent) of the women opted for an IUD or implant, with the remainder opting for non-LARC methods that rely on consistent and correct use for effectiveness. For both groups, rates of pregnancy, birth and abortion were at least 75 percent lower compared with rates of sexually active teens in the United States in 2008. (Secura et al., 2014)

Endometriosis

High-Tech Analysis of Genetic Data May Yield New Test for Endometriosis. As many as 11 percent of women have endometriosis, an often painful condition that occurs when tissue that normally lines the inside of the uterus grows on the pelvic wall and otherwise outside the uterus. Currently, the only way to diagnose endometriosis and its stage definitively is laparoscopy, a surgical procedure. A new, nonsurgical diagnostic alternative may eventually be available, thanks to a study using sophisticated computer-based technology to analyze genetic data obtained from uterine tissue of women with endometriosis, women with other uterine or pelvic problems, and women without such problems. The analysis identified patterns of genetic activity that enabled the researchers to tell which women had endometriosis; they could also tell the difference between earlier and more advanced stages of the disorder and could identify endometriosis at different points in the menstrual cycle. Further research, including research with a larger group of women, may lead eventually to a definitive, nonsurgical test for endometriosis. (Tamaresis et al., 2014)

Fertility and Infertility

Drug Improves Birth Rates for Women with Fertility Disorder. Women with polycystic ovary syndrome, a leading cause of female infertility, are typically treated for infertility with clomiphene. Clomiphene has multiple side effects (e.g., mood changes, hot flashes), its success rate for live births is relatively low (22 percent), and women who become pregnant are at elevated risk for multiple births. A recent trial comparing clomiphene with letrozole, a drug used to treat breast cancer, found that it is a promising alternative to clomiphene. Women treated with letrozole were more likely to have live births than those receiving clomiphene (27.5 percent versus 19.1 percent). Letrozole also led to significantly increased ovulation rates compared to clomiphene (61.7 percent versus 48.3 percent). (Legro et al., 2014)

Increased Antioxidant Intake May Shorten Time to Pregnancy in Women with Infertility. Oxidative stress, which can disrupt normal mechanisms of cellular signaling, may be related to female infertility, according to some evidence. A study of self-reported dietary information from more than 400 infertile women, on their intake (dietary and supplemental) of the antioxidants vitamin C, beta carotene and vitamin E, found results that varied by age and body mass index (BMI). Shorter time to pregnancy was related to increased intake of vitamin C in women with BMIs less than 25, increased intake of beta-carotene in women with BMIs greater than 25, increased intake of beta-carotene and vitamin C in women younger than 35, and increased intake of vitamin E in women 35 and older. Thus, though influenced by age and BMI, increased antioxidant intake appeared to be associated with time to pregnancy in women with unexplained infertility. Further research is needed with a more diverse study population and biologic measurement of antioxidant levels, together with prospective collection of biologic samples to measure oxidative stress. (Ruder, Hartman, Reindollar, & Goldman, 2014)

International Women's Health

Program for Orphan Girls in Zimbabwe Provides Cost-Effective Assistance. Adolescent orphan girls in countries with limited resources are a particularly vulnerable group. They are more likely to drop out of school and engage earlier in sexual behavior, marry earlier, and become infected with HIV. A controlled trial of an assistance program for a group of orphan girls in Zimbabwe provided the girls with school fees, uniforms, supplies and a school-based teacher "helper" to monitor attendance and to encourage and assist the girls. After 2 years, girls who received this assistance were less likely than peers in the trial's control group to drop out of school. They were also less likely to marry early, which is particularly important because early marriage for these girls carries a higher health-related quality of life. The estimated value of the program's benefits exceeded program costs more than 200-fold, thus demonstrating its cost-effectiveness. (Miller, Hallfors, Cho, Luseno, & Waehrer, 2013)

Pelvic Organ Prolapse

Long-Term Follow-Up of Surgical Treatment for Pelvic Organ Prolapse. Pelvic organ prolapse occurs in women when the pelvic muscles and tissues can no longer support one or more pelvic organs, causing them to drop or press into the vagina or outside the body. More than 225,000 surgeries are performed annually in the United States for pelvic organ prolapse. One type of surgery, abdominal sacrocolpopexy, is considered the most durable treatment. However, little is known about the long-term effectiveness of this type of surgery. Researchers followed up with more than 200 women who received the surgery between 2002 and 2005. The scientists discovered that 7 years after treatment, between 20 percent and 30 percent of women either had some symptoms return or showed some signs of recurrent prolapse when examined by a physician. However, most of the women with recurrent prolapse did not receive additional treatment. The researchers concluded that although the surgery is effective for most women, the long-term success rate (measured by anatomic scoring) was lower than expected. (Nygaard et al., 2013)

Preeclampsia

Molecular Basis and Biomarkers for Preeclampsia. While some risk factors for preeclampsia are known, how to identify individual pregnant women with or without known risks is not understood, nor is what causes this serious complication of pregnancy. Identifying specific preeclampsia biomarkers for preeclampsia is considered critical, both for early prediction of its onset and for unraveling its causes. The recent discovery of a "micro-RNA" biomarker, miR-210, adds another clue to understanding the condition. Researchers found elevated levels of serum miR-210 in placental tissue of women in two clinical studies who had preeclampsia. The elevated levels were associated with an abnormality in the very earliest stages of the development of the fertilized egg. Serum miR-210 may be involved in the causes of preeclampsia and may be new predictive and diagnostic biomarker of preeclampsia, because it was elevated months before the onset of preeclampsia. If these findings are borne out by further research, miR-210 levels could aid in treatment and the early identification of pregnant women at risk of preeclampsia. (Anton et al., 2013)

Vitamin D and the Risk of Preeclampsia. Vitamin D deficiency appears to play a role in preeclampsia, according to a new analysis of data and stored serum samples in a large, 6-year (1959–1965) cohort of women who were followed through the course of their pregnancies. The analysis of samples taken at approximately the 26th week of pregnancy found that women who had experienced severe preeclampsia were deficient on vitamin D, while those with mild preeclampsia had vitamin D levels within the normal range. (Bodnar et al., 2014)

Pregnancy

Antibiotics for Pregnant Women. Little is known about the safety for the developing fetus of medications used to treat illness in pregnant women. Studies of macrolides, a class of antibiotics that include erythromycin, have yielded conflicting data on whether their use during pregnancy may increase the risk of birth defects, specifically a congenital heart defect and a malformation that can prevent the stomach from emptying into the small intestine (pyloric stenosis). To try to resolve the conflicting evidence, researchers studied 4,132 infants with congenital heart defects, 735 infants with pyloric stenosis, and 6,952 healthy infants whose mothers had taken erythromycin or another macrolide in the first trimester or the third trimester of pregnancy. The researchers found no associations between maternal use of these antibiotics and the congenital

heart defect, pyloric stenosis, or other major congenital malformation. They did, however, find a possible association between use of the drug and genital system defects. (Lin, Mitchell, Yau, Louik, & Hernández-Díaz, 2013)

Large Numbers of Women Are Prescribed Opioids for Pain During Pregnancy. Untreated, severe pain for a pregnant woman can create health risks for her and the fetus, but taking pain-relieving medications may also be risky, and little is known about the extent of this problem. Using a database from a large commercial health insurance plan in the United States, researchers found that more than 14 percent of women who had babies between 2005 and 2011 were prescribed opioid pain relievers during pregnancy. Most were for short courses of treatment, usually less than a week, although 2.2 percent of the women received three or more courses of these medications. Back pain was the most common condition (37 percent) for which opioids were prescribed. Other conditions included abdominal pain, migraine, joint pain, and fibromyalgia. Patterns of prescribing opioids varied regionally, from a low of 6.5 percent in the northeast to the highest in the south, with prescription rates exceeding 20 percent of pregnant women in Alabama, Arkansas, and Mississippi. The unexpected finding of significant opioid prescriptions during pregnancy indicates a need for more research on the use and effects of these medications. (Bateman et al., 2014)

Reasons for Cesarean Delivery Among First-Time Mothers. Although cesarean delivery risks potentially serious complications for both the mother and the infant, almost a third of U.S. deliveries in 2009 were cesarean, one of the highest rates in the world. About a fourth of first children are born by cesarean. To help identify opportunities to safely reduce the rate of cesarean deliveries, researchers reviewed clinical records for cesarean deliveries in 19 hospitals across the United States. They found that the most common reasons for cesarean delivery were the failure of labor to progress, the baby's heart rate, and the position of the baby's head (not down near the birth canal). By far the most common reason recorded for cesarean delivery of a woman's first baby was failure of labor to progress. This finding suggests that as long as the mother and baby are doing well during labor, waiting longer for labor to progress may help lower the rate of cesarean delivery. (Boyle et al., 2013)

Flu in Pregnancy May Greatly Increase Child's Risk for Bipolar Disorder. The effects of flu are likely to be more severe, even fatal, in pregnant women compared with women who are not pregnant. The effects of the infection may cause preterm labor and delivery, among other problems. Although public health authorities recommend flu immunizations to protect both the mother and child, only a fraction of pregnant women are immunized. The known dangers of flu during pregnancy prompted research on whether flu during pregnancy could cause long-term problems for the child. Following up the offspring of a group of women in the same health plan 40 years after they had had flu (between 1959 and 1966), researchers found that fetal exposure to flu dramatically increased the risk of an individual's risk of bipolar disorder in adulthood. The increased risk was even higher for a subtype of bipolar disorder with psychotic features. These findings reinforce recommendations that prospective mothers get flu shots prior to and in the early stages of pregnancy and avoid contact with people who have flu symptoms. In addition, the results may add to emerging evidence that bipolar disorder and schizophrenia may share some of the same underlying causes, because some studies have also linked schizophrenia to prenatal exposure to influenza. (Parboosing, Bao, Shen, Schaefer, & Brown, 2013)

Perceived Socioeconomic Status Is Associated with Postpartum Depression. Depression after giving birth (postpartum depression) affects about 8 percent of new mothers. To identify risk factors for such depression, researchers surveyed 300 rural women, 1 month and 6 months after giving birth, to assess rates of depression and possible risk factors, including race, marital status, whether a family received public assistance, and perceived socioeconomic status. Shown a picture of a ladder and told that it represented the status of all people in the United States with regard to money, education, and respected jobs, with those at the top best off, women who saw themselves low on the ladder 1 month after delivering a child had the highest risk of depression at 6 months. Those seeing themselves as having the highest socioeconomic status at 1 month were significantly less likely to be depressed 6 months after having a child. When all possible risk factors were considered together, only such perceived socioeconomic status was associated with postpartum depression risk. (Dolbier, Rush, Sahadeo, Shaffer, & Thorp, 2013)

Preterm Birth

Vaginal Progesterone and Cervical Cerclage Both Can Help Prevent Premature Birth for Some Women at High Risk. Studies of strategies to prevent preterm birth have shown the effectiveness of two treatments for pregnant women who have previously given birth and whose cervix is short in the second trimester—a powerful predictor of preterm birth. However, a direct comparison of the two strategies has been lacking until now. A recent comparison of four trials of one treatment, vaginal progesterone and five trials of the second, surgical closure ("cervical cerclage") found that they were equally effective in reducing risks for preterm birth and infant complications for this group of pregnant women. The comparison found the two strategies to be equally effective in reducing risks for premature birth and infant complications. This finding suggests that doctors should consider the costs and associated adverse event risks of each approach in considering which to recommend to patients. (Conde-Agudelo et al., 2013)

Primary Ovarian Insufficiency

Genetic Clue to Menopause-Like Condition in Young Women. The ovaries of women with Primary Ovarian Insufficiency (POI) stop producing estrogen before the age of 40, impairing the fertility of affected women and putting them at high risk for osteoporosis and heart disease. Researchers recently discovered a genetic clue to POI's origins in six young women with POI who had gene alterations that hamper the repair of damaged DNA. The altered genes belong to a family of genes, the minichromosome maintenance (MCM) family, which is known to help repair damaged DNA in egg cells. Genetic analyses of blood and skin samples from three nuclear families in which at least one woman had POI found that two of the affected women had a mutation of the gene MCM9, while a third had a mutation of the gene MCM8. None of the men or the women without POI had these mutated genes. The researchers plan next to find out if the MCM8 and MCM9 mutations play a role in any other health disorders. (Wood-Trageser et al., 2014; AlAsiri et al., 2014)

Hormone Treatment Restores Bone Density for Young Women with Menopause-Like Condition. A controlled clinical trial of two combinations of hormones for women ages 18–42 with POI showed that each combination treatment led to increases in bone density for them, but not in the control group of women with normal ovarian function. These results were determined by hip and lower-back bone scans at the outset of the trial and at its conclusion. In the 145-member experimental group, women received estradiol and testosterone patches plus progestin pills or the estradiol and progestin medications plus a placebo. Those with POI had lower bone mineral density at baseline, reflecting the estrogen deficits that characterize POI. By the end of the trial, bone density measures for both experimental groups with POI had increased to the same level as those of the control group. The inclusion of testosterone in the treatment combination did not prove statistically significant in helping to increase bone density. (Popat et al., 2014)

Uterine Fibroids

(See also Health Disparities, below)

Reducing the Structural Rigidity of Uterine Fibroids. Scientists recently found that restoring a missing, tumor-suppressing RNA molecule in a mouse model of uterine fibroids inhibited the growth of these noncancerous tumors. The pain, discomfort, and excessive bleeding associated with fibroids are seen to be associated with the stiffness and rigidity of the tissues, primarily collagen, that hold cells together in fibroids. Loss of the tumor-suppressing molecule, miR-29b, seemed to be associated with that rigidity. In a recent study, scientists examined the function of miR-29b in fibroids and found that when it was restored, the accumulation of the stiffening tissues and the growth of uterine fibroids were inhibited. They noted, however, that hormones and other factors are involved in the complicated development of fibroids. (Qiang et al., 2014)

Vulvodynia

Many Women Experience Vulvodynia, but Few Receive Diagnosis and Treatment. Vulvodynia, or chronic pain or discomfort in the vulvar region, is poorly understood, although it has potentially serious consequences for women's reproductive health and quality of life. Several recent population-based surveys of women offer some about how many women may experience vulvodynia-type pain and how it may last in affected women or patients. A southeastern Michigan survey found that more than 100,000 women in the Detroit area had vulvodynia symptoms at the time of the survey and an additional

218,000 women had had such symptoms in the past. Women of all ages as well as girls reported symptoms that, on average, lasted 12 years. Most women did not seek medical care, and only a small percentage of those seen by a clinician were diagnosed with vulvodynia; instead, estrogen deficiency or yeast infections were most commonly diagnosed. Women receiving or not receiving medical care were equally likely to report resolution of their symptoms. Boston and Minneapolis-St. Paul surveys found similar results. For example, by age 40, 7 percent to 8 percent of women experienced vulvar pain. Care seeking and lack of vulvodynia diagnosis were similar to results reported for the Michigan women. (Harlow et al., 2014)

Understanding the Process Underlying Vulvodynia Pain. A relatively simple touch test has expanded scientists' understanding of brain mechanisms involved in the localized pain of vulvodynia and generalized pain felt throughout the body, such as in fibromyalgia. It has not been clear whether the same mechanisms underlie localized and generalized pain, and better understanding of such mechanisms is critical step toward improving diagnosis and treatment of vulvodynia. Using functional magnetic resonance imaging, researchers captured images of brain response to pressure on a research subject's thumb, as pressed by a researcher. Three groups of women were studied: those with vulvodynia, those with fibromyalgia, and healthy women with neither condition. Brain responses of the women with the two disorders were very similar, while the brain responses of the healthy women were different. Moreover, the women with vulvodynia who experienced pain at the touch of the thumb ("provoked" vulvodynia) showed a different pattern of brain activation than those with vulvodynia who were in pain even without the thumb pressure ("unprovoked" vulvodynia). The results suggest that the same brain mechanisms may underlie both localized and generalized pain disorders and that it may become possible to distinguish subtypes of vulvodynia on the basis of differences in brain responses to provoked and unprovoked vulvar pain (Hampson et al., 2013)

No Connection Found Between Oral Contraceptives and Risk of Vulvodynia. If risk factors for developing vulvodynia were known, that could advance research on both the origins of this disorder and possible interventions to prevent or mitigate its symptoms. Using a population-based sample of more than 900 women younger than age 50, scientists explored whether using contraceptive hormones in the form of a pill could increase a woman's risk of eventually developing vulvodynia. No evidence emerged, however, connecting oral contraceptives to vulvodynia. Such negative results help scientists to narrow the search for possible risk factors. (Reed et al., 2013)

NICHD Scientific Research Advances in Sex and Gender Influences on Health and Disease

Developmental Origins of Sex and Gender Differences

Low Birthweight or Growth Restriction Affects Female and Male Rat Drug Responses Differently. Low weight at birth or lower than normal weight gain in the fetus and very young infant are known to elevate risks of type 2 diabetes, hypertension and/or obesity in adulthood. Scientists hypothesize that the insufficient flow of nutrients causing the weight problems may prompt the body to prioritize development of the brain and certain other organs at the expense of others, notably the kidneys. To assess the effects of growth restriction on kidney function, scientists compared how a diuretic drug affected kidney function in normal rats and those bred to have growth restriction. Compared with controls, the experimental rats had significantly less excretion of urine, less excretion of the drug, and certain other alterations in normal kidney function and structure. These effects were greater in female rats than in male rats. Compared with controls, growth-restricted female rats had 26 percent less urine excretion, while growth-restricted males had 12 percent less. Creatinine clearance, an indicator of kidney health, was 19 percent less in female than in male growth-restricted rats. (Dubois et al., 2014)

Animal Study Reveals Sex-Specific Patterns of Recovery from Newborn Brain Injury. Temporary cutoff of oxygen to the fetal or infant brain before, during, or immediately after birth can cause a range of neurologic, developmental, and learning disorders, including cerebral palsy. Newborn boys have been known for years to have a higher risk of this type of brain injury and more severe injury than girls. Now scientists have uncovered one possible reason for this disparity. Studies of male and female mice found that their brains react differently to injury caused by the temporary

oxygen loss. Male and female brain neurons underwent different types of cell death, possibly due to presence of certain types of receptors. This finding helped clarify earlier findings that while the brains of male mice sustain worse damage overall, they tended to respond better to certain types of therapies to halt neuronal cell death, compared with girls. (Chavez-Valdez, Martin, Razdan, Gauda, & Northington, 2014)

Influences of Sex and Gender Differences on Health

Sex Differences in Brains in Alzheimer's/Down Syndrome Mouse Models. Individuals with Down syndrome experience early-onset of dementia and nerve disease processes that resemble what is seen in the most common form of Alzheimer's disease. In both disorders, there are functional abnormalities in a critical neurologic brain system (basal forebrain cholinergic neuron [BFCN] system) that synthesizes a type of chemical (neurotransmitter) involved in memory and learning. Using two types of experimental mice engineered to have chromosomal abnormality typical of the two disorders, investigators found significant differences between the brains of female and male mice. Compared with the male mice, the female mice had about a third fewer BFCN neurons and smaller BFCN systems in all subregions. Further research is needed to fully understand the mechanisms underlying these differences and their significance for health. Such research should also yield clues to the vulnerability of the BFCN system in Down syndrome and Alzheimer's disease. (Kelley et al., 2014)

Osteoarthritis (OA) Is Often More Severe for Women than for Men. OA is the most common form of arthritis, affecting millions of people worldwide. It occurs when the protective cartilage on bones wears down over time. OA of the knee is very common in men and women but tends to be more prevalent and more severe in older women than in older men. Scientists looked at the differences between men and women with OA to better understand their functioning and outcomes. They studied nearly 300 patients with OA, some of whom were seeking surgical treatment. They found that women with knee OA, whether or not they were having surgery, were not able to function (e.g., stand up from a sitting position, walk, climb steps) as well as well as men with knee OA. Since individuals with greater impairments and challenges in functioning are more likely to have poorer outcomes after knee surgery, they should receive more targeted interventions to improve their strength and performance. These results suggest that women may benefit from earlier counseling as well as additional rehabilitation and treatment, such as strength training, to improve their outcomes. (Logerstedt, Zeni, & Snyder-Mackler, 2014)

Free Fatty Acid (FFA) Flux Is Significantly Different Between Obese Adolescent Girls and Boys. A recent study found that obese adolescent girls have a greater rate than obese adolescent boys of a biomarker for development of insulin resistance, which in turn is related to development of metabolic syndrome, type 2 diabetes, and cardiovascular disease. The biomarker is the rate at which molecules known as FFAs travel through blood when they are released from fat, used for energy, and returned to fat. The rate of this FFA flux in adults has been shown to predict development of insulin resistance, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Obesity, distribution, and sex are known to affect FFA flux; also known is that adult women are more highly affected than adult men. Rising rates of adolescent obesity prompted scientists recently to investigate FFA flux in this age group. Their analyses of blood samples, body fat distribution, and energy expenditure in a group of adolescent girls and boys suggested greater FFA flux in the girls, and thus greater risk of future disease, than in the boys. (Adler-Wailes et al., 2013)

Hypertension Elevated in Young Gay Men but Not Women. High rates of mental health conditions and sexually transmitted diseases in lesbian, gay, bisexual and transgender (LGBT) populations, but little research had addressed other physical health disparities between them and populations or among different LGBT populations. A recent analysis of data from the "fourth-wave" survey of the National Longitudinal Study of Adolescent health looked for such differences and unexpectedly found that young gay men had significantly higher prevalence of hypertension than their peers with traditional sexual orientation (38.7 percent prevalence and 27.2 percent prevalence, respectively). This difference was not seen between young lesbian women and those with traditional sexual orientation. The data analyzed were sexual orientation as reported by respondents 24–36 years old and objective measures of

hypertension (systolic and diastolic blood pressure). (Everett & Mollborn, 2013)

Lower Self-Reported Health Among Sexual Minorities. Researchers use the minority stress model to understand the cumulative effects the stress from experiencing stigma, prejudice, and discrimination as a member of a minority group, in addition to the general stressors that everyone experiences. Testing this minority model with gay, lesbian, and bisexual individuals has enhanced understanding of their higher rates of depression, anxiety, and substance abuse compared with populations with traditional sexual orientation. Only limited studies of transgender individuals, however, have suggested that stigma harms their mental health. Limited data on transgender populations were recently expanded when researchers tested the minority stress model in analyzing data on a large, diverse sample of transgender individuals in all regions of the United States. Close to half (44.1 percent) of survey respondents reported high rates of clinical depression, a third (33.2 percent) reported anxiety, and more than a fourth (27.5 percent) experienced stress as physical illness. Social stigma was associated with psychological distress while support of family and pride in identity had protective effects. (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013)

Career Development for Women in the Sciences

(See also Executive Summary, above)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program. NICHD participates in the BIRCWH program, which is led by ORWH along with nearly a dozen other NIH ICs. BIRCWH research centers provide "bridging support" to physician-scientists as they move between completion of clinical or postdoctoral training and an independent research career. BIRCWH research subjects span the spectrum of women's health topics and the program is open to all types of clinicians and nonclinicians.

Reproductive Scientist Development Program. The FI Branch continued to support a national career development program with the goal of developing a cadre of reproductive physician-scientists based in academic departments who could employ cutting-edge cell and molecular technologies to address important problems in the field of obstetrics and gynecology. The mentored research experiences this program offers seek to assist junior faculty in their transition to productive, independent physician-scientists who are highly competitive for research funding. The program accepts approximately four scholars each year for a 5- to 6-year training period. (http://www.nichd.nih.gov/research/supported/pages/rsdp.aspx)

Women's Reproductive Health Research Career Development Program. NICHD and ORWH support a national program of mentored institutional career development programs for junior faculty who have recently completed postgraduate clinical training in obstetrics and gynecology and are committed to an independent research career in women's reproductive health. The supervised research training will assist junior faculty in their transition into productive, physician scientists in areas related to obstetrics and gynecology and its subspecialties. (http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-026.html)

Inclusion

Within NICHD, responsibility for direct oversight implementation of inclusion policy rests with the Institute's Office of Extramural Policy, which oversees a range of specific activities involving scientific program, review, contracts management, grants management, and support staff, with Institute staff participating as appropriate. Specific activities range from communication by scientific program staff with potential applicants in the pre-application stage to ensure outreach and dissemination of inclusion requirements, administrative review of all grant applications and contract proposals by scientific review officers to ensure accurate coding of applications prior to peer review, peer review of applications and proposals with respect to adequacy of investigator plans for meeting inclusion requirements, and scientific program staff interaction with investigators whose applications or proposals were deemed unacceptable with regard to inclusion requirements. Activities also include review of annual progress reports (Public Health Service Form 2590) by scientific program staff to assure appropriate accrual and achievement of inclusion targets and entry and approval of both target and actual enrollment data into the Population Tracking System. In addition, NICHD program, review grants management, and contracts management staff are

encouraged to participate in all NIH training opportunities relevant to inclusion. Newly hired staff are required to have such training as soon as possible after assuming their position. The full report of the Institute's inclusion-related policies, strategies, and specific activities for FY 2013–2014, *2015 Biennial Advisory Council Report Certifying Compliance with Inclusion Guidelines* (January 2015), will be posted at http://www.report.nih.gov/special_reports_and_current_issues/index.aspx.

Funding Initiatives, Workshops, and Conferences

Funding Opportunity Announcements

The Cooperative Multicenter Maternal Fetal Medicine Units Research Network (RFA-HD-13-013; Data Coordinating Center for the NICHD Cooperative Multicenter Reproductive Medicine Network (RFA-HD-14-018 [U10]). The networked research units and their data coordinating center conduct studies on the health of the pregnant woman and the developing fetus.

Data Coordinating Center for the NICHD Cooperative Multicenter Reproductive Medicine Network (RFA-HD-14-018 [U10]). This data-coordinating center facilitates interventional and observational studies of problems in reproductive medicine, gynecology, endocrinology, urology, and andrology that affect fertility.

Developmental Pharmacology and Toxicology: Role of Ontogeny (PAR-13-306 [R01]; PAR 307 [R03]; PAR 13-308 [R21]). The purpose of this FOA is to stimulate multidisciplinary, investigator-initiated basic and translational research in developmental pharmacology and toxicology, with an emphasis on the role of ontogeny (development of an organism) on drug-metabolizing enzymes, transporters, receptors, and signaling pathways across developmental periods (fetus to adolescence) that affect drug action and toxicity.

Discovery of Molecular Targets for Pregnancy-Related/Induced Diseases and Development of Therapeutics to Prevent/Treat Diseases (PAR-13-398 [R01]; RFA-HD-14-031 [R43/R44], RFA-HD-14-032 [R41/R42]). The purpose of these FOAs is to stimulate research to identify molecular disorders associated with or induced by pregnancy (e.g., gestational diabetes mellitus, hypertension, preeclampsia, preterm labor), leading to new therapeutics that are safe and effective for the pregnant woman and the developing fetus.

Enhancing the Capacity for Biomedical Research on Tuberculosis for HIV-Infected Mothers and Children in India (RFA-HD-14-025). The purpose is to stimulate inclusion of HIV-positive and HIV-negative women and children exposed to or with tuberculosis in research of project units.

Female Contraceptive Development Program (RFA-HD-14-024 [U01]). The goal of this FOA is to continue NICHD's efforts to stimulate basic and clinical research leading ultimately to safer and more effective nonhormonal contraceptive options for women.

Global "Omics" Approaches Targeting Adverse Pregnancy and Neonatal Outcomes Utilizing Existing Cohorts (PAR-14-264 [R01]). The purpose of this FOA is to stimulate application to existing data from research on maternal and neonatal health problems of "high-throughput" technologies and techniques of comprehensive ("omic") studies of animal and human genes, proteins, and influence on molecular anomalies underlying disease processes that cause poor pregnancy outcomes.

In Vivo Methods for Assessing Placental Development and Function (RFA-HD-14-004, RFA-HD-14-005 [R42/R42]). The purpose of this Request for Application (RFA) is to stimulate research on development of safe, real-time, non- or minimally invasive in vivo methods to assess the development and function of the human placenta.

Postdoctoral Training Program in Obstetric and Pediatric Pharmacoepidemiology (PAR-13-112 [T32]). The goals of this multidisciplinary postdoctoral training program are to (1) encourage and support training in pediatric or obstetric pharmacoepidemiology and (2) produce a well-qualified cadre of academic investigators capable of conducting such research.

Safety and Effectiveness of Triple Antiretroviral Drug Strategies for Prevention of Mother-to-Child HIV Transmission (RFA-HD-14-027 [R01]). The purpose of this RFA is to stimulate research to evaluate the safety and effectiveness of implementing triple antiretroviral drug

strategies for preventing mother-to-child HIV transmission in resource-constrained settings.

Specialized Cooperative Centers Program in Reproduction and Infertility Research (RFA-HD-14-017 [U54]). This national network of research-based centers promotes multidisciplinary interactions between basic and clinical scientists interested in establishing high-quality translational research programs in the reproductive sciences. The centers also serve as national resources for the training and career development of young scientists electing careers in research in high-priority areas of reproduction and infertility.

Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (PAR-13-309 [R01]; PAR-13-310 [R03], PAR-13-311 [R21]). Recent advances in molecular profiling of many diseases of pregnant women and children and identification of new molecular targets in these diseases create new opportunities for novel research and drug development for these understudied conditions. Research efforts envisioned by this FOA complement NICHD's Obstetric-Fetal Pharmacology Research Units network.

Requests for Proposals

Data Analysis of Stillbirth Collaborative Research Network, Request for Proposal (RFP) NIH-NICHD 2014–2015. Awarded as contract HHSN275201400015C. This contract supports analyses of data collected through the NICHD Stillbirth Collaborative Research Network, designed to obtain data on the causes of and factors in stillbirth.

Diet, Obesity and Weight Change in Pregnancy, RFP NIH-NICHD-DESPR-2013-17-1. Awarded as contract HSSN2752013000015C. This contract supports a prospective cohort study of pregnant women to evaluate dietary intake during pregnancy and postpartum, weight change, and body composition change.

NICHD Contraceptive Clinical Trials Network, Female Sites, RFP-NICHD-CRHB-2013-03. This RFP resulted in the award of 19 Indefinite Deliverable, Indefinite Quantity contracts one to two task orders each for clinical trials of potential new contraceptives for women.

NICHD International and Domestic Pediatric and Maternal HIV Studies Coordinating Center, RFP NIH-NICHD-CRMC-2013-01. Awarded as contract HHSN275201300003. This center supports activities of the NICHD Maternal and Pediatric Infectious Disease Branch, which develops, implements, and directs domestic and international studies for the treatment and prevention of HIV infection and its infectious and noninfectious complications in women (pregnant and nonpregnant) as well as infants, children, and adolescents.

Workshops and Conferences

(See also Health Disparities, below)

2012 International Conference on Stillbirth, SIDS, and Infant Survival. The purpose of the conference was to bring together researchers and consumers of research to exchange information on the topics of stillbirth and sudden infant death syndrome (SIDS). October 2012.

Mississippi SIDS/Infant Mortality Conference. The purpose of the conference was for the Mississippi State Department of Health, public health researchers, health providers, and other stakeholders to discuss lessons learned from the 6 years of NICHD SIDS outreach project outcomes and address current challenges. October 2012.

Global Network for Women's and Children's Health Research Steering Committee Meeting. The purpose of the meeting was to facilitate the protocol development for the research network by its Steering Committee, with assistance from the Network's Advisory board. January 2013.

NIH Development Conference: Diagnosing Gestational Diabetes. The purpose of the conference was to advance understanding of the benefits and risks of gestational diabetes mellitus by considering findings of a rigorous review of the relevant scientific literature. The conference was sponsored by NICHD and the NIH Office of Disease Prevention and cosponsored by ORWH, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Nursing Research. The Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality were conference partners. March 2013. Conference materials and findings are available at http://consensus.nih.gov/2013/gdm.htm.

Identifying Elements Towards Diagnostic Case Criteria for Research in Vulvodynia. The purpose of this meeting was to facilitate development of reliable, valid and standardized measures for diagnosis and outcome

measurement for vulvodynia, as recommended by the 2012 NIH Research Plan for Vulvodynia. Consistency in evidence-based definitions is needed to further epidemiological, etiological and clinical studies and allow for comparisons across studies, thus moving the science forward more quickly. March 2013.

Down Syndrome and Alzheimer's Meeting. The purpose of the meeting was to discuss the association between Down syndrome and Alzheimer's disease and to develop a research agenda for advancing treatment of Alzheimer's and other dementias in individuals with Down syndrome. The meeting was convened by NICHD, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke. April 2013.

The 37 Percent: Developing a Research Agenda for Addressing Mistimed, Unintended, Unplanned, and/or Unwanted Pregnancies in the U.S. The purpose of the meeting was to respond to the NICHD Scientific Visioning priority of identifying the determinants of use and nonuse of contraceptives, identifying what interventions can help increase contraceptive use and decrease contraceptive failure, and developing a 10-year research agenda. The meeting also built on World Health Organization, U.S. Agency for International Development, and Bill and Melinda Gates Foundation efforts in international family planning. June 2013.

NICHD Young Investigators Conference for Maternal Fetal Medicine, Neonatal Perinatal Medicine, and Reproductive Endocrinology. This meeting for fellows and junior faculty members nominated by their research programs includes lectures on cutting-edge topics; a mock study section; a clinical trial design workshop; and sessions on balancing career, work, and home. August 2013.

Determinants of Gamete and Embryo Quality. The purpose of the meeting was to address high-priority research areas in the NICHD FI Branch's portfolio of ovarian biology and oocyte maturation, spermatogenesis and sperm function, and the genetics and epigenetics of reproduction and environmental and metabolic influences on gamete quality. October 2013.

Developing an Interdisciplinary Research Agenda for Genetics of Birth Defects. The purpose of the meeting was to discuss how informative experimental model systems are for understanding human birth defect etiologies, the value of epigenomics in understanding etiologies of such birth defects, and epidemiological approaches for answering questions on risk/preventive factors for human birth defects. January 2014.

The Spelman Project. The purpose of this project was to bring together students, faculty, and staff of the historically Black women's college (Spelman College); health professionals; community members; and other stakeholders to promote the health of young women and their families and prevent disease. February 2014.

Growing Up with DSD: Critical Developmental Issues for Children and Families Affected by Disorders of Sex Development. The purpose of this workshop was to identify scientific research questions to fill in the substantial gaps in understanding the origins and effects of DSD and their implications for developmental processes and clinical care. An important topic in workshop discussion was possible biological influences of DSD on the gender identity and sexual orientation of affected individuals. March 2014.

Breastfeeding Outreach Meeting. The purpose of the meeting was to gain knowledge from key stakeholders from national breastfeeding organizations on the best ways to promote breastfeeding to breastfeeding educators and breastfeeding mothers and disseminate safe infant sleep messages. May 2014.

The First Annual C. Everett Koop Memorial Symposium on Women's Health Research: Empowering Women with Uniformed Service. Symposium speakers made presentations on community-based participatory research (CBPR), lessons from military medicine, and epigenetic reprogramming of female reproductive tract function by neonatal estrogen exposure, as well as a discussion of CBPR. May 2014.

Fragile X-Primary Ovarian Insufficiency (FX-POI). The purpose of the meeting was for FX-POI scientists to update attendees on research results and to advise NICHD on priority areas and research needs. An additional purpose was to update the scientists on the sites and research objectives in the Institute's Fragile X Centers program. September 2014.

The Human Placenta Project. The purpose of the first annual project meeting was for experts in placenta research, other creative thinkers who have not previously applied their expertise to placenta research, and other potential partners to help define scientific opportunities and approaches, long-term goals, intermediate metrics and deliverables, and a timetable for the project. May 2014.

Health Disparities

The NICHD Office of Health Equity (OHE) within the Office of the Institute Director develops, coordinates, and supports programs targeted on health disparities, enhancing research capacity development in emerging research institutions both domestically and abroad and developing research and scientific leadership in colleges and universities worldwide (http://www.nichd.nih.gov/about/org/od/ohe/Pages/overview.aspx). To accomplish its mission, OHE works closely with other NICHD branches and offices as well as other NIH organizations. OHE's activities pertaining to women's health research include:

The Biomedical and Behavioral Research Innovations to Ensure Equity in Maternal and Child Health Program (R15). This ongoing program supports basic, translational, and clinical research on maternal and child health disparities at emerging women's colleges as well as emerging institutions that serve students from underrepresented minorities or disadvantaged backgrounds. The program is designed to strengthen the research environment at these institutions and expose their students to this research.

The NICHD Health Equity Seminar Series is a forum, open to the public, for raising awareness of populations at risk for disparate outcomes in maternal and child health, providing leadership in the scientific community and sharing research findings on maternal and child health issues that impact diverse populations. Seminars in the series have included the following:

- **NICHD Health Equity Seminar Series: The Rise of Maternal Mortality in Women of Color: Research Update, Observations, and Future Directions.** The purpose of this seminar was to review the current status of female mortality, specifically in pregnancy-related women of color; to determine the current status and research in regard to such mortality; and to explore directions for future biobehavioral, basic, and clinical research and outreach. July 2013.
- **NICHD Health Equity Seminar Series: Moving Toward Reproductive Health Equity: Implications of Unintended Pregnancy.** The purpose of the meeting was to highlight research focused on the social and economic consequences of unintended pregnancy, strategies for increasing access to safe and effective methods, and factors related to contraceptive behavior among populations at increased risk for unintended pregnancy. June 2014.
- **NICHD Health Equity Seminar Series: Toward Understanding the Pathobiology of Preeclampsia and the Underlying Mechanism of Vitamin D Involvement: Unpacking the Placental, Immune, and Demographic Components.** The purpose of the meeting was to review the status of basic research on placental development and preeclampsia and discuss research directions that include strategies for understanding vitamin D as a risk factor for preeclampsia, both of which are seen disproportionately in Black women. September 2014.

Scientific Research Advances

African-American Women Have Higher Rate of Fibroids, Even Before Symptoms Appear. Uterine fibroids (leiomyomas), the most common indication for hysterectomies, may not become symptomatic until many years after they begin to develop, or may remain asymptomatic. Symptoms can include heavy bleeding, pain, and reproductive dysfunction. These benign gynecological tumors affect up to 65 percent of women by age 50. For reasons that are not understood, they occur far more frequently in African-American women than in women of other races. A recent study, however, provides evidence that this racial disparity begins in early reproductive years, before fibroid symptoms appear. The study, to determine the prevalence of asymptomatic fibroids in young (aged 19–30 years) African-American and White women found that the overall prevalence of ultrasound-diagnosed fibroids was 15 percent. For the African-American women, however, the prevalence rate was 26 percent, compared with a rate of 7 percent for White women. An additional finding that requires further study is that the lining of the uterus (endometrium) was thicker in the African-American women than in their White peers. (Marsh et al., 2013)

Racial and Ethnic Variations in Rates of Preeclampsia. An analysis of more than 56,000 medical records of women in their first pregnancy found significant disparities in risk of preeclampsia, a complication of pregnancy that is serious and may be fatal for the woman and the fetus. Preeclampsia, characterized by dangerously high blood pressure, also raises a woman's risk of heart problems later in life. Analyzing their data by race and ethnicity, the researchers found that non-Hispanic Black women were more likely than non-Hispanic White women to have a history of high blood pressure before they became pregnant. Non-Hispanic Black women without a prior history of high blood pressure were also more likely to develop preeclampsia than non-Hispanic White women. Hispanic and Asian women were the least likely to develop preeclampsia in a first pregnancy. Noting similar racial and ethnic differences in heart disease, the researchers suggested that preeclampsia and heart disease may share common pathways or similar risk factors. (Ghosh et al., 2014)

Trends in Age of Menarche Over Time. The younger the age at which a girl begins menstruating (menarche), the higher her risk of becoming pregnant or developing breast cancer or cardiac disease later in life. Early maturation also increases a girl's risk of being precociously sexualized and sexually harassed. Data, however, are both quite limited and conflicting on whether the age of menarche is declining in the United States. A new analysis of survey data from 1959–1962, 1971–1994, and 1999–2008 found that the average age of menarche in the United States had declined overall for both African-American and White women. For both racial groups, the proportion of women in lower socioeconomic groups more than doubled from the first to the last survey. (Krieger et al., 2015)

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National Institute on Deafness and Other Communication Disorders

Executive Summary

Established in 1988, the National Institute on Deafness and Other Communication Disorders (NIDCD) is mandated to conduct and support biomedical and behavioral research and research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language. The Institute also conducts and supports research and research training related to disease prevention and health promotion; addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders; and supports efforts to create devices which substitute for lost and impaired sensory and communication function.

It is estimated that more than 46 million people in the United States suffer from some form of disordered communication. NIDCD has focused national attention on disorders of human communication and has contributed to advances in biomedical and behavioral research that will improve the lives of millions of individuals with communication disorders. NIDCD has made important contributions to the body of knowledge needed to help those who experience communication disorders and to advance research in all aspects of human communication.

Several diseases, disorders, or conditions within the mission of NIDCD disproportionately affect women. Examples of significant research programs have been selected for inclusion in this report, with the latest research advances and the future directions of these projects being highlighted.

Accomplishments and Activities

Voice Disorders

Voice production and its quality influence communicative exchange throughout the life span, with some voices being perceived as pleasing and facilitating to reception of a message and others being perceived as unpleasant and not communication-enhancing. Voice disorders affect millions of Americans, influencing their quality of life and impairing their ability to communicate effectively and to function in our society. Voice disorders are not trivial, although they are overwhelmingly under-recognized. A number of voice disorders, such as occupational voice disorders and spasmodic dysphonia, appear to affect women more frequently than men.

Occupational voice disorders are estimated to affect 28 million Americans and have a significant impact on the livelihoods of teachers and professors, TV and radio journalists, lawyers, and singers. Data in the literature clearly identify voice disorders as teachers' primary occupational risk not only in the United States but also internationally. Women constitute the largest proportion of teachers in U.S. classrooms. Moreover, voice problems constitute a global women's health concern. Until recently, few reports have been available on the treatment of these problems in teachers, and even fewer have addressed the equally important question of prevention.

NIDCD supports basic, clinical, and translational research studies that focus on normal voice production and the prevention and treatment of voice disorders. Of note are the studies examining behavioral vocal hyperfunction. Vocal hyperfunction is not organic in origin, but rather a result of a habitual pattern of voice use, which may be traumatic to laryngeal tissue and function. NIDCD-supported investigators are conducting a study within the context of the long-range goal of identifying effective intervention methodologies for both the prevention and treatment of voice problems in teachers, taking into consideration multicultural and linguistic factors (R01 DC008567). Another multidisciplinary research team is investigating specific gender-based speech production differences that may underlie women's elevated incidence of vocal health problems, especially in high-voice use professions (R01 DC012315).

Spasmodic dysphonia (SD) is a voice disorder that predominantly affects women, with estimates as high as 80 percent of affected individuals being female. SD is a neurological disorder (dystonia) affecting the voice muscles in the larynx. In SD, the muscles inside the vocal

folds experience sudden involuntary movements—called spasms—which interfere with the ability of the folds to vibrate and produce voice. SD causes voice breaks and can give the voice a tight, strained quality. People with SD may have occasional breaks in their voice that occur once every few sentences. Usually, however, the disorder is more severe, and spasms may occur on every other word, making a person's speech very difficult for others to understand. At first, symptoms may be mild and occur only occasionally, but they may worsen and become more frequent over time. SD is a chronic condition that continues throughout a person's life. It is a rare disorder, occurring in roughly 1 to 4 people per 100,000 people and estimated to affect 50,000 people in North America. The first signs of this disorder are found most often in individuals between 30 and 50 years old. There is no cure for SD, and the most common treatment is the injection of very small amounts of botulinum toxin directly into the affected muscles of the larynx. Repeat injections are necessary, because the effects last only a few months.

NIDCD currently funds research aimed at determining the causes and pathophysiology of SD in order to develop new diagnostic and better treatment options. NIDCD-supported scientists are using multimodal imaging and next-generation DNA sequencing to identify brain abnormalities and genetic risk factors for SD (R01 DC008567 and R01 DC012545). The identification of genes responsible for this voice disorder may lead to better and more accurate detection and diagnosis in this clinical population. Locating specific brain areas involved in regulating laryngeal muscles and understanding the neural mechanisms by which they exert their control may open avenues for new pharmacological therapies and surgical interventions.

NIDCD will continue to support voice disorders research based on recommendations from a 2013 NIDCD-sponsored workshop on voice sciences and disorders. The consensus of leading experts in the field was that it is essential to strengthen the pipeline of future voice scientists from various academic backgrounds to encourage collaborative efforts to address lingering research questions. As a result of the workshop, NIDCD issued two funding opportunity announcements (FOAs) on advancing research in voice disorders. The FOAs call for cutting-edge research proposals such as the development of biomaterials for engineering vocal fold tissue and development of ambulatory biofeedback approaches for management of patients with voice disorders. Additionally, patient outcomes research, health services research, and community-based research—with special attention to the needs of low socioeconomic status populations, populations with health disparities, rural populations, second language populations, and women's health—have been highlighted and are especially encouraged.

Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. Maternal transmission of CMV is well recognized as a common cause of sensorineural hearing loss (SNHL). CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of SNHL per year. NIDCD-sponsored scientists continue to make significant progress to fully characterize the effects of CMV on SNHL as well as the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on the development of late-onset SNHL (HHSN263201200010C).

NIDCD-supported investigators conducted a preclinical animal trial of delivering antiviral drugs to the inner ear via an intratympanic route. Drawing upon the vast otologic experience with intratympanic administration of drugs (such as corticosteroids or aminoglycosides) to treat the cochlea and inner ear, the investigators proposed that the intratympanic delivery of antiviral agents (ganciclovir and cidofovir) can be used to effectively treat CMV-related hearing loss while avoiding the numerous and significant potential side effects of these antiviral drugs. They tested this hypothesis using their well-developed guinea pig model of CMV infection and hearing loss. The results will inform future clinical trials designed to administer antiviral drugs to the middle ear space as a means to treat CMV-related inner ear disease. The potential benefits of delivering antivirals intratympanically include increased efficacy as well as reduced toxicity (R01 DC008651).

Otosclerosis

Otosclerosis is caused by abnormal bone remodeling in the middle ear. Bone remodeling is a lifelong process in which bone tissue renews itself by replacing old tissue with new. In otosclerosis, abnormal remodeling disrupts the ability

of sound to travel from the middle ear to the inner ear. Otosclerosis affects more than 3 million Americans. Many cases of otosclerosis are thought to be inherited. White, middle-aged women are most at risk.

The complicated architecture of the ear makes it difficult to study. Because researchers can't remove and analyze a sample of the inner ear from a living person who has otosclerosis (or other hearing disorders), they must study ear bone samples from cadavers donated for research. These samples, called temporal bones, are in short supply. To encourage more research on otosclerosis, NIDCD supports the National Temporal Bone, Hearing, and Balance Pathology Registry at the Massachusetts Eye and Ear Infirmary (U24 DC013983). This effort coordinates the collection and sharing of temporal bone tissue among laboratories. In addition, the NIDCD Otopathology Research Collaboration Network encourages scientists to combine modern biology, imaging, and computer technologies with information from patient history and pathology reports to look for new clues and solutions to ear disorders caused by bone abnormalities (U24 DC013983, U24 DC011962, U24 DC11943, and U24 DC011968).

NIDCD also funds genetic studies and bone-remodeling research to better understand the causes of otosclerosis as well as to investigate potential new treatments. NIDCD-supported researchers are currently testing—in animals—the effectiveness of an implantable device that can deliver a bone growth–inhibiting drug directly into the inner ear to correct the bone abnormalities that cause otosclerosis. If the results are promising, testing will later be done in people (R01 DC009837).

Balance Disorders

NIDCD supports research on balance and the vestibular system, which is housed in the inner ear and helps with maintaining balance and navigation. Normal balance is maintained by an interaction among vision, vestibular, proprioceptive (position sensation), and musculoskeletal systems. All of these systems can deteriorate with age, and the American population is aging. Vestibular disorders, some of which are more common in women, can lead to dizziness, vertigo, nausea, and various forms of balance disturbances. More than 4 in 10 Americans, especially the elderly, will experience an episode of dizziness sometime during their lives that is significant enough to send them to a doctor. Balance disturbances can lead to falls that can result in severe trauma and even death.

Linear acceleration detectors of the vestibular system, the otolithic organs, detect the forces produced by head tilt and by linear (front-to-back, side-to-side) head movements. How the vestibular and the nervous systems resolve gravitational from linear accelerations in order to accurately perceive motion and control balance is currently under active study by NIDCD-supported scientists (R01 DC004260 and R56 DC012038).

Ménière's disease is one vestibular disorder of the inner ear that causes severe dizziness (vertigo), ringing in the ears (tinnitus), hearing loss, and a feeling of fullness or congestion in the ear. Ménière's disease can develop at any age, but it is more likely to first occur in adults between 40 and 60 years of age and is more common in women. NIDCD estimates that approximately 615,000 individuals in the United States are currently diagnosed with Ménière's disease and that 45,500 cases are newly diagnosed each year. Endolymph fluid buildup in the labyrinth is believed to contribute to vertigo and other symptoms of Ménière's disease. Researchers are hoping to develop methods for manipulating inner ear fluids that could lower endolymph volume and reduce or eliminate dizziness (R01 DC001368).

Vestibular migraine, a variant of migraine in which dizziness is a prominent feature, affects about 1 percent of the general population and 10 percent of patients seen in dizziness and headache clinics. Like conventional migraines, vestibular migraines are more prevalent in females. Little is known about the clinical course of this disorder or the functional impairment that it causes, and there is no proven therapy. NIDCD-supported investigators are conducting a phase II clinical trial to assess the efficacy of a drug, rizatriptan, in treating vestibular migraines. If successful, this study will provide the first data for an evidence-based treatment of vestibular migraines and set the stage for larger phase III trials (U01 DC013256).

NIDCD research is attempting to develop vestibular prosthetic devices and minimally invasive surgery techniques to control imbalance and vertigo while preserving hearing and other functions. Dysfunctions of the vestibular system can occur independently or with a hearing loss. NIDCD has encouraged translational research in nonhuman primates towards development of a vestibular implant similar to the cochlear implant. In FY 2013, NIDCD issued an FOA and

made two awards (R01 DC014002 and R01 DC013536) to encourage continued research and development efforts for translation of electrical stimulation of the vestibular nerve to studies in human subjects to replace balance and positional information lost through disorders like Ménière's disease or vestibular migraines.

Funding Opportunities

A number of FOAs have been released to encourage research in issues relevant to women's health, including voice and vestibular disorders, hearing health care, development of measures that determine hearing outcomes, and the translation of basic research into clinical tools.

PA-13-102: Disorders of Human Communication: Effectiveness, Outcomes and Health Services Research. The goal of this FOA is to accelerate the translation of research discoveries into practice, to increase access to health care, and to enhance the delivery, quality, and effectiveness of care with the purpose of improving personal and public health.

RFA-DC-14-002: NIDCD National Temporal Bone, Hearing & Balance Pathology Resource Registry (U24). The NIDCD Temporal Bone Registry is a national research resource for human otopathology. Its fundamental purpose is to coordinate information about specimens of the human ear and its disorders. The registry coordinates specimen collection, information recording, and data management of specimens and provides public information, including an up-to-date Web site about human ear research. It is not a simple database or tissue bank for human ear specimens. This FOA supports these functions to enhance and promote critically needed research on the middle ear and inner ear that cannot be done in living humans.

PA-14-009: NIDCD Research Grants for Translating Basic Research into Clinical Tools. The intent of this FOA is to provide a new avenue for basic scientists, clinicians, and clinical scientists to jointly initiate and conduct translational research projects. The scope of this FOA includes a range of activities to encourage translation of basic research findings, which will impact the diagnosis, treatment, and prevention of communication disorders.

PA-14-091: NIDCD Research on Hearing Health Care. This FOA encourages research leading to accessible and affordable hearing health care. The overarching emphasis is on the acquisition of knowledge that can be rapidly translated into new or enhanced approaches for access, assessment, or interventions with a goal of delivering better hearing health care outcomes. Applications that seek quality approaches that are effective, affordable, and deliverable to those who need them, as well as implementable and sustainable in settings beyond the research environment, are encouraged.

PA-14-236: Advancing Research in Voice Disorders. This FOA encourages research focused on advancing our scientific knowledge of the human larynx and human voice production in health and disease and optimal ways to prevent, evaluate, diagnose, and clinically manage voice disorders.

RFA-DC-13-001: Development of a Vestibular Neural Prosthesis. This FOA solicits grant applications that advance the development of a vestibular neural prosthesis towards studies in human subjects. Responsive applications must employ electrical stimulation of the vestibular nerve to diminish sensory impairments arising from damage or disease to the vestibular endorgans.

Awards Cited

R01 DC008567: Prospective Study on Prevention and Treatment of Voice Problems in Teachers

R01 DC012315: Gender Differences and Speech Accommodation in Occupational Settings

R01 DC012545: Voice Tremor in Spasmodic Dysphonia: Central Mechanisms and Treatment Response

HHSN263201200010C: The Natural History of CMV Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing in the Newborn

R01 DC008651: A Preclinical Trial of Intratympanic Antivirals for CMV-Related Hearing Loss

U24 DC013983: NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry

U24 DC011962: The Otopathology of Hearing Loss: Genotype-Phenotype Correlation in Human Temporal Bone

U24 DC11943: Otopathology by Light Microscopy and Molecular Techniques

U24 DC011968: Pathology and Pathogenesis of Otitis Media, Syndromic Ear, and Ménière's Disease

R01 DC009837: Drug-Eluting Stapes Prosthesis for the Prevention of Sensorineural Hearing Loss

R01 DC004260: Neural Mechanisms of Vestibular Function

R56 DC012038: Innovative Methodology for Measuring Vestibular Thresholds

R01 DC001368: Inner Ear Fluid Interactions

U01 DC013256: A Phase II Trial on Rizatriptan for Vestibular Migraine

R01 DC014002: Optimization of a Human Vestibular Prosthesis

R01 DC013536: Multichannel Vestibular Prosthesis Pilot Early Feasibility Trial

National Institute of Dental and Craniofacial Research

Executive Summary

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving dental, oral, and craniofacial health through research and research training. This includes funding clinical and basic research to understand, prevent, and treat oral diseases and craniofacial conditions that disproportionately or solely affect women. These diseases include orofacial pain, temporomandibular joint disorder (TMD), osteoporosis of the craniofacial complex, and autoimmune salivary gland diseases. NIDCR also supports research related to the oral health of pregnant women and mothers, including their own oral health and that of their children, and conditions related to unborn children such as craniofacial development. This report highlights accomplishments and initiatives in key areas related to women's health, including oral health disparities and the oral effects of HIV infection.

In FY 2013 and FY 2014, NIDCR supported a variety of studies designed to identify risk factors and characterize diseases affecting women. NIDCR-supported investigators are studying how various sex hormones affect TMD and pain sensitivity. Other researchers are investigating potential risk factors and treatments for TMD, including the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, which continues to explore genetic and other risk factors associated with TMD. NIDCR-funded investigators have made recent advances in studying osteoporosis, which disproportionately affects women, including identifying risk factors for osteonecrosis of the jaw that is associated with several drugs used to treat osteoporosis. NIDCR supports a number of studies on Sjögren's syndrome, an autoimmune disease with dramatic oral health consequences that affects women nine times more frequently than men. This includes support of the Sjögren's International Collaborative Clinical Alliance (SICCA) biorepository, which distributes clinical samples to investigators worldwide. NIDCR also supports research to define the best methods to eliminate disparities in oral health that often are found in women and their children.

Recognizing the importance of gene-gene, gene-environment, and behavioral interactions, the Institute has long emphasized basic, genetic, behavioral, social science, and epidemiological research. Researchers supported by NIDCR during FY 2013 and FY 2014 continue to define genes associated with craniofacial anomalies such as cleft lip and palate and other problems with facial development such as craniosynostosis. This could lead to improved prevention, diagnosis, and treatment in pregnant women at risk for giving birth to children with craniofacial abnormalities. NIDCR also supports basic science studies

examining growth and development of teeth, cartilage, and bone that provide the scientific foundation for understanding oral diseases.

Accomplishments and Activities

Pain Research

For many years, NIDCR-supported research has explored many aspects of pain, ranging from basic science studies to efforts to develop new therapies for acute and chronic pain, including conditions that primarily affect women. Findings from these studies demonstrate that men and women respond differently to painful stimuli and that women are more likely to develop certain chronic pain conditions. Human and animal studies include research in the following areas.

Neuropathic Pain

The prevalence of chronic orofacial pain conditions such as burning mouth syndrome (BMS) is greater in perimenopausal and postmenopausal females. BMS is characterized by ongoing burning pain within the mouth, which may be due to a variety of causes. One possibility is damaged neurons in the pathways related to taste. Researchers have shown that the taste system itself is likely not involved in BMS by testing capsaicin avoidance in a perimenopausal and postmenopausal animal model using surgical disruption of the chorda tympani, a facial nerve that originates from the taste buds and carries taste messages to the brain. The surgical procedures did not reduce the amount of capsaicin consumed by the rats and indicated that damage to the taste system is likely not involved in nociception, or pain receptor activity (Boucher, Simons, M. I. Carstens, & E. Carstens, 2014). Further, NIDCR recently funded a clinical study that proposes to assess multiple potential central nervous system (CNS) abnormalities that could further our understanding of BMS symptoms. By combining data from multiple levels of CNS function, this study will seek to identify CNS markers that may contribute to the pathophysiology and clinical presentation of this poorly understood orofacial pain condition that primarily affects women.

Recent research on the prolactin receptor in trigeminal neurons, which are responsible for sensation in the face, suggests that prolactin plays a role in pain sensation differences between males and females. The prolactin receptor exists in two isoforms, long and short. Only the short isoform was able to mediate responses from capsaicin in both male and female trigeminal neurons, yet prolactin can differentially activate these nociceptors in a sex-dependent manner (Belugin et al., 2013). Further studies on the prolactin receptor will help elucidate the different mechanisms of nociception in male and female trigeminal neurons.

An improved understanding about the pathophysiology and clinical presentation of orofacial pain conditions may contribute to the development of better measures or tests of pain receptor activity. A recent study by NIDCR-funded researchers investigated the effect of craniofacial pain modulation on sensation using quantitative sensory testing, a method to measure pain levels. Sex differences were not detected, which highlights the need for continued investigation and development of tools to measure sensory pain (Oono, Baad-Hansen, Wang, Arendt-Nielsen, & Svensson, 2013).

Chronic Overlapping Pain Conditions

In September 2014, two funding opportunity announcements (FOAs) were issued soliciting Research on Chronic Overlapping Pain Conditions. These FOAs encourage epidemiologic, clinical, and translational research to increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors, including sex and gender, responsible for the presence of multiple chronic pain conditions. One study of TMD and irritable bowel syndrome, co-occurring chronic pain conditions, employed a novel animal model that combined craniofacial masseter muscle inflammation, stress, and estradiol. Researchers reported that a combination of these three factors was required to induce estradiol-dependent chronic visceral hypersensitivity characteristic of irritable bowel syndrome. The information gained from this model on the mechanisms underlying overlapping pain conditions will help future investigations for clinical management of pain (Traub et al., 2014).

Pain Management

Opioid drugs such as morphine are usually taken orally, leading to the peripheral distribution of the drug. This sometimes results in serious side effects, including breathing problems, nausea, constipation, addiction, and tolerance. However, by injecting the drugs centrally (directly into the cerebrospinal fluid), excellent pain relief can be achieved using much smaller doses, reducing the risk of these side effects. Previous research has suggested that centrally administered opioids are more potent in males than in females. Currently, little is known about possible sex differences when opioids are given peripherally. Using an animal model, ongoing work by NIDCR-funded investigators has shown sex differences are also present when a specific subtype of opioid is given by the peripheral route. Using this particular type of opioid has many advantages, including reduced side effects; however, the drug was found to be much more effective in alleviating pain in male rodents compared to females, suggesting that alternative drug treatments precisely tailored for men and women are needed.

Temporomandibular Joint and Muscle Disorders

Temporomandibular joint and muscle disorders are a diverse group of orofacial conditions associated with persistent orofacial pain and jaw dysfunction. Approximately 5 percent to 10 percent of the adult population reports symptoms of TMD at any one time. Most cases resolve with minimal or no treatment; however, some individuals develop a chronic, painful disorder that is associated with a significant functional, emotional, and financial burden. Despite its high societal cost, the natural history of TMD is not well characterized, and minimal treatments for chronic TMD are available.

More women develop chronic TMD and report higher levels of pain than men in experimental settings. This suggests that sex hormones may play a role in disease onset and pain sensitivity. Understanding how sex hormones affect disease and pain sensitivity could guide design of individualized treatments for TMD. Several NIDCR-funded research groups are studying such differences. One team, using a rodent model of acute inflammatory pain, showed that the female sex hormone estradiol has a profound effect on numerous genes important in pain modulation and regulation of nerve inflammation. These effects were seen throughout the trigeminal system, which controls the sensory and motor functions in the face, teeth, mouth, nasal cavity, and the temporomandibular joint (TMJ) itself. The genes involved are likely targets for relieving chronic TMD pain. A different study examining the sensory fibers supplying the TMJ found that estrogen status plays a role in their discharge rate, magnitude, and duration at the earliest stages of TMJ nociceptive processing (Tashiro, Bereiter, Thompson, & Nishida, 2014). At the basic science level, there are ongoing studies examining the mechanics of the joint, including one to understand how forces affecting the TMJ disc differ in males and females. Their findings suggest there are sex differences underlying TMJ pathophysiology (Wright et al., 2013).

Since TMDs primarily affect women of childbearing age, this suggests female hormones may play an important role in the development of this painful condition. To test this hypothesis, NIDCR-supported investigators are addressing potential involvement of estrogen in TMD pathogenesis using mouse models that lack specific types of cellular receptors for estrogen and thus are unable to properly control estrogen-mediated gene expression. Early results from this investigation indicate that estrogen might inhibit cell proliferation in the TMJ, thereby interfering with the capacity of the joint to withstand mechanical stress associated with jaw movement and mastication. This, in turn, can result in TMD. Currently, the investigators are further validating these findings that may lead to new therapeutic strategies to prevent and treat TMD through inhibition of certain components of estrogen action on the TMJ in premenopausal women.

Orofacial Pain: Prospective Evaluation and Risk Assessment

In 2004, NIDCR funded the OPPERA study, the first large, multisite prospective clinical study that seeks to identify biological, psychological, and social factors that increase the risk of developing TMD and transitioning to chronic TMD. During the past year, initial results suggest there are two components of how pain is perceived: pain amplification and psychological distress. These components interact with environmental and genetic factors and contribute to TMD pain persistence.

The OPPERA study has identified new risk factors and confirmed others previously reported. For example,

consistent with previous results, chronic TMD is more common in women and the non-Hispanic white population. This study has found that increasing age within the range of 18 to 44 years is associated with higher risk of chronic TMD. Signs and symptoms associated with chronic TMD risk include greater facial pain, pain-related interference with function, greater limitations in jaw function and movement, past jaw injury, and a higher frequency of other pain conditions such as fibromyalgia. Major psychosocial risk factors strongly associated with chronic TMD include heightened somatic awareness (sensitivity to physical sensations and bodily activity), active distress, and catastrophizing. When tested in the laboratory, those with chronic TMD had different quantitative pain scores, and there are suggestions that autonomic system dysfunction, a condition in which the nervous system that controls much of the involuntary functions breaks down, plays a role in chronic TMD (Smith et al., 2013). In addition, this study assessed genetic risk factors. A screen of about 320 candidate genes identified several genetic changes associated with higher risk of chronic TMD. These included changes in a number of genes associated in pain signaling and genes for various types of pain receptors. In addition, this study confirmed the role of catechol-O-methyltransferase, an enzyme that helps to inactivate certain neurotransmitters, in TMD. Cumulatively, these results demonstrate that a group of factors influence one's risk for developing chronic TMD. These results are in the process of being confirmed with data generated in the second phase of OPPERA, which follows those who have just developed TMD, termed "first-onset TMD."

Additional results from OPPERA were published as a set of manuscripts detailing the risk factors for first-onset TMD. The incidence of first-onset TMD was higher for people with low-back pain or genital pain symptoms than those without this history of pain. Factoring in exposure to sex hormones, this revealed a significant association with TMD incidence. The importance of this work is the finding that multiple overlapping health conditions were predictors of first-onset TMD. OPPERA II explores in greater depth genetic risk factors for chronic and first-onset TMD and determines the prevalence of other chronic pain conditions that frequently co-occur with TMD and can also disproportionately affect women, such as headache, irritable bowel syndrome, chronic low-back pain, and chronic widespread pain (Sanders et al., 2013).

Other Examples of NIDCR-Supported TMD Research

- The widely used Research Diagnostic Criteria for Temporomandibular Disorders, originally published in 1992, included an Axis I physical assessment and diagnostic protocol and an Axis II assessment of psychological status and pain-related disability. Recently, researchers conducted a validation project, during which they revised and validated the Axis I diagnostic algorithms to improve sensitivity and specificity. The Axis II instruments were shown to be both reliable and valid for screening, but revision was warranted to increase the scope and improve efficiency in a clinical setting. After two international consensus workshops provided recommendations for revision of the Axis I algorithms, the revisions were assessed for validity and reliability. The newly recommended Diagnostic Criteria for TMD (DC/TMD) Axis I protocol includes both a valid screener for detecting any pain-related TMD and valid diagnostic criteria for the most common pain-related TMD. Diagnostic criteria for other common intra-articular disorders lack adequate validity for clinical diagnoses, but they can be used for screening purposes. The recommended evidence-based new DC/TMD protocol is appropriate for use in both clinical and research settings. More comprehensive instruments augment short and simple screening instruments for Axis I and Axis II. These validated instruments allow for identification of patients with a range of simple to complex TMD presentations. The new DC/TMD protocol is a step toward the ultimate goal of developing a mechanism- and etiology-based DC/TMD that will more accurately direct clinicians in providing personalized care for their patients.
- NIDCR-funded researchers recently launched a study to evaluate the utility of TMJ imaging in diagnosing and managing TMD. Old TMJ images of approximately 600 patients (mostly female) treated for TMD over the past 6 to 10 years will be compared to new images to determine the degree to which progressive change in TMJ structures contributes to pain and dysfunction in TMD patients. The widespread availability of cone beam computed tomography imaging and proteomics technology is allowing a more detailed look at the structural architecture and molecular makeup of the

TMJ. A recent cross-sectional analysis of females with TMJ osteoarthritis found several local and systemic biomarkers were significantly correlated with morphological flattening of the lateral pole of the condylar articular surface. This suggests this bone resorption profile could contribute to the initial diagnosis of TMJ osteoarthritis (Cevidanes et al., 2014).

- NIDCR also supports a study to assess the ability of a brief survey to predict whether or not a patient with acute TMD is likely to progress to chronic disease and to determine the best therapy to prevent chronic TMD development in those most likely to develop chronic TMD.

Reconstruction of the TMJ

Severe TMD can lead to degeneration of the jaw joint itself. The TMJ is a complex joint that includes bone, cartilage, and muscle. Tissue engineering provides a promising approach toward regenerating tissues of the joint in patients affected by severe TMDs. Studies are underway to improve the level of tissue organization of the engineered cartilage by recapitulating certain processes that operate during normal cartilage development. This knowledge is key to engineering a TMJ disc prototype approximating the normal anatomical structure and function of the TMJ that will be tested in large animal models. If successful, the disc will be tested in human clinical trials for treatment of TMJ destruction. Additionally, researchers are exploring the role of estrogen in predisposition to and pathogenesis of TMD using mutant mouse models. These studies may lead to biologics-based noninvasive therapeutic approaches to prevent and treat TMD. Research in these areas includes the following studies:

- Collagen crosslinking endows cartilage, including the TMJ disc, with the mechanical properties and elasticity necessary for its proper function. Recapitulation of these properties in engineered cartilage constructs constitutes a difficult task. To address this need, NIDCR-supported investigators are attempting to increase the levels of collagen crosslinking in the engineered cartilage by manipulating activity of the enzyme lysyl oxidase (LOX), which is normally responsible for collagen crosslinking during native cartilage development. The results of this study show that increasing the levels of LOX in the engineered cartilage improves its mechanical properties, making them similar to those of native tissue. These new findings have a strong potential to improve the functional properties of engineered TMJ disk constructs.
- Work is underway to develop scaffold-free approaches for tissue engineering of the TMJ disk and other cartilaginous tissues. This approach relies on cartilage self-assembling processes that mimic those that take place during normal embryonic development. New strategies are also being explored for engineering osteochondral TMJ components that involve both scaffold-based and scaffold-free approaches that can create seamless interfaces between the bone (scaffold-based engineering) and the cartilage (scaffold-free engineering).

Mineralized Tissue Studies in Health and Disease

The study of teeth, bone, and other mineralized tissues has been a mainstay of NIDCR-supported research since the Institute's inception, not only because of its importance to oral health, but also to the growth and development of the entire body. Bone is an active and dynamic tissue that continuously remodels throughout life. The process of bone remodeling consists of cycles of bone formation and resorption. An imbalance between bone formation and resorption will lead to a change in bone mass. In children and young adults (< 20 years old), bone formation dominates resorption, resulting in bone growth and development. In healthy adults (20–40 years old), the processes of bone formation and resorption are delicately equilibrated, and no increase or decrease in bone mass occurs. However, in aging bone, an imbalance of resorption over formation often induces loss of bone mass and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture. Osteoporosis disproportionately affects women, who are four times more likely than men to develop the disease earlier in life. Those who take drugs orally for osteoporosis are also at risk for developing osteonecrosis of the jaw (ONJ), a painful lesion that develops in the jaw bone. NIDCR supports foundational research on the development and maintenance of mineralized tissue that could inform future prevention, diagnostic, management, and treatment strategies for osteoporosis and ONJ.

Development and Maintenance of Mineralized Tissue

Diseases that affect mineralized tissues of the craniofacial complex include periodontal disease, osteoporosis, and drug-induced osteonecrosis. NIDCR-funded investigators are studying the basic biological processes involved in the development and maintenance of bone, cartilage, and teeth.

- Defining the roles of bone cells, namely osteoblasts, osteoclasts, and osteocytes, is a primary focus in studies of bone remodeling. How these cells regulate bone mass through a balance of their activities is well described; however, the molecular process that regulates bone quality remains unclear. A group of NIDCR-funded investigators studied proteins that might participate in active regulation of bone quality in response to biological stimuli. A strong candidate that maintains bone quality is the extracellular collagen-degrading matrix metalloproteinase (MMP-13), which appears to have a novel role in remodeling of cortical bone matrix. This is particularly true during lactation when there is great demand to release calcium stores from bone, the regulation of which is another important area under study. The finding that MMP-13 is essential for bone quality could lead to therapies to prevent or reverse compromised bone fracture toughness. This work also has significant implications for understanding the bone changes and fragility that accompany steroid-induced osteoporosis, since these commonly prescribed drugs can regulate MMP-13 expression.
- Bone growth, development, and mineral balance are orchestrated by a complex repertoire of molecular switches. Problems with any of the components may lead to debilitating bone disorders and serious consequences such as fractures. Several ongoing projects are studying candidate genes and cellular pathways critical for the maintenance of bone forming and resorbing cells (osteoblasts and osteoclasts, respectively). Estrogen has been known to regulate the gene known as TGFβ inducible early gene (*TIEG*) in osteoblasts, and studies are underway to understand why mutation of *TIEG* leads to smaller and weaker bones in female mice but not in male mice. Bone homeostasis is the tightly controlled biological program of bone formation and bone resorption maintained by a healthy body. It is often affected by factors that influence gene activity, called epigenetic factors. Each step of this program is regulated by a series of activators and inhibitors. One project studying control of gene regulation in bone focuses on a metabolic pathway that serves as a major conduit for extracellular signals influencing bone cell response to hormones or mechanical loading. In other studies, microRNAs, which are small noncoding RNAs that regulate protein expression, were found to influence the formation of osteoblasts, the cells that form new bone. MicroRNAs were also found to regulate the differentiation of certain stem cells into osteoblasts, cartilage-forming cells, and even fat-forming cells. These studies showcase the importance and value of functional studies that follow up on evidence generated from high-throughput screening assays. An increase of bioinformatics data from these screens is leading to investigations of new molecular pathways and networks that will continue to enhance our understanding of bone homeostasis. Potential targets for therapeutics may emerge from studies of large datasets.
- A study including intramural NIDCR investigators examined the relationship between brown fat and bone mass. There is a well-established relationship between brown fat and bone mass in most animals, but whether such a relationship exists in humans is not known. In this study, NIH researchers investigated the relationship between brown fat and bone mass in healthy volunteers, as measured by dual-energy X-ray absorptiometry. They found that brown fat volume correlated positively with bone mass in women but not in men (Lee et al., 2013). This interesting finding suggests additional physiologic mechanisms, besides sex steroids, that may account for sex-associated bone mass differences.

Osteonecrosis of the Jaw

Bisphosphonates (BPs) are drugs that inhibit the activities and functions of osteoclasts and perturb the differentiation of osteoblasts. Intravenous BPs are used primarily to treat and control pain associated with cancer metastasis to bone, Paget's disease, and multiple myeloma. Oral BPs are used to prevent bone loss and are prescribed for patients with osteoporosis or osteopenia. In 2003, case reports suggested use of BPs could lead to development of nonhealing, exposed necrotic bone in upper or lower jaws. The clinical

condition was named medication-induced ONJ. Most cases of medication-induced ONJ are related to intravenous BP use in cancer patients, but several cases are associated with oral BPs. In 2009, cases began to surface of medication-induced ONJ in patients treated with the antiresorptive drug denosumab, which inhibits the osteoclastogenic factor RANKL. Solicitations for research on ONJ resulted in the funding of a number of projects in this area. These include investigations into the risk factors for development of ONJ, how ONJ involves the oral mucosa and the immune system, epidemiologic assessment of ONJ in osteoporotic and osteopenic patients and cancer patients using BPs, the fate and role of BPs in a variety of cells, the role of periodontal disease in ONJ development, and studies of the pathophysiologic mechanisms of ONJ.

Early stages of ONJ may not present with exposed lesions in the mouth. Researchers have shown that microstructural changes may occur before exposure and that these changes can be detected in the bone. This may offer an opportunity to prevent full lesion development. Another group of NIDCR-funded investigators are studying the role of inflammatory factors in the development of spontaneous cases of ONJ using an animal model.

NIDCR also funds studies examining the etiology and epidemiology of ONJ.

- Using dental records from dentists in three NIDCR dental practice–based research networks, one study investigated which dental procedures were associated with ONJ. This study was important to both dentists and their patients because some previous studies had suggested that dental problems play a significant role in the development of these lesions, without defining the nature of the dental problem. In this study, investigators found that extraction was the only dental procedure associated with subsequent ONJ development among patients taking oral BPs. Results of this study suggest that routine dental procedures are not associated with development of ONJ in patients taking BPs (Barasch et al., 2013).
- Another research team investigated the effects of BPs on healing of oral mucosal tissue. When pamidronate, a BP commonly prescribed to cancer patients, was added to cultures of normal oral keratinocytes and fibroblasts, these cells aged and died more rapidly than untreated cells. The results suggest that these cellular changes might be partly responsible for the poor tissue healing observed in ONJ. Other researchers are trying to establish why ONJ occurs primarily in the oral cavity by studying bone cells from the jaw. To date, they found that pamidronate significantly decreased cell viability, proliferation, osteogenesis, and wound healing in tissue cultures of these cells. New labeling tools have also allowed those researchers to visualize the preferential binding kinetics of BPs on alveolar bone. Additional work is underway to examine other processes such as osteomucosal healing involving both hard and soft tissues, lymphocytes and other cells of the innate immune system, and the growth of lymphatic vessels that may play important roles in the pathogenesis of ONJ.

Oral Health Disparities Research

NIDCR's strategic plan includes as a goal the elimination of disparities in oral health. Vulnerable populations include women of racial and ethnic minority backgrounds, the poor, and those with developmental or acquired disabilities. In addition, NIDCR supports research on the oral health of children, including the impact of primary caregivers, often mothers, on the oral health of their children.

- Evidence suggests that the risk for early childhood caries (ECC), the most common chronic infectious disease in childhood, is increased by specific eating behaviors. To identify whether consumption of added sugars, sugar-sweetened beverages (SSBs), and 100 percent fruit juice, as well as eating frequency, are associated with severe ECC, cross-sectional data collected from a sample of low-income, racially diverse children ages 2 to 6 were assessed. Four hundred fifty-four children with severe ECC and 429 caries-free children were recruited, and dietary data were obtained. On average, children with severe ECC consumed 3.2 to 4.8 fluid ounces more SSBs than caries-free children. Children with the highest SSB intake were 2.0 to 4.6 times more likely to have severe ECC compared with those with the lowest intake. This analysis shows that SSBs and added sugars from both foods and beverages play a significant role in severe ECCs in young children from low-income, racially diverse families. Given the substantial and immediate consequences of untreated caries, specific dietary

guidance for mothers about consumption of added sugars and SSBs may be effective.

- There is a complex relationship among maternal behaviors, maternal oral health, and children's oral health. Three interventional studies supported by NIDCR are testing behavioral interventions directed at pregnant women or mothers of very young children to determine whether the interventions will reduce dental decay in study participants' children. Analysis of baseline data from one of the trials initiated by the Center for Native Oral Health Research at the University of Colorado examined sociodemographic characteristics of Navajo Nation children and their parents or caregivers and psychosocial characteristics of parents or caregivers. Caries scores were greater in older children, lower in females ($p = 0.01$), and lower with higher caregiver scores on oral health behavior questions. Intervening to improve parent or caregiver oral health behaviors may improve the oral health status of their children.

Influence of Maternal Health on Child Oral Health

NIDCR-funded investigators studied a birth cohort of very low birth weight (VLBW) and normal birth weight infants to assess the incidence of early childhood caries and of developmental defects of enamel, which can increase susceptibility to primary dental caries. At ages 8 months and 18–20 months, the VLBW infants had significantly higher incidence of enamel hypoplasia. The VLBW group had significantly greater medical needs, suggesting that altered calcium homeostasis combined with local insults during the prenatal and postnatal periods may have had an effect on the enamel matrix formation and mineralization phases.

It is likely that multiple mechanisms underlie the association between parental dental status and early childhood caries, including genetic predisposition, shared social environments, and parental oral health knowledge and attitudes. To assess the potential mechanism of maternal-child transmission of oral bacteria, an NIDCR-sponsored study followed a birth cohort of low-income Hispanic children whose mothers received repeated dental and salivary bacterial assessments for both *Streptococci mutans* (MS) and *Lactobacilli* (LB) during their children's first 3 years. Salivary MS and LB levels were greater among mothers of caries-affected 3-year-olds versus mothers of caries-free children. Higher maternal salivary challenge of both MS and LB over the study period predicted nearly double the child caries incidence versus lower MS and LB.

Periodontal Health in Women

In the Women's Health Initiative Observational Study (WHI-OS) cohort, a clinical oral examination was not feasible; instead, periodontal disease was assessed by questionnaire. An ancillary study supported by NIDCR, the Osteoporosis and Periodontal Disease (OsteoPerio) study, examined the periodontal disease status in a subsample of 972 postmenopausal WHI-OS participants.

To better understand the relationship of vitamin D status to both acute oral inflammation (e.g., gingival bleeding, probing pocket depth) and measures of past destructive periodontal disease (e.g., alveolar crestal height, clinical attachment level), NIDCR-supported investigators used baseline data from the OsteoPerio study to do a cross-sectional analysis of the association between plasma vitamin D (25-hydroxyvitamin D) levels and periodontal disease in 920 postmenopausal women. The findings suggested that Vitamin D status is more associated with acute measures of periodontal health (e.g., percentage of gingival sites that bleed and pocket depth) rather than with measures of disease over lifetime (e.g., clinical attachment level or oral bone loss).

The OsteoPerio study also considered the possible association between metabolic syndrome and periodontitis. Metabolic syndrome is a condition of coexisting factors, including elevated blood pressure, dyslipidemia, hyperglycemia, and obesity; presence of metabolic syndrome more than doubles the relative risks of diabetes and atherothrombosis. In this WHI-OS ancillary study, cross-sectional associations between metabolic syndrome and periodontitis were examined in 657 postmenopausal women ages 50 to 79. Investigators performed clinical periodontal examinations and measures to define metabolic syndrome using National Cholesterol Education Program criteria. A consistent association between metabolic syndrome and measures of periodontitis was not seen in this cohort of postmenopausal women, but the study did find an association between metabolic syndrome and supragingival plaque, suggesting a need for further investigation.

Oral Human Papillomavirus (HPV) Infection

The causal role of HPV in cervical and other anogenital malignancies is well established. The presence of HPV in the cervicovaginal region of U.S. females has been monitored through the National Health and Nutrition Examination Survey (NHANES) since 2002. Data collected between 2003 and 2006, before HPV vaccine introduction, showed an overall prevalence of 43 percent among females ages 14 to 59. The association of HPV with a subset of head and neck cancers has stimulated interest in investigating the prevalence of HPV infection in the oral cavity. Therefore, oral rinse and gargle specimens for determining the prevalence of HPV infection in the entire oral cavity, including the tongue and tonsils, have been collected through NHANES since 2009, with an overall prevalence of 7 percent among males and females ages 14 to 59 in 2009–2010. A recent study examined concurrent oral-cervical HPV infection, including type-specific concordance, in the 2009–2010 NHANES sample. In that sample, the prevalence of HPV infection among women was 42.7 percent in the cervix and 3.8 percent in the oral cavity. The prevalence of oral HPV infection was fivefold higher among women with cervical HPV infection than among those without infection. Among the 3 percent of women with HPV detected at both sites, complete type concordance was detected in 6.6 percent, and partial agreement was detected in 37.7 percent. These data suggest that HPV infections at these two sites are not independent, although type-specific concordance is low. The biological relationship between the two sites might be complex, but the higher prevalence in oral samples among women positive for cervical HPV indicates that such infections are unlikely to be independent of one another.

Salivary Hypofunction (Dry Mouth)

The secretion of saliva is vitally important for a healthy mouth. The salivary glands produce saliva, a complex fluid that is central to maintenance of oral health. If insufficient quantities of saliva are made, oral health deteriorates. These problems can include dramatic increases in dental caries; difficulty in swallowing, chewing, and speaking; loss of enjoyment of food; mouth sores; mucosal infection with *Candida* species; and reduced quality of life. Many diseases and conditions can reduce salivary gland function. Patients with Sjögren's syndrome, an autoimmune disease nine times more prevalent in women than men, often have salivary dysfunction that is thought to be caused by an infiltration of the salivary glands by white blood cells.

NIDCR-funded investigators are studying conditions that result in "dry mouth." The goal of one such study is to use a combined experimental and theoretical modeling approach to understand how saliva is secreted and the processes that are altered in pathological states. This novel multiscale modeling approach will ultimately be used to suggest novel therapies for dry mouth.

Currently, no conventional therapy exists for the dramatic loss of salivary function in most surviving head and neck cancer patients. NIDCR intramural investigators are focusing on transferring the water channel gene for aquaporin 1 inside the cells of damaged salivary glands to stimulate saliva flow. An initial clinical trial was completed at the NIH Clinical Center with 11 head and neck cancer survivors and showed that aquaporin gene transfer can increase saliva flow and relieve dry mouth symptoms. Some subjects responded for much longer than expected, so follow-up was extended to 4 years from the vector delivery. The team is now using a new vector which in toxicology studies has promoted long-term gene transfer with minimal side effects (Momot et al., 2014).

Autoimmune Diseases and Sjögren's Syndrome (SS)

Autoimmune disorders cause an unintended destruction of the body's own tissues and disproportionately affect women. SS, an autoimmune disease characterized by reduced secretions from salivary and lacrimal glands, is the second most common autoimmune disease in the United States. SS affects an estimated 1 million to 4 million people, 90 percent of whom are women. Typically, patients with SS have increased numbers of lymphocytes and other immune cells in their salivary and lacrimal glands, a process thought to result in the ultimate reduction of saliva and tear production. The most serious complication of SS is the greatly increased risk for developing malignant lymphoma, which occurs an estimated 40 times more frequently in these patients.

In 2003, NIDCR, the National Eye Institute, and ORWH provided support for SICCA. SICCA is an integrated

research network that spans seven countries (Argentina, China, Denmark, India, Japan, United Kingdom, and the United States). By sharing their scientific resources, the researchers assembled a large international SS patient registry, a major step forward in studying this condition. The registry, designed by an international expert panel of ophthalmologists, rheumatologists, and oral medicine and pathology specialists, used standardized tests to evaluate more than 1,900 participants enrolled in the SICCA Registry. All had possible signs and symptoms of SS typical of patients seen in a clinical practice and were drawn from ethnically diverse patient populations worldwide. The goal of this activity was to develop new diagnostic criteria for SS that could be used by clinicians and researchers developing new therapies for this condition. The new criteria were published in 2012 and were provisionally approved by the American College of Rheumatology (ACR). This marked the first time that ACR has approved classification criteria for SS despite its recognition as a distinct condition for more than 80 years. Efforts continue to harmonize the new ACR criteria with those of the American-European Consensus Group and receive final approval from both ACR and the European League Against Rheumatism. This registry is also analyzing DNA of subjects to determine the genes associated with SS and the frequency of other types of diseases in this population. In addition, the registry is distributing data and linked biospecimens to investigators throughout the world to promote research on SS. To date, 22 investigators have been approved to receive specimens and data. One NIDCR-supported study is using whole saliva samples obtained from SICCA to discover and verify candidate biomarkers of primary SS (pSS) with untargeted and targeted mass spectrometry–based strategies. The goal of this study is to identify candidate biomarkers of pSS that could lead to a noninvasive clinical test for diagnosing this condition.

NIDCR intramural scientists continue to evaluate patients with SS. The goal of their natural history protocol is to identify the genetic disease mechanisms of SS by carefully studying the clinical features of SS patients and patients with SS-like conditions over time, as well as to collect serum and tissue samples for analysis in the laboratory. The following progress has been made recently by NIDCR intramural investigators:

- Studies using microarray technology are identifying epithelial cell changes in SS that result in the loss of fluid movement. Increased expression of the regulatory protein bone morphogenetic protein 6 was reported in the salivary glands of SS patients. When this protein was expressed in mouse models, it reproduced clinical aspects of the disease. The salivary or lacrimal glands of mice secreted less tears and saliva. This research points towards the future use of systems biology and computational analysis to assist in the direct comparison of data between humans and animal models to identify common pathways for future target-based research and therapies (Yin et al., 2013).
- Nonobese diabetic mice are used to study SS and possible therapies. Using gene therapy to deliver anti-sense inhibitors to the epithelia of the gland, investigators were able to block B-cell activation factor (BAFF), which is involved in activation of immune cells. Their results indicated that blocking BAFF significantly decreased BAFF protein expression and lymphocytic infiltrates and improved salivary flow. This study offers a rationale for localized therapeutic BAFF inhibition in pSS (Roescher et al., 2014).
- Genetic defects in the epithelial barrier cells are linked to a spectrum of allergic and autoimmune diseases. In this respect, the etiology of pSS is still incompletely understood, and both epithelial dysfunction and primary immune defects have been proposed as initiating factors. Embryonic disruption of epithelial barriers in the salivary gland of animal models resulted in the loss of secretory epithelial cell function and the induction of autoimmunity similar to that observed in pSS. Moreover, a significant decrease in matriptase gene expression, which is critical for epithelia barrier formation, was detected in the minor salivary glands of pSS patients compared with healthy volunteers. These findings demonstrate that impairment of epithelial barrier function may be involved in the initiation of SS (Yin et al., 2014).
- Maintaining primary epithelial cells from human salivary gland tissue is critical for studying the underlying mechanisms of the salivary gland disorders. NIDCR intramural investigators are using two culture system techniques with human minor salivary gland epithelial cells to develop a model system to study salivary secretion in vitro (Jang et al., 2014).

- Advances in next-generation sequencing (NGS) technology enable a thorough characterization of DNA and RNA sequences found in saliva, allowing for the discovery of previously unknown and uncharacterized sequences. Small RNAs such as microRNAs are of particular interest for researchers who study their potential role in progression and pathogenesis of many diseases. In SS, changes in microRNAs not only are useful as a potential diagnostic tool but may also provide insight into the mechanisms underlying salivary dysfunction. Researchers have successfully applied NGS to find and quantify microRNAs in minor salivary gland biopsies of SS patients and have recently validated five novel microRNAs (Gallo, Tandon, Illei, & Alevizos, 2014).

Sjögren's Syndrome Genetics

A large-scale genetic study of SS was published in 2013 and established IRF5-TNPO3, STAT4, IL12A, FAM167A-BLK, DDX6-CXCR5 and TNIP1 as risk loci. In addition, there are likely multiple independent effects within the HLA and IRF5 regions. These results highlight the importance of the innate and adaptive immune systems in the etiology of SS (Lessard et al., 2013).

HIV Linked to Oral Health

The study of the oral manifestations of HIV infection has been of great interest for NIDCR because oral changes in HIV-infected individuals are frequent, varied, affect quality of life, represent the first symptoms of infection, and may persist even under antiretroviral therapy (ART). The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic.

In 2006, NIDCR collaborated with the National Institute of Allergy and Infectious Diseases to implement an oral health agenda linked to HIV/AIDS in the AIDS Clinical Trials Group (ACTG), the largest HIV clinical network in the world to assess therapeutic interventions in HIV/AIDS individuals. A collaborative group called the Oral HIV/AIDS Research Alliance (OHARA) was started within ACTG. OHARA's main objective is to investigate the oral complications associated with HIV/AIDS and to address such overarching questions as the effects of potent ART on the development of opportunistic infections, variation, and resistance of opportunistic pathogens in the context of immune suppression. OHARA has conducted noninterventional and interventional clinical studies in 72 ACTG-affiliated sites in the United States and resource-poor countries. These studies have assessed differences in the oral manifestations and therapeutic outcomes of infected men and women. Recently updated clinical case definitions for HIV-related oral diseases have been used to measure standardized clinical endpoints in OHARA studies. Implementation of these new endpoints will allow researchers to determine which HIV therapies have the biggest impact on improving oral health post-HIV symptoms. In FY 2013 and FY 2014, OHARA completed eight out of nine observational and phase I to phase III clinical studies. Results are being processed and manuscripts are in preparation.

In 2011, NIDCR, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, began an observational study on "Oral Health Among Participants in the Pediatric HIV/AIDS Cohort Study." This is a multicenter subproject of the Adolescent Master Protocol within the Pediatric HIV/AIDS Cohort Study. This study is examining the oral health of HIV-infected and HIV-exposed but uninfected children and adolescents, including girls, with the following objectives: (1) to estimate and compare the prevalence of dental, periodontal, and oral mucosal diseases and (2) to explore the associations between these oral outcomes and indicators of overall health, quality of life, neurocognition, HIV disease severity, and ART use. In FY 2013 and FY 2014, enrollment of nearly 400 participants was completed at 11 U.S. clinical sites. Additionally, this oral health study was expanded to include an assessment of oral inflammation and immune activation and to characterize the oral microbiome, peptidome, and metabolome. This scientific expansion will link oral and systemic health parameters as done for the original study. Results are being processed, and manuscripts are in preparation.

Craniofacial Anomalies

NIDCR supports research designed to identify the genetic and molecular mechanisms underlying oral health problems and craniofacial disorders. Craniofacial abnormalities, such as cleft lip and cleft palate, ectodermal dysplasias, craniosynostosis, and amelogenesis and dentinogenesis imperfecta, may be the result of spontaneous or inherited

genetic variants. Often, the causes are complex, involving environmental factors and gene-gene and gene-environment interactions. NIDCR support of this research area includes studies to understand the role of women's health during pregnancy, in particular how changes in nutrition and other environmental factors can affect craniofacial development. Advances in this area were numerous in FY 2013 and FY 2014.

Craniosynostosis results from premature fusion of one or more cranial sutures, occurring at a rate of approximately 3 to 5 of every 10,000 live births. In most instances, craniosynostosis occurs with no other major malformations (nonsyndromic craniosynostosis, NSC). Rare genetic variants in a few genes have been associated with NSC, occurring in a small proportion of individuals with NSC. Sagittal craniosynostosis is the most common type of NSC; because the sagittal suture lies along the midline of the skull, the premature fusion in sagittal craniosynostosis prevents the head from growing in width to accommodate the expanding brain. Research continues to identify and characterize genetic variants that affect susceptibility to sagittal NSC, including research that follows up on earlier results identifying promising candidate regions in proximity to two genes involved in skeletal development (*BBS9* and *BMP2*). Recent research indicates that genetic variants in a transcription factor (*TCF12*) play a role in the development of coronal craniosynostosis; research using mouse models of craniosynostosis is consistent with these findings (Sharma et al., 2013).

Other groups continued to expand our knowledge of the genetic contribution to nonsyndromic cleft lip with or without cleft palate (NSCL/P), one of the most common birth defects. Genetic studies have identified several genomic regions or genes that affect susceptibility. Research continues to identify and characterize genes and genetic variants that influence development of NSCL/P, as well as the interplay of genetic variants with maternal risk factors such as smoking cigarettes during pregnancy. Advancements were also made in syndromic forms of CL/P, van der Woude syndrome (VWS), and popliteal pterygium syndrome: additional variants in *IRF6* were identified in diverse populations (Butali et al., 2014; Leslie et al., 2013), and the role of variants in another gene, *GRHL3*, were identified for VWS in humans and verified in zebrafish and mouse models (Peyrard-Janvid et al., 2013). In addition to improving counseling for families with syndromic forms of CL/P, research on syndromic forms of CL/P provides information about development of CL/P that may also be applicable to NSCL/P.

NIH Strategic Plan for Women's Health Research

Many investigators supported by NIDCR conduct studies that support the goals of the NIH Strategic Plan for Women's Health Research.

Examples below support Goal 1, "Increase sex differences research in basic science studies," and selected objectives.

Objective 1.2: "Explore Sex Differences in the Structure and Function of Male and Female Cells (Including Stem Cells), Tissues, Organs, and Physiological Systems." Understanding how sex hormones affect disease and pain sensitivity could guide design of individualized treatments for TMD. Several NIDCR-funded research groups are studying such differences. One team, using a rodent model of acute inflammatory pain, showed that the female sex hormone estradiol has a profound effect on numerous genes important in pain modulation and regulation of nerve inflammation. These effects were seen throughout the trigeminal system, which controls the sensory and motor functions in the face, teeth, mouth, nasal cavity, and the TMJ itself. The genes involved are likely targets for relieving chronic TMD pain. A different study examining the sensory fibers supplying the TMJ found that estrogen status plays a role in their discharge rate, magnitude, and duration at the earliest stages of TMJ nociceptive processing. At the basic science level, there are ongoing studies examining the mechanics of the joint, including one to understand how forces affecting the TMJ disc differ in males and females.

Objective 1.4: "Include Sex Parameters in the Design of Experiments Using Animal Models." Opioid drugs such as morphine are usually taken orally, leading to a peripheral distribution of the drug. This sometimes results in serious side effects, including breathing problems, nausea, constipation, addiction, and tolerance. However, by injecting the drugs centrally (directly into the cerebrospinal fluid), excellent pain relief can be achieved using much smaller doses, reducing the risk of these side effects. Previous research has suggested that centrally administered opioids are more potent in males than in females. Currently,

little is known about possible sex differences when opioids are given peripherally. Using an animal model, ongoing work by NIDCR-funded investigators has shown sex differences are also present when a specific subtype of opioid is given by the peripheral route. The drug was found to be much more effective in alleviating pain in male rodents compared to females, suggesting that alternative drug treatments precisely tailored for men and women are needed. These studies demonstrate the need to include both male and female animals in studies of pain.

The example below supports Goal 3, "Actualize personalized prevention, diagnostics, and therapeutics for girls and women," and selected objectives.

Objective 3.9: "Examine Health Disparities Among Women Stemming from Differences in Such Factors as Race and Ethnicity, Socioeconomic Status, Gender Identity, and Urban-Rural Living, as They Influence Health, Health Behaviors, and Access to Screening and Therapeutic Interventions." There is a complex relationship among maternal behaviors, maternal oral health, and children's oral health. Three studies supported by NIDCR are testing behavioral interventions directed at pregnant women or mothers of very young children to determine whether the interventions will reduce dental decay in study participants' children. Baseline data from one of these trials found caries scores were greater with older children, lower in females ($p = 0.01$), and lower in those with higher caregiver scores on oral health behavior questions. Improving parent and caregiver oral health behaviors may improve the oral health of their children.

Initiatives: Funding Opportunity Announcements

Advancing Novel Science in Women's Health Research (ANSWHR), PAS-10-226. The purpose of this FOA issued by ORWH and cosponsoring NIH ICs is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

Mechanisms, Models, Measurement, & Management in Pain Research (R01), PA-13-118; (R21), PA-13-119; and (R03), PA-13-117. The purpose of this FOA, issued by the National Institute of Nursing Research in conjunction with members of the NIH Pain Consortium, is to inform the scientific community of the pain research interests of the various NIH ICs and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R01), PAR-12-032; and (R21), PAR-12-033. This FOA issued by ORWH and cosponsoring NIH ICs encourages investigator-initiated applications that propose to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome, sometimes referred to as myalgic encephalomyelitis, in diverse groups and across the life span.

NIDCR Institutional Career Development Award for Enhancing Research Capacity in Temporomandibular Joint Disorders and Orofacial Pain (K12), PAR-11-289. The purpose of this FOA is to expand and strengthen the community of investigators engaged in research on TMDs and orofacial pain.

Pathophysiology and Clinical Studies of Osteonecrosis of the Jaw (R01), PAR-11-082; and (R21), PAR-11-083. The purpose of this FOA is to stimulate clinical and basic science research to examine the etiology, diagnosis, and pathophysiology of medication-induced ONJ.

Research on Chronic Overlapping Pain Conditions (R01), PA-14-244; and (R21), PA-14-243. The purpose of this FOA is to encourage epidemiological, clinical, and translational research that will increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors responsible for the presence of multiple chronic pain conditions in people with pain.

Biology of the Temporomandibular Joint in Health and Disease (R01), PA-14-358; and (R21) PA-14-359. The purpose of this FOA is to encourage research that will advance our understanding of the TMJ in health and disease and to stimulate research that complements previous efforts and focuses on the biology of joint function and the tissues that make up the TMJ.

Neurobiology of Migraine (R01), PA-14-068; and (R21), PA-14-069. This FOA is issued by the National Institute of Neurological Disorders and Stroke in conjunction with the

NIH Pain Consortium. It solicits R01 grant applications from institutions and organizations to perform innovative research that will elucidate the mechanisms underlying migraine; expand our current knowledge of the role of genetic, physiological, biopsychosocial, and environmental influences in migraine susceptibility and progression; and explore new therapeutic targets and therapies for acute migraine management and longer term prevention.

Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01), PA-13-292; and (R21), PA-13-288. The purpose of this FOA is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U.S. population, including disparities in the health of women.

Conferences, Symposia, Workshops, Consortia, and Working Groups

8th Annual NIH Pain Consortium Symposium on Advances in Pain Research. The 8th Annual NIH Pain Consortium Symposium on Advances in Pain Research was held May 29–30, 2013, in the Natcher Auditorium on the NIH campus. The symposium, titled "Integrated Self-Management Strategies for Chronic Pain," featured topics including self-management strategies in community health care settings, tailored self-management strategies for patients and caregivers, and predictors and indicators of outcomes in integrated self-management strategies. A poster session included a broad selection of current pain research findings presented by young investigators.

Roundtable on the Temporomandibular Joint in Health and Disease. A roundtable meeting on the biology of the TMJ, held May 3, 2013, was sponsored by NIDCR, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Biomedical Imaging and Bioengineering. It brought together scientists with expertise in areas related to the structures and tissues of the TMJ to explore new research approaches to advance our understanding of TMJ function. The goal of the meeting was to provide a set of research recommendations to the scientific community that will create and develop a path forward in contemporary, multidisciplinary research on TMJ function in health and disease.

Health Disparities Roundtable. In June 2013, NIDCR convened a multidisciplinary group representing the wide-ranging diversity of the Institute's constituency. Roundtable attendees included researchers in public health, epidemiology, health policy, and health disparities; academic and community dentists; and social and behavioral scientists. This group, which represented individuals within and outside dental and oral health foci, was tasked with considering broadly the state of affairs in oral health disparities research and which directions NIDCR might take to align with the evolution of science and health care and to meet the oral health needs of the nation. Among the issues discussed at the roundtable were emerging interventional research strategies, multidisciplinary and multilevel research, community engagement and partnerships, and training and career development.

9th Annual NIH Pain Consortium Symposium. On May 28–29, 2014, NIH hosted the 9th Annual NIH Pain Consortium Symposium on the NIH campus. The keynote address was "TRP Channels of the Pain Pathway: Connecting Physiology to Atomic Structure" by Dr. David Julius of the University of California, San Francisco. Also featured were three panel sessions titled "Shared Mechanisms of Pain and Depression," "Pain and Sleep Disorders," and "Neuro-Immune Function in Pain and Associated Disorders."

7th Scientific Meeting of The TMJ Association. The 7th Scientific Meeting of The TMJ Association, which was cosponsored by NIDCR, took place September 7–9, 2014, in Bethesda, MD, at the FASEB Conference Center. The theme was "Genetic and Epigenetic Basis of Temporomandibular Disorders and Related Chronic Overlapping Conditions." The goal of the meeting was to explore the molecular and genomic basis of TMDs and related chronic pain disorders.

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National Institute of Diabetes and Digestive and Kidney Diseases

Executive Summary

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic, clinical, and translational research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that disproportionately, differently, predominantly, or solely affect women include diabetes, obesity (especially in racial and ethnic minority populations), eating disorders, irritable bowel syndrome (IBS) and other functional gastrointestinal disorders, osteoporosis, thyroid diseases (including Graves' disease and hypothyroidism), hyperparathyroidism, gallstones, primary biliary cirrhosis, interstitial cystitis/painful bladder syndrome (IC/PBS), urinary tract infections (UTIs), urinary incontinence, and lupus nephritis (the kidney disease of systemic lupus erythematosus). Some NIDDK-supported research, such as study of the relationship of obesity and diabetes to cardiovascular disease (CVD) and study of diabetes during pregnancy, may also have an important impact on diseases and conditions that are primarily within the mission of other ICs. NIDDK supports research on ways to improve women's health and to advance understanding of sex and gender differences in health and disease, both through basic research directed at understanding underlying disease processes and through clinical research that translates this understanding into therapies and preventive interventions. In FY 2013 and FY 2014, the Institute made progress in the following areas important to women's health and to sex differences research, which are highlighted in this report: diabetes and cardiovascular risk factors; diabetes and metabolic health during pregnancy; obesity; IBS; endocrine problems, including breast cancer; liver disease; biliary pain; and women's urologic health. ORWH worked with NIDDK to foster research in many of these areas.

Introduction

NIDDK supports biomedical and behavioral research to address some of the most common, costly, and chronic diseases and conditions affecting U.S. and global populations. Many of these diseases and conditions affect women solely, disproportionately, or in unique ways. For example, only women develop gestational diabetes mellitus (GDM); women lose their comparative CVD risk protection when they develop chronic diabetes; African-American women experience the highest rates of obesity; obesity increases risk for myriad health problems of special interest for women, including CVD, gallbladder disease, and GDM; women are more prone to autoimmune disorders, including autoimmune thyroid and liver diseases; lupus, and hence kidney disease of lupus (lupus nephritis), predominantly occurs in women; bowel and bladder control problems are much more prevalent in women; and women are most highly affected by pelvic pain syndromes associated with the bladder and gut. NIDDK supports a diverse portfolio of research important to women's health, including studies of the following:

- Diabetes in women (including type 1, type 2, and GDM);
- Diabetes health complications, including sexual dysfunction and depression;
- Obesity prevention and treatment;
- Thyroid and parathyroid conditions and diseases;
- Endocrine regulation of bone metabolism and osteoporosis;
- IBS;
- IC/PBS;
- Fecal and urinary incontinence;
- Kidney diseases and kidney failure;
- Liver and biliary diseases; and
- UTIs.

Sex and gender differences research is also revealing new information about how susceptibility, onset, progression,

or treatment efficacy for diseases and conditions within NIDDK mission may differ between women and men.

The scope of NIDDK women's health research crosses the Institute's three extramural research divisions—the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases—as well as NIDDK's Intramural Research Program. Their efforts are enhanced by activities of NIDDK's Office of Obesity Research, Office of Minority Health Research Coordination, and Office of Nutrition Research (formerly the Division of Nutrition Research Coordination). NIDDK promotes public health education and awareness through the efforts of its Office of Communications and Public Liaison. Key efforts include the National Diabetes Education Program (NDEP), a joint effort of NIDDK and the Centers for Disease Control and Prevention (CDC); the National Kidney Disease Education Program; and the Weight-Control Information Network. Finally, NIDDK conducts strategic planning efforts for research in major areas of its portfolio on a regular basis; many of these are germane to women's health and include input or partnership from ORWH. Examples of women's health and sex differences research accomplishments supported by NIDDK follow.

Accomplishments and Activities

Diabetes

Type 2 Diabetes Prevention—Understanding Risk Factors in Women

Information important to diabetes prevention in women continues to emerge from the Diabetes Prevention Program (DPP) and its long-term follow up, the DPP Outcomes Study (DPPOS). In 2002, the DPP clinical trial results showed that, in a racially, ethnically, and age-diverse cohort of obese and overweight adults with elevated blood glucose levels, an intensive lifestyle intervention (ILI), or exercise and diet to induce moderate weight loss, reduced risk of developing type 2 diabetes by 58 percent. The diabetes drug metformin reduced diabetes risk by 31 percent (Knowler et al., 2002). Sixty-eight percent of the DPP study participants were women, of whom 16 percent had a history of GDM, which has enabled researchers to study the efficacy and long-term effects of DPP interventions in women with this risk factor; ORWH support facilitated recruitment and retention of these women. Previously, DPP researchers found that, though ILI was more effective than metformin in the DPP participants as a whole and in parous women without GDM, metformin was as effective as ILI in women with a history of GDM. The finding that metformin was much more effective in women with GDM than in those who had not had GDM with previous pregnancies has important implications for personalized medicine. To determine whether genetic variability might influence GDM risk and treatment response, investigators developed and studied a genetic risk score. This new study of GDM and genetic risk in DPP participants has found that the genetic risk score was associated with GDM history but not with treatment response and progression to type 2 diabetes (Sullivan et al., 2014). These results suggest that a genetic risk score may identify women at risk of developing GDM, although the question of what influences response to metformin in women with a history of GDM remains. Postmenopausal women are also at higher risk for developing type 2 diabetes and associated metabolic problems, contributing to CVD risk. These risks may be affected by levels of endogenous sex hormones (including related factors, such as sex hormone binding globulin) and the use of hormone therapy for menopausal or postmenopausal symptoms. NIDDK-supported researchers have examined in the DPP cohort whether use of oral estrogen (with or without progestin) by postmenopausal women affected glucose metabolism and other metabolic factors in response to DPP interventions and whether sex hormone levels in these women influenced or were influenced by the interventions. Researchers did not find a significant influence of endogenous sex hormones or estrogen use on observed blood pressure reductions (Kim, Golden, et al., 2014) or weight loss or changes in waist circumference (Kim, Barrett-Connor, et al., 2014) at 1 year of the DPP interventions. In contrast, hormone use appeared to influence lipid responses to DPP interventions. At 1 year, DPP interventions reduced low-density lipoprotein ("bad") cholesterol and raised high-density lipoprotein ("good") cholesterol in women using estrogen therapy, whereas no effect was seen in nonusers. At the same time, ILI induced significant lowering of triglycerides in nonusers of estrogen but no significant changes in users, whereas metformin did not induce

significant changes among nonusers but actually increased triglycerides in estrogen users. These results suggest that estrogen use can modulate some health benefits of DPP interventions (Golden et al., 2013). Another study revealed complex interactions between DPP interventions, glucose metabolism, and use versus nonuse of estrogen, suggesting that the glucose-lowering effects of ILI and metformin may be mediated differently depending on hormone use (Kim et al., 2013). These findings contribute new knowledge about the impact of endogenous sex hormones and use of hormone therapy on factors associated with diabetes and CVD in overweight and obese prediabetic postmenopausal women, who are at increased risk for both.

Identifying Risk for Diabetes and Heart Disease in Black and White Women

Racial and ethnic differences exist in CVD risk associated with metabolic problems such as insulin resistance and diabetes. For example, prevalence of cardiometabolic disease is greater in African-Americans than in Whites, but triglyceride levels are lower in African-Americans. This difference is even more marked in African-American women, making triglyceride tests an even less effective predictor of CVD risk in this population. NIDDK intramural scientists and collaborators recently examined in a small clinical trial the underlying reasons for the difference in triglyceride levels between African-American and White women. They examined metabolic measures that normally interact to promote high triglycerides: insulin resistance, visceral fat, and apolipoproteins that associate with triglycerides. Their results suggest that, although they have higher insulin resistance and insulin levels than White women, African-American women are protected from having high triglycerides by a combination of lower levels of visceral adipose tissue and lower levels of apolipoprotein C-III, which interferes with triglyceride clearance (Sumner et al., 2013). NIDDK intramural researchers have initiated a clinical trial to determine whether there are differences between African, African-American, and White women in the relationship of triglyceride levels to insulin resistance, hepatic glucose production, and liver fat (NCT01809288), which should help advance the overall effort to find better predictors of risk for diabetes and heart disease in African-American women and reduce health disparities in this area.

Understanding the Course and Impact of Diabetes in Youth

Girls are disproportionately represented in the pediatric population with type 2 diabetes—a difference not observed in adults with the disease. New findings about the impact of diabetes in youth have emerged from the nationwide NIDDK-supported Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. This clinical trial compared the efficacy of three treatment arms—metformin, the only Food and Drug Administration (FDA)–approved oral drug for treatment in children; metformin plus rosiglitazone; and metformin plus an ILI—in youth from 10 to 17 years old, using time to treatment failure based on glycemic control as the outcome measure; about 65 percent of the cohort was female. In 2012, TODAY found a higher than expected failure rate for all treatments; that treatment with metformin alone may be inadequate for a majority of youth with type 2 diabetes; that metformin plus rosiglitazone was the most effective treatment, especially in girls (however, current FDA restrictions on rosiglitazone mean that it is not recommended for use in children); and that type 2 diabetes is actually more aggressive in youth than adults (TODAY Study Group et al., 2012). Now, in a series of sobering papers, TODAY researchers have reported that prognosis was poor in all three treatment groups, with worsening blood pressure (especially in boys) and blood lipids, emergence of retinopathy and markers of kidney disease, and a rapid progression of diabetes and loss of insulin production capacity, which explains previous findings that many participants required insulin by the end of the study (The TODAY Study Group, 2013a; 2013b; 2013c; 2013d). In addition to these shared risks and outcomes, of particular concern for girls is the impact of type 2 diabetes on pregnancy. In a follow-up study of outcomes, TODAY2, researchers have continued to examine the impact of type 2 diabetes in youth on pregnancy outcomes and anticipate publishing these results in 2015.

Progress in Combating the Consequences of Diabetes During Pregnancy

Uncontrolled diabetes during pregnancy has significant metabolic consequences for the woman and her offspring, including risk of birth defects for the latter. Neural tube

defects result from disruption of neural tube formation or failure of the neural tube to close during embryonic development. In the context of maternal diabetes, it has been hypothesized that hyperglycemia contributes to oxidative stress and cell-death pathways implicated in neural tube defects. NIDDK-supported researchers recently reported the identification of proteins in the pathway from the oxidative stress of maternal hyperglycemia to excess cell death during neural tube formation. Using a rodent model, the scientists found that deletion of the genes encoding Ask1, Caspase 8, or Foxo3a proteins, or the chemical inhibition of Ask1 protein, dramatically reduced the rate of neural tube defects in offspring from diabetic female mice. Moreover, they found activation of these proteins in affected tissues from three of four human fetuses with neural tube defects but not in unaffected control tissues, suggesting that this pathway is relevant in human disease. This work points to a potential target (Ask1) for drug development to prevent this embryopathy in women with diabetes. (Yang et al., 2013)

Obesity

Look AHEAD (Action for Health in Diabetes)—Cardiovascular Outcomes, Diabetes Remission, and Depression

The long-term, multicenter Look AHEAD clinical trial has sought to determine whether lifestyle intervention can improve cardiovascular outcomes in obese patients with type 2 diabetes. Spearheaded by NIDDK, Look AHEAD cosponsors include the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Nursing Research; ORWH; the National Institute on Minority Health and Health Disparities (NIMHD); and CDC. More than 5,100 participants, nearly 60 percent of whom were women, were randomly assigned to either an ILI group or a diabetes support and education (DSE) group. For all participants, Look AHEAD investigators recorded CVD events, including instances of death from any cardiovascular cause, nonfatal heart attack or stroke, and hospitalization for angina. In 2012, the trial was concluded early because, after nearly 10 years of follow-up, the researchers found that the numbers of CVD events were not significantly different between the ILI group and the DSE group. This similar number of CVD events was observed even though there were improvements in a number of disease risk factors in the lifestyle intervention group, with less use of medication. These benefits included greater weight loss; improved blood pressure; increased fitness, as measured by an exercise test; and improved blood glucose (sugar) control (Look AHEAD Research Group et al., 2013). Additional analyses of data from the first several years of the Look AHEAD trial have identified many other health benefits of the lifestyle intervention. For example, the researchers found that, compared to DSE, ILI led to partial or complete remission of type 2 diabetes over the first 4 years of the study, although at modest rates. Remission was more likely among those who had lived with diabetes for less than 2 years at the study's outset and who had relatively low (although still diabetic) glucose levels, did not yet need insulin therapy for their diabetes, and had greater weight loss and fitness improvements during the study. The association between remission and shorter duration of type 2 diabetes suggests that starting healthy lifestyle changes early in the course of the disease may lead to better outcomes (Gregg et al., 2012). Depression is a common comorbidity of both type 2 diabetes and obesity that disproportionately affects women. Look AHEAD researchers found that, compared to DSE, ILI protected participants from progression to mild or greater depression symptoms over 8 years of follow-up, without concomitant differences in use of antidepressant medications (Rubin et al., 2014). Although the intervention phase of Look AHEAD has now concluded, researchers are continuing follow-up of the study participants to evaluate longer-term effects. This research will help inform decisions about management of type 2 diabetes, to help women and men improve their health and quality of life.

Weight-Loss Surgery to Treat Obesity and Type 2 Diabetes

One treatment approach for extreme obesity is bariatric surgery—a form of weight-loss surgery that involves reducing stomach size and, in some cases, bypassing part of the small intestine (gastric bypass). More than 80 percent of persons undergoing this surgery are female, and the majority of patients are White. Results from an NIDDK-supported observational study have shown that adults with severe obesity had substantial weight loss 3 years after bariatric surgery, with significant improvements in type 2 diabetes, high blood pressure, and cholesterol outcomes; the study also revealed that weight loss and other outcomes varied greatly among study participants,

including wide variability in weight loss trajectories. These findings emerged from research conducted in the Longitudinal Assessment of Bariatric Surgery (LABS), a prospective study of patients undergoing weight-loss surgery at one of 10 different hospitals across the United States. The study included more than 2,000 adults (about 80 percent women) who underwent either Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB)—two different, commonly performed bariatric surgery procedures (Courcoulas et al., 2013). The NIDDK-supported Teen-LABS study is assessing the short- and longer-term safety and efficacy of bariatric surgery among teens with severe obesity; procedures under study are RYGB, sleeve gastrectomy, and gastric banding. A recent report from Teen-LABS found that teens (also mostly females) showed relatively few short-term complications 30 days after surgery (Inge et al., 2014); participants are continuing to be evaluated for longer-term outcomes. Although previous and ongoing studies have indicated the apparent benefit of type 2 diabetes remission in persons with severe obesity who undergo bariatric surgery, researchers want to determine whether less obese persons might benefit, as well. Two small NIDDK-supported clinical trials conducted in mostly female cohorts have found that, after 1 year of treatment, bariatric surgery (RYGB and LAGB) may be more effective than nonsurgical approaches for treating type 2 diabetes in adults who have mild or moderate levels of obesity (Courcoulas et al., 2014; Halperin et al., 2014). In both studies, moderate or severe complications were observed with surgical procedures but not with nonsurgical intervention (e.g., diet and exercise). The studies also identified challenges (e.g., recruitment and retention and cost) that, along with the evolution of bariatric surgical procedures over time, should be taken into account in designing future, larger-scale studies. These NIDDK-supported studies provide further insight into health benefits and risks of a procedure used predominantly by women.

A Weight Management Approach to Help Women Already Overweight or Obese

Prevalence of overweight and obesity in the United States remains highest among non-Hispanic Black women (Flegal, Carroll, Kit, & Ogden, 2012). Researchers have achieved promising results in an intervention to help overweight and obese African-American women prevent further weight gain, using a combination of primary care and community settings and technology accessible to those who are socioeconomically disadvantaged. The intervention aimed not for weight loss, but rather to improve the overall well-being of the participants and maintain their current body shape—thereby potentially fending off further weight gain and additional health risks. Measuring weight at the end of the 12-month intervention, and then again at 18 months, the researchers found that the women in the intervention group better maintained their initial weight: 53 percent had weights at or even below their weight at the start of the study, compared to 39 percent of those in usual care. The intervention did not affect blood pressure, blood glucose, or several other cardiovascular risk factors. Importantly, although recruiting from a primary care system, the intervention was largely delivered in the community with dietitians and relatively inexpensive electronic health technologies. This strategy circumvents issues related to insufficient reimbursement, time, and training that may hinder effective weight management solely by primary care physicians. This strategy could also be implemented broadly in communities disproportionately affected by obesity. Longer-term studies may help researchers determine whether—by fending off the usual weight gain over time—this intervention could reduce type 2 diabetes and other obesity-associated diseases (Bennett, et al., 2013).

Antibiotic Exposure in Early Life: Microbiome, Metabolism, and Sex Differences

Research continues to demonstrate important links between the gut microbiome and human health that could contribute to efforts to prevent obesity, and sex differences are emerging as well. Early exposure to antibiotics has been linked to greater risk of obesity later in life. NIDDK-supported scientists recently studied the timing of antibiotic exposure and gut microbial changes, altered metabolic and immune indicators, and interactions with diet and resulting obesity risk in a rodent model; they also analyzed the results by sex. They found that mouse pups whose mothers had been given penicillin in drinking water right before birth and prior to weaning were bigger and had more fat mass than the controls as adults, including in the liver, where their fat cell production genes were more active. Mice treated directly with antibiotics from a young age also showed altered shifts in the maturing gut microbial

composition as they grew, compared to untreated mice. Moreover, antibiotic-treated mice fed a high-fat diet after weaning experienced a large increase in weight gain by 30 weeks (adulthood in mice)—particularly the female mice, whose fat mass doubled. Metabolic changes in the mice included fatty livers, especially in the male mice, as well as changes in the activity of genes associated with carbohydrate and fat metabolism. Similar effects on weight gain were found in mice given just a limited course of antibiotic for 4 to 8 weeks during early life and fed the high-fat diet. These mice also had reduced activity of cells and genes involved in intestinal immunity. Surprisingly, following the short-term antibiotic exposure, the mice's gut microbe populations slowly returned to a normal mix of bacterial species, even though the metabolic effects persisted. Finally, this altered metabolism could be transferred between individuals by transplanting the antibiotic-treated mice's intestinal contents into the guts of germ-free mice, demonstrating that it was changes in the gut microbes themselves, not direct effects of the antibiotic, causing the altered metabolism. These studies show that changes early in life in the structure of the gut microbial community, due to factors such as antibiotics, could have life-long consequences by "programming" an organism's future metabolism and immune function, and that the effects may differ by sex. If these results in mice hold true for humans, they would provide compelling reasons for devising ways to restore normal gut microbial composition in girls and boys exposed to antibiotics, both to reduce risk of metabolic disorders and establish healthy immunity (Cox et al., 2014).

Fundamental Factors Imparting Sex Differences in Metabolic and Other Conditions

NIDDK-supported researchers continue to make progress in understanding—and uncovering—cellular and molecular factors that underlie sex differences in diseases and conditions within NIDDK's mission. For example, a recent study focused on metabolic outcomes in a set of mouse models that were engineered to allow researchers to disentangle the hormonal and genetic aspects of X and Y sex chromosome complement from each other. The results suggest that while gonadal hormones influence weight, simply possessing two functional sex chromosomes—XX or XY—versus just one (X) influences weight gain, adiposity, and glucose tolerance independent of gonadal hormones in adult animals. This study expands on previous results in another mouse strain background, which had initially suggested that possessing two X chromosomes has a greater influence on weight gain than possessing X and Y; the new work allowed the researchers to unmask a potential role for Y chromosome genes and points to the small number of X-Y gene pairs with similar coding sequences as candidates for these effects. If true in humans, these findings could be relevant to prevention and treatment of obesity and other metabolic problems in situations such as menopause and aging, in which loss of gonadal hormones will potentially reveal a stronger role for genetic factors (Chen, McClusky, Itoh, Reue, & Arnold, 2013). Fragile X–associated primary ovarian insufficiency involves infertility, irregular menses, and early menopause; it is one of a number of disorders caused by expansion of tandem repeat sequences in the untranslated leader region of the X-linked *FMR1* gene. NIDDK researchers have developed a mouse model with this mutation type and, while seeking to learn more about the mechanism underlying expansion and contraction in the number of repeat sequences, simultaneously discovered intriguing sex- and age-related differences in the transmission of larger and smaller repeats to offspring—namely, while males transmit large repeats across the reproductive life span, females transmit large repeats less often to offspring as they age. This previously unappreciated difference may have interesting ramifications both for expansion mechanisms in male and female germlines and risk assessments in humans (Zhao & Usdin, 2014). In another study, NIDDK-supported researchers elucidated the contribution of certain epigenetic factors to profound sex biases in liver gene expression, which have been observed in rodent and humans (Sugathan & Waxman, 2013). About 1,000 genes are expressed in a sex-biased manner in the liver; this difference affects diverse physiological processes—including steroid, lipid, and drug metabolism by the liver—and contributes to sex differences in CVD risk, nonalcoholic fatty liver disease, and other metabolic problems. Understanding the mechanisms that regulate these differences could therefore provide targets for sex-based interventions in metabolic disease.

Healthy Pregnancy Program

Pregnancy is a key period of study and potential intervention to protect the metabolic health of women and

their offspring. Numerous observational studies have linked preexisting overweight or obesity or excessive gestational weight gain during pregnancy to short-term and long-term adverse health consequences in both mothers and offspring. However, additional research is needed to identify effective interventions that will improve weight, glucose levels, and other pregnancy-related outcomes in mothers and determine whether these interventions affect obesity and metabolic abnormalities in the offspring. Five percent to 7 percent of women will develop GDM during pregnancy, placing them at greatly increased risk for developing type 2 diabetes in the 5 to 10 years post-partum and increasing risk for obesity and diabetes in their offspring. Moreover, results from the Hyperglycemic and Adverse Pregnancy Outcome (HAPO) study have suggested that elevated maternal glycemia even below levels diagnostic of GDM is associated with adverse pregnancy outcomes. To help address these key issues surrounding obesity and diabetes and hyperglycemia during pregnancy, NIDDK supports a Healthy Pregnancy Program. This effort encompasses the following:

- **Lifestyle Interventions for Expectant Moms (LIFE-Moms).** The LIFE-Moms Consortium is testing lifestyle interventions in overweight and obese pregnant women that may reduce inappropriate gestational weight gain and/or improve metabolic status, with potential short- and long-term health benefits for mothers and offspring. The consortium consists of seven clinical studies in a broad range of populations, including minority and socioeconomically disadvantaged groups, and a research coordinating unit. Several intervention strategies are being tested, such as in the home with visits by parent-educators and in clinical settings. LIFE-Moms is currently recruiting study participants; recruitment should end in 2015. This effort is led by NIDDK and cosponsored by NHLBI, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Complementary and Integrative Health (formerly the National Center for Complementary and Alternative Medicine), ORWH, and the Office of Behavioral and Social Sciences Research (OBSSR).
- **HAPO Follow-Up Study.** This multisite observational study conducted at 10 of the original HAPO sites is leveraging the well-characterized HAPO study population to determine whether hyperglycemia during pregnancy less severe than GDM influences later levels of body fat in children and development of diabetes in mothers after giving birth. As of the end of FY 2014, HAPO had recruited more than 2,300 mother-child pairs. This study is cosponsored by NIDDK and NICHD.
- **Post-Gestational Diabetes Awareness Campaign.** This campaign is an ongoing effort of NDEP and is part of its "Small Steps, Big Rewards. Prevent Type 2 Diabetes" campaign. One goal for this educational component is to help women with a history of GDM and children affected by GDM adopt and maintain healthy behaviors. Another is to expand outreach to health care professionals who are counseling women and families affected by GDM.

In related efforts, NIDDK, with cofunding from ORWH, is supporting a randomized controlled trial evaluating the effect of a remotely delivered weight loss intervention in overweight and obese women who are likely to become pregnant. This proof-of-concept and feasibility study will assess outcomes including fertility, gestational weight gain, infant birth weight, and other pregnancy-related conditions. Such a study will begin to address whether modest weight loss and control of gestational weight gain can improve the future health of the woman and their offspring (R01DK 099882). NIDDK and ORWH have also supported a project testing an intervention to limit weight gain in White and African-American women diagnosed with GDM and promote postpartum weight loss, including through electronic delivery of the intervention to help new mothers who face many competing demands on their time. The overall goal is to break the vicious cycle of obesity and diabetes in pregnant women and their offspring, to the benefit of women and their families (R21DK095189).

Endocrinology

Advancing Breast Cancer Treatment

Although cancer lies primarily in the purview of other NIH ICs, NIDDK supports research related to endocrine and endocrine hormone–driven tumors, primarily hormonal regulation of cellular growth and function by both steroid hormones and growth factors. NIDDK intramural scientists also continue to make important contributions to the understanding and treatment of breast cancer associated

with mutations in the *BRCA1* and *BRCA2* genes. Drug resistance and metastasis are twin challenges in breast cancer treatment. In a recent study, NIDDK scientists leveraged the development of resistance by mouse *Brca1* tumors to the therapeutic drug cisplatin to identify two cellular attributes (cytoskeleton remodeling and PI3K signaling) that contribute to mobility and viability of breast cancer stem cells—cell populations that are hypothesized to be significant contributors to metastasis. Blocking these pathways synergistically might inhibit both primary and metastatic cancer growth (Vassilopoulos et al., 2014). Another report from NIDDK scientists focused on optimizing a promising therapy that targets *BRCA* tumors, PARP1 inhibitor therapy, for use against breast cancers in general. The screening approach applied in this study identified another anticancer drug, lestaurtinib, as both an effective monotherapy and a strong enhancer of the inhibitory effect of the PARP1 inhibitor AG14361 against both BRCA1 mutant and non-BRCA1 mutant breast cancer cells. As both drugs have been approved for clinical trials for other cancers, these promising results suggest that the combination may be applicable for testing in a future breast cancer intervention trial (Vazquez-Ortiz et al., 2014).

Digestive Conditions and Diseases

Understanding Sex Differences and Advancing Treatment for IBS

The functional gastrointestinal disorder IBS causes pain and constipation or diarrhea and is more common in women than in men. Although diet and stress contribute to this disorder, the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. A key goal for research is to understand the interplay of gut and brain pathways in these disorders and to build upon this knowledge to design effective treatments. Researchers are also examining sex and gender differences in this interplay. Pivotal work in these areas has been conducted by investigators at a Specialized Center of Research (SCOR) on Sex Differences at the University of California, Los Angeles, cofunded by NIDDK and ORWH. For example, prior research had shown sex differences in brain responses to visceral stimuli or its anticipation in people with IBS; now, SCOR researchers have shown for the first time sex differences both between healthy women and men and between women and men with IBS in "resting state" activity of brain networks involved in processing stimuli related to pain and emotion (Hong et al., 2013). Results from another study suggest that, in women and men who develop IBS, a history of early adverse life events (EALs) helps shape the resting state of a brain network that has been implicated in the pathophysiology of pain amplification, and that men with IBS experience EAL-related alterations in an additional brain network that is associated with fear perception, motor function, and visual-motor learning (Gupta et al., 2014). A third study uncovered sex differences in brain responses of women and men with IBS who were presented with images of human faces expressing fear and anger; in contrast to prior findings with IBS-related stimuli, these non–IBS-related stimuli evoked greater responses in men with IBS than in women with IBS (Labus, Gupta, Coveleskie, et al., 2013). These studies underscore the importance of examining sex differences to potentially better target interventions for women and men with IBS. SCOR investigators have also made progress in IBS therapy. Although evidence supports the effectiveness of cognitive behavioral approaches in improving the symptoms of IBS, duration, cost, and resistance of many patients toward a psychological therapy have limited their acceptance. Results from a randomized, controlled clinical trial showed symptom improvement in IBS patients following a short course (5 weeks) of group therapy involving psychological and educational approaches emphasizing self-efficacy and practical relaxation techniques; the therapy was particularly helpful for those individuals who had a low or average quality of life prior to starting the intervention. This study demonstrated an effective, low-cost method of treating IBS symptoms and could pave the way for the adoption of such an approach as an alternative to, or a supplement for, pharmacological therapy (Labus, Gupta, Gill, et al., 2013).

Complex Factors Influence Experience of IBS

The NIDDK-sponsored IBS Outcome Study is a multicenter, placebo-controlled randomized clinical trial with the goal of determining whether self-administered cognitive behavioral therapy is as helpful as standard therapy with a therapist in reducing IBS symptoms and overall burden. The majority of study participants are women. In addition to addressing the primary study

aim, researchers have used data generated by the study to understand the impact of specific factors on the experience of women and men living with IBS. Two analyses of data from this study point to several key determinants of quality of life and feeling healthy in people with IBS. One analysis has shown that the fear of IBS symptoms had a large impact on reducing individuals' day-to-day quality of life, even more so than the symptoms themselves (Lackner, Gudleski, Ma, et al., 2014). Another analysis has revealed that factors such as stress, depression, and anxiety were associated with a perception of being in worse health in those with IBS; surprisingly, as with the other analysis, the severity of IBS symptoms played a lesser role in participants' self-assessments of their overall health (Lackner, Gudleski, Thakur, et al., 2014). Greater awareness and attention to these complex factors influencing individual experience of IBS may help health care providers in delivery and effectiveness of care, relationships with patients, and patient satisfaction and compliance with medical care.

Endoscopic Surgical Procedure Fails to Reduce Biliary Pain

The gallbladder is often removed to treat conditions such as chronic gallstones, local inflammation, or pain that is suspected to originate in the gallbladder or bile ducts; women are at higher risk than men of developing gallstones, the most common reason for surgery. Patients occasionally experience recurrent abdominal pain after this surgery. One suspected cause has been a condition called sphincter of Oddi dysfunction (SOD); although not proven, it has been suggested that this condition is caused when the sphincter that allows bile and pancreatic juices to flow into the intestine does not relax properly. Typical treatment is an endoscopic procedure to cut the sphincter open, called sphincterotomy; sometimes an additional procedure is carried out to measure pressure in the sphincter. However, the suggested benefits of these procedures are controversial, and they carry a substantial risk of significant complications, including pancreatitis or perforation of the bowel wall. The NIDDK-supported Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction clinical trial compared sphincterotomy to a sham procedure to discover whether sphincterotomy actually reduced pain following gallbladder surgery. This multicenter, randomized trial included more than 200 participants, 92 percent of whom were women. While both the sphincterotomy and the sham procedure control groups experienced a reduction of pain severity, sphincterotomy did not reduce abdominal pain compared to sham. Additionally, between 11 percent and 15 percent of participants developed pancreatitis, underscoring the risk of complications that may occur as a result of the invasive operations. Furthermore, sphincter pressure measurements had no correlation with the outcomes, calling into question the idea that high pressure in the sphincter is the cause of symptoms in these patients. The results of this trial suggest that sphincterotomy does not improve pain in cases of suspected SOD following gallbladder removal—information that could save patients from the burden of this unnecessary and risky procedure (Cotton et al., 2014).

Urologic Health

Women's Urologic Health Research Program: Focus on Prevention of Lower Urinary Tract Symptoms

A variety of problems can affect the bladder and the urethra, including urinary incontinence, UTIs, overactive bladder, and IC/PBS; these conditions and many others occur much more frequently in women than in men. Researchers and health care providers use the term lower urinary tract symptoms, or LUTS, to refer to symptoms associated with any type of lower urinary tract dysfunction or condition, as well as those with as-yet unidentified cause. LUTS can include frequent or urgent urination, needing to get up multiple times at night to urinate, and problems with voiding. LUTS and their associated conditions have not only a direct negative impact on health but also exacerbate or contribute to other chronic health problems in women, including obesity, diabetes, and depression. To date, the majority of public and private research efforts have focused on management and treatment of severe LUTS. NIDDK is spearheading a new Women's Urologic Health Research Program with an emphasis on prevention of LUTS in women; NIDDK is consulting with other ICs and Offices, including ORWH and OBSSR, as well as the HHS Office on Women's Health, in the development of this program. Key accomplishments in FY 2013 and FY 2014 include a series of scientific workshops and symposia that laid the foundation for two requests for applications (RFAs), issued in FY 2014, to establish a multicenter, multidisciplinary research consortium that will plan, perform, and analyze

research studies necessary to establish the scientific basis for future prevention intervention studies for LUTS and conditions in women; it is anticipated that this consortium will be funded in summer 2015.

Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The multicenter MAPP Research Network is conducting innovative, collaborative studies of the two most common urologic chronic pelvic pain conditions (UCPPS)—IC/PBS in women and men and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men. Since its inception in 2008, the network's unique approach has entailed searching "beyond the bladder/prostate" to find the causes of these conditions, including studying the possible relationships between these conditions and other chronic pain disorders, such as IBS, fibromyalgia, and chronic fatigue syndrome. Groups of patients displaying these comorbid disorders are being recruited and characterized within the network. Findings emerging from network studies include new insights into the course of UCPPS conditions; potential biomarkers; microbiome differences between patients and healthy controls; different, potentially clinically relevant "sub-phenotypes" among people diagnosed with these conditions; and the importance of recognizing symptom "flares" in assessing these conditions. One important aspect of network studies is expanding knowledge of how different parts of the brain may become altered in a way that augments or maintains the experience of pain. Using a sophisticated brain imaging technique, network researchers have identified several brain regions in which women with IC/PBS have a significantly greater volume of gray matter than healthy counterparts, including three pain-processing regions; notably, greater gray matter volume in one of these three regions, called the right S1, was associated with greater symptoms of overall pain, urinary urgency, and anxiety reported by women with IC/PBS on the day of the brain scan (Kairys et al., 2015). This is the first study to show regional brain differences between women with IC/PBS and healthy counterparts; future studies may help researchers understand the relationship between altered brain regions and pain sensitivity in IC/PBS patients, as well as the impact of co-occurring pain conditions, gender, and other variables on these brain changes. In FY 2014, NIDDK, with cosponsorship from the ORWH, renewed the network for a second 5-year phase to continue studies that could provide a foundation for effective clinical interventions for IC/PBS and CP/CPPS. The network now consists of nine discovery sites (previously six), a data coordinating center, and a tissue and technology center. Visit the MAPP Research Network Web site at http://www.mappnetwork.org.

Bacteria that Cause UTIs Flourish in Multiple Reservoirs

Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract, and many women suffer from recurrent infections. The leading cause of UTIs is exposure to uropathogenic *Escherichia coli* (*E. coli*) bacteria, also referred to as UPEC. Scientists at a SCOR at Washington University in St. Louis that is cosupported by ORWH and NIDDK continue to gain insights into host and bacterial factors that contribute to UTIs. These researchers have developed a model for chronic or recurrent UTIs that relies on the existence of intracellular bacterial communities in the bladder that can protect UPEC from antibiotics, allowing them to re-emerge later and cause recurrent infection. SCOR investigators recently collaborated with NIDDK-supported researchers in the microbiome field and others in a study that suggests that the source of recurrent UTIs in women is even more complex than previously thought, with potential implications for therapy. Normally, *E. coli* strains reside in the human gut; however, through genetic changes, *E. coli* can acquire the ability to infect the bladder. Scientists have wondered whether these genetic changes require a "trade-off" in which the resulting bacteria are less fit to flourish in the gut. By analyzing *E. coli* from urine and fecal samples of several women at each of three episodes of UTI, the researchers uncovered evidence that the acquisition of genetic traits enabling *E. coli* to infect the bladder does not require a fitness trade-off for growth in the gut and that *E. coli* well-suited to cause UTIs may exist and flourish simultaneously in both the gut and the bladder—an aspect of UPEC that can be explored further as researchers consider how to design effective preventive and therapeutic strategies to combat recurrent UTIs. This research was also supported by the National Institute of Allergy and Infectious Diseases. (Chen, Wu, et al., 2013)

Treatment with Two Antibiotics Dramatically Reduces Risk of UTIs in Girls and Boys with Vesicoureteral Reflux

Children with vesicoureteral reflux (VUR) have developmental abnormalities in one or both ureters that allow urine to flow back from the bladder into the ureters and sometimes into the kidneys; as a result, children with VUR are more likely to have recurrent UTIs, which can increase their risk of kidney scarring and the potential for kidney failure. It is estimated that girls are twice as likely as boys to experience VUR. For decades, doctors have treated children who have VUR with a small daily dose of the antibiotics trimethoprim and sulfamethoxazole (TMP/SMZ), often for years, with the hope of preventing recurrent UTIs and kidney damage; however, there was no conclusive evidence that this approach provided long-term benefits. The NIDDK-supported Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study recently demonstrated that long-term use of this drug combination can reduce the risk of recurrent UTI by up to 80 percent in children with VUR. The study was conducted over a 2-year period in more than 600 young children with VUR whose ages ranged from 2 months to 6 years; 92 percent of study participants were female. Notably, while TMP/SMZ significantly reduced the incidence of recurrent UTIs during the trial, the number of children who developed kidney scarring did not decrease in the group receiving the antibiotics; the researchers suggest this may be due to parents' heightened vigilance for UTI symptoms and early treatment in the trial and because most of the children were enrolled after their first infection rather than after multiple infections, when more scarring might occur. Further analysis of data from the RIVUR trial may provide insight into other factors that could reduce susceptibility to recurrent UTIs and kidney scarring. For now, though, the RIVUR study has demonstrated that treatment with TMP/SMZ offers the possibility of fewer infections for children with VUR, which may provide an opportunity for many of them to outgrow reflux as their bodies develop and mature. (RIVUR Trial Investigators, 2014)

Identifying Novel Non-Antibiotic Antimicrobials to Treat UTIs

Although UTIs are currently treatable with antibiotics, the emergence of antibiotic resistant microbes, combined with the personal and medical costs of care, makes finding better therapeutic strategies a priority. NIDDK-supported researchers are making advances in this area. For example, human ribonuclease 7 (RNase 7) is a potent antimicrobial peptide that is part of the body's innate defense system. NIDDK-supported scientists found that RNase 7 is produced constitutively under normal (healthy) conditions by cells lining the human bladder and ureters, as well as by α-intercalated cells in the kidney collecting tubule, and is present in uninfected urine in sufficient quantity to kill bacteria (Spencer et al., 2011). Building on that work, the investigators have now reported that RNAse 7 levels are elevated in the human urinary tract and urine during infection. They also found new sites of RNAse 7 production in the kidney during inflammation. Further, they demonstrated that RNase 7 is a potent, broad-spectrum antimicrobial agent against a variety of bacteria that cause UTIs (Spencer et al., 2013). Another group of researchers studied another suspected innate antimicrobial peptide, lipocalin 2 (LCN2), which is known to arrest the growth of *E. coli* and certain other bacteria by limiting their access to the essential nutrient iron. They found that levels of LCN2 are very high in the urine of patients suffering from UTIs and fall as UTIs resolve. Through studies in female mice, they discovered that LCN2 is produced by α-intercalated cells of the kidney in response to UTI (Paragas et al., 2014). Characterization of these antimicrobial molecules provides not only greater knowledge of the body's innate defenses against UTIs but also hope that further insight into their production and activity could lead to alternatives to standard antibiotics in the prevention or treatment of UTIs.

NIH Strategic Plan for Women's Health Research

NIDDK Activities Mapped to Strategic Plan

Fundamental Factors Imparting Sex Differences in Metabolic and Other Conditions

Strategic Plan Goals and Objectives:

Goal 1: "Increase sex differences research in basic science studies"
Top objective:

1.1: "Encourage genetic and epigenetic studies to identify sex differences in gene expression."

Other objectives:

1.2: "Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems."

Women's Urologic Health Research Program and Initiatives

Strategic Plan Goals and Objectives:

Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women"
Top objective:

3.5: "Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span."

Other objectives:

3.1: "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."

3.8: "Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life."

LIFE-MOMS

Strategic Plan Goals and Objectives:

Goal 3: "Actualize personalized prevention, diagnostics, and therapeutics for girls and women"
Top objective:

3.3: "Encourage research on safe and effective interventions for conditions affecting pregnant women."

Other objectives:

3.4: "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."

Other NIDDK Activities Relevant to the Strategic Plan

As noted under "Accomplishments," NIDDK has fostered both basic and clinical research resulting in advances in understanding of sex and gender differences in disease areas within its mission. In addition to continued sex and gender analysis in or ancillary to large-scale clinical studies, a number of new efforts will promote analysis of sex and gender differences. For example, NIDDK is supporting a career development award focused on gender disparities and vascular function in chronic kidney disease outcomes (1 K23 DK094829-01A1). NIDDK also participated in the ORWH-led effort to provide administrative supplements for research on sex and gender differences in both FY 2013 and FY 2014, and the Institute will continue to work with ORWH to identify new opportunities to promote sex and gender differences research. In addition, in FY 2014, the NIDDK Director approved a general modification of writing style in NIDDK lay-friendly documents such that summaries of scientific research involving rodents and certain other animal models will indicate whether males, females, or both sexes were used; in this way, NIDDK hopes to model—and encourage—the routine reporting of biological sex as a scientific variable. This change was announced in an annual NIDDK publication that is distributed to NIDDK constituents and is available on the NIDDK Web site.

NIDDK Positions Relevant to Women's Health

The NIDDK scientific staff includes a Program Director for Women's Urologic Health who, with input from ORWH, the HHS Office on Women's Health, and other ICs, is developing the prevention-focused research program to improve women's urologic health described previously. NIDDK's Healthy Pregnancy Program involves the efforts of program directors from two extramural research divisions plus the NIDDK Office of Obesity Research. A Women's Health Liaison to ORWH in NIDDK's Office of Scientific Program and Policy Analysis coordinates efforts across NIDDK and works with ORWH to foster partnerships in areas of joint interest in women's health.

Inclusion

NIDDK activities that have expanded or laid the foundation to expand participation of girls and women in clinical research in trials include the new Women's Urologic Health Research Program, which is bringing girls and women into clinical research focused on prevention of urologic symptoms across the life span, with the anticipated accompanying benefit of improved overall health.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

Ongoing research training initiatives developed by the NIDDK Office of Minority Health Research Coordination (OMHRC) focus on improving training of new and young investigators who are underrepresented in biomedical research, including students with disabilities, those from disadvantaged backgrounds, and those from certain racial and ethnic minorities in the United States. Although they are not focused solely on girls and women, these initiatives—separate Short Term Research Experience for Underrepresented Persons programs for high school and undergraduate students and the Diversity Summer Research Training Program—encourage entry into NIDDK-relevant STEM areas by girls and women who might not otherwise have an opportunity to do so. In FY 2013 and FY 2014, girls and women constituted the majority of participants in all three programs.

Information and Education Initiatives

NIDDK continues to support a number of education and awareness campaigns important to women's health. In addition to efforts already cited under "Accomplishments," these include:

The Weight-Control Information Network Program, "Sisters Together: Move More, Eat Better." In FY 2013 and FY 2014, Sisters Together continued its efforts to develop and promote relevant tools and tips that help African-American women and their families get more physical activity and consume healthier foods and beverages. For example, Sisters Together revised its community program guide. The "Sisters Together Program Guide" walks individuals and groups through the steps of developing and implementing a Sisters Together program in their community. The revised guide includes the following:

- Tip sheets on addressing barriers to physical activity and healthy eating;
- Advice on planning start-up meetings; and
- Tips on using tools such as Facebook and Web sites to spread the word about program activities.

The revised "Sisters Together Program Guide" has been promoted to community health clinics, health departments, and the media. The program also used Facebook messages to encourage groups and individuals to become health champions. Visit the program guide at http://win.niddk.nih.gov/sisters/index.htm.

NIDDK Bowel Control Awareness Campaign. The NIDDK Bowel Control Awareness Campaign provides resources to inform and improve the lives of women and men living with fecal incontinence. The campaign's Web site, at http://www.bowelcontrol.nih.gov, offers expert guidance for health care professionals and patients on the prevention and management of fecal and urinary incontinence as well as easy-to-read booklets and other publications for patients and the public.

Outreach and Promotion Related to Women's Health. In FY 2013 and FY 2014, NIDDK sought to raise awareness and provide evidence-based information about diseases and conditions commonly affecting women through a variety of channels, including "eblasts" to raise awareness of national

health observances, topical articles in its five disease-specific quarterly newsletters (diabetes, digestive diseases, celiac disease, kidney disease, and urologic diseases), Facebook posts to promote NIDDK publications related to women's health and to highlight National Women's Health Week, and distribution of more than 2,700 publications related to women's health at conferences and health fairs and during National Women's Health Week.

Funding Initiatives, Workshops, and Conferences

Requests for Applications

Nociceptive GenitoUrinary Development Molecular Anatomy Projects (nGUDMAP) (U01) (RFA-DK-12-024). This RFA solicited applications to help build a murine molecular anatomy atlas of the nociceptors (pain receptors) and associated cell types in pain processing of the urinary tract and the pelvic region. RFA sponsor: NIDDK

Urologic Chronic Pelvic Pain Syndrome (UCPPS) Research (R01) (RFA-DK-12-025). This RFA solicited innovative research proposals to improve understanding of the etiology, pathology, natural history, and risk factors for UCPPS, traditionally referred to as IC/PBS and CP/CPPS. Eight grants were cofunded by NIDDK and ORWH; examples include a study of urinary metabolites in IC/PBS diagnosis and a clinical study with cyclosporine A in IC/PBS patients refractory to other treatments. RFA sponsors: NIDDK, ORWH

Limited Competition of the MAPP Research Network (U01) (RFA-DK-13-507). The purpose of this RFA was to invite applications from the current MAPP discovery and core sites for a second 5-year project period through a limited competition. RFA sponsors: NIDDK, ORWH

Expansion of the MAPP Research Network (U01) (RFA-DK-13-025). The purpose of this RFA was to expand the MAPP Research Network by adding new discovery sites. RFA sponsor: NIDDK

Limited Competition for the Continuation of the Diabetes Prevention Program Outcomes Study (DPPOS) (U01) (RFA-DK-14-501). The primary purpose of this RFA is to continue follow-up of the DPPOS cohort to examine the effectiveness of early metformin treatment on the development of CVD and cancer. RFA sponsor: NIDDK

Limited Competition: Continuation of the Type 2 Diabetes in Adolescents and Youth (TODAY) Study (U01) (RFA-DK-14-502). The primary purpose of this RFA was to continue follow-up of the TODAY cohort to define the long-term clinical course of youth-onset type 2 diabetes. RFA sponsor: NIDDK

Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCs) (U01) (RFA-DK-14-004). The purpose of this RFA was to establish a multicenter, multidisciplinary consortium (PLUS Consortium) that will help expand NIH's research emphasis from treatment of women with established LUTS to prevention of LUTS. The PLUS Consortium will conduct studies to develop the evidence base for normal or healthy bladder function and to identify behavioral and other risk factors for conditions associated with LUTS, which will help form the scientific basis for future prevention intervention studies in adolescent girls and women. Symptoms associated with the diagnosis of bladder infections, urinary incontinence, voiding dysfunction, overactive bladder, and IC/PBS will be a particular focus. RFA sponsors: NIDDK, ORWH, National Institute on Aging (NIA)

Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (PLUS-SDCC) (U01) (RFA-DK-14-018). This RFA solicits a scientific and data coordinating center to support efforts of the PLUS Consortium. RFA sponsors: NIDDK, NIA, OBSSR, ORWH

Identification of Novel Targets and Pathways Mediating Weight Loss, Diabetes Resolution, and Related Metabolic Disease After Bariatric Surgery in Humans (R01) (RFA-DK-14-025). The purpose of this RFA is to support human studies that address the mechanisms by which novel, unexplored targets and pathways, or known targets, mediate the sustained weight loss, diabetes resolution and improvements, in other obesity-related metabolic diseases reported following bariatric surgery in humans. RFA sponsor: NIDDK

Psychosocial and Behavioral Aspects of Bariatric Surgery (R01) (RFA-DK-14-026). The purpose of this RFA is to support research to measure psychosocial and behavioral variables in individuals undergoing bariatric surgery to understand how they predict success and risk and examine mechanisms of behavior change. RFA sponsor: NIDDK

Program Announcements (PAs)

Addressing Health Disparities in NIDDK Diseases (R01) (PA-13-183). Several diseases that disproportionately afflict underserved populations are high priority research areas for NIDDK. This PA invites research applications addressing high priority diseases within the scientific mission areas of NIDDK in which there are opportunities to improve understanding of disease causes and to develop and test more effective interventions for reducing or eliminating health disparities. PA sponsor: NIDDK

Mechanistic Insights from Birth Cohorts (R01) (PAR-13-109). This PAR is intended to support novel research on how prenatal exposures contribute to the etiology of chronic diseases and health conditions later in life. The goal of this initiative is to stimulate research by leveraging existing birth cohorts to address targeted mechanistic questions regarding the normal and abnormal developmental origins of organ systems or diseases of interest to the participating NIH ICs. PAR sponsors: NIDDK, NHLBI, NICHD, National Cancer Institute, National Institute of Environmental Health Sciences

Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R18) (PAR-13-366). The purpose of this PAR is to support research to test approaches to improve diabetes treatment and prevention in existing health care settings. Applications are sought that test practical and potentially sustainable strategies, delivered in routine clinical care settings, to improve processes of care and health outcomes of individuals who are at risk for or have diabetes. The goal is for the research results to improve routine clinical practice and inform policy in representative health care settings. GDM is an area of potential intervention. PAR sponsor: NIDDK

Planning Grants for Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R34) (PAR-13-367). The purpose of this Planning Grant (R34) PAR is to support research to develop and pilot test approaches to improve diabetes treatment and prevention in existing health care settings. The goal is—if the pilot study shows promise—to use the data from the R34 to support a full-scale trial that could improve routine clinical practice and inform policy in representative health care settings. PAR sponsor: NIDDK

Understanding Factors in Infancy and Early Childhood (Birth to 24 Months) That Influence Obesity Development (R01) (PAR-14-323). The purpose of this PAR is to support research to characterize or identify factors in early childhood that may increase or mitigate risk for obesity or excessive weight gain or to fill methodological research gaps relevant to the understanding of risk for development of obesity in children; such research could contribute to efforts to break the vicious cycle of diabetes and obesity in women and their offspring in future generations. PAR sponsors: NIDDK, NICHD, NIMHD, OBSSR

NIDDK also participated in:

- Genetic Susceptibility & Variability of Human Structural Birth Defects (R01) (PA-14-056)
- Research on Chronic Overlapping Pain Conditions (R01) (PA-14-244)
- Mechanisms, Models, Measurement, & Management in Pain Research (R01) (PA-13-118)
- Administrative Supplements for Research on Sex/Gender Differences (Admin Supp) (PA-13-018)
- Administrative Supplements for Research on Sex/Gender Differences (Admin Supp) (PA-14-027)
- Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp) (PA-12-150)

Conferences and Workshops

Long Term Outcomes of Bariatric Surgery. May 22–23, 2014. The purpose of this workshop was to review the current state of the science in regards to long-term outcomes of bariatric surgery, determine critical gaps in understanding, and strategize about methods to leverage existing clinical studies to fill those gaps.

Basic Behavioral Science Research in Obesity Meeting. April 24–25, 2013. The overarching goal of this workshop was to identify potential behavioral mechanisms relevant to obesity, such as determinants of food intake, physical activity, and sedentary behavior.

Developing a Clinical Research Agenda for Fecal Incontinence. August 19–20, 2013. This workshop convened experts in epidemiology, gastrointestinal physiology, gastroenterology, colorectal surgery, urogynecology, psychology, and behavioral medicine to identify and discuss major issues in the diagnoses and treatment of fecal incontinence. In addition, the panel examined the barriers encountered in addressing fecal incontinence and developed research priorities in both basic and clinical research to further advance treatment strategies for fecal incontinence. The workshop proceedings and recommendations, which focus on epidemiology, pathophysiology, classification, and treatment, have been published and will serve to guide future NIDDK efforts in this area (Bharucha et al., 2015; Whitehead et al., 2015).

Path to Prevention of Lower Urinary Tract Symptoms (LUTS) in Women: Bladder Health. May 3–4, 2014. This NIDDK-sponsored workshop brought together medical, nursing, physical therapy, patient education, behavioral change, epidemiology, public health, and prevention experts in a scientific workshop framed around defining bladder health as a first step along the path to prevention of LUTS in women. The goal of this workshop was to provide a scientific background that can inform research to identify and establish modifiable risk factors for LUTS in women and help lay the foundation for future prevention studies. Workshop organizers included representatives from several NIH ICs and the HHS Office on Women's Health. A workshop summary is available at http://www.niddk.nih.gov/news/events-calendar/Pages/LUTS.aspx#ui-tab-minutes.

Urinary Incontinence Summit. March 20, 2014. This meeting brought together health care professionals from a variety of disciplines, consumer advocates, and Federal scientists to review information garnered from several large scale NIH-sponsored clinical trials to treat urinary incontinence and determine what can be communicated to patients and the public about urinary incontinence in messages informed by these research results, which were unavailable several years ago. The meeting also sought to address gaps in understanding of urinary incontinence and how those gaps can be translated into future studies supported by NIDDK. A workshop summary is available at http://www.niddk.nih.gov/news/events-calendar/Pages/summit-urinary-incontinence-clinical-research-women.aspx#ui-tab-minutes.

Health Disparities

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high-priority research areas for NIDDK. Some of these diseases, such as obesity and type 2 diabetes, also affect women and men differently within these disproportionately affected groups. OMHRC oversees Institute efforts to address these disparities. Visit the OMHRC Web site at http://www2.niddk.nih.gov/OMHRC/OMHRCHome/OMHRCHome.htm. Several major NIDDK-supported research efforts pertain to health disparities in women. For example, the DPP/DPPOS and TODAY study cohorts, which have more females than males, are highly ethnically and racially diverse, reflecting the disproportionate burden of diabetes in racial and ethnic minority girls and women. The composition of study populations in the LIFE-Moms Consortium also reflects the burden of obesity or postpartum weight retention in women from racial and ethnic minority populations in the United States. A new NIDDK-supported study will examine data from the Nurses' Health Study II to examine the extent to which type 2 diabetes and related risk factors may disproportionately affect lesbian and bisexual women across the life span compared to their heterosexual counterparts (1R01DK099360-01A1). NIDDK's intramural research program also supports projects highly relevant to health disparities in women, such as differences in fat metabolism between African-American and White women that are

relevant to effectively diagnosing vascular disease risk, and studies of obesity and GDM in Pima Indian women through participation in DPP/DPPOS, Look AHEAD, and LIFE-Moms, and through other efforts. In addition to support for pertinent "Information and Education Activities" already described, NIDDK communications activities important to health disparities in women include providing a variety of health information publications in Spanish and some in multiple languages. Publications in the Awareness and Prevention series, which are distributed as one- or two-sheet flyers with English on one side and Spanish on the other, include, "Bowel Control Problems: What You Need to Know" and "What I Need to Know About Gestational Diabetes."

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Conferences and Workshops

Developing a Clinical Research Agenda for Fecal Incontinence: Workshop Proceedings

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Health Disparities

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National Institute on Drug Abuse

Executive Summary

As the foremost authority on drug abuse and addiction, sponsoring the vast majority of the world's research on the subject, National Institute on Drug Abuse (NIDA)–supported science addresses the most fundamental and essential questions about drug abuse. We do this by monitoring emerging trends, by identifying and studying underlying biological and social factors and consequences, and by determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within NIDA's mission is a focus on studying issues specific to women and identifying and studying sex/gender differences in both clinical and preclinical research. Research over the past few decades has shown that there are male-female differences in the initiation and progression of drug use and addiction, the risk and protective factors, and the consequences of drug abuse, and that intervention outcomes may be enhanced by sex/gender-specific considerations. In recognition of the important role of sex/gender differences in drug abuse, NIDA continues its commitment to support research to identify sex/gender-specific aspects of drug abuse and addiction across the life span and to apply these findings to improve outcomes for both males and females.

This 2013–2014 biennial report highlights NIDA's research on women and sex/gender differences and our activities to promote research in this area, including our science, technology, engineering, and mathematics (STEM) efforts, which are very successful in attracting females. Our featured programs and our research advances include both basic and clinical neuroscience and are shedding light on sex differences in biological and behavioral mechanisms as well as the consequences of addiction. A striking feature of our research presented in this report is its translational implications. Brain imaging studies with smokers, for example, are revealing sex differences in the neurobiological underpinnings of nicotine addiction, findings that hold promise for achieving sex-based nicotine cessation treatments. Our cannabis studies, which are so important given the changes in marijuana laws across the nation, are showing sex differences in marijuana use outcomes. Studies of children who are prenatally exposed to drugs continue to find that impairments often differ in boys and girls. Research on drug-abusing women and girls within the criminal justice system is showing the importance and need for sex/gender-specific prevention and treatment strategies—especially for those with HIV/AIDS. Studies on medications to treat drug addiction are finding outcomes that differ in men and women.

Collectively, these and other research advances described herein continue to provide evidence of the importance of conducting research specific to women, of taking a sex/gender-based research approach, and of analyzing data separately for males and females. Ultimately, this approach will have implications for tailoring prevention and treatment interventions that will optimize outcomes for both males and females. This is at the heart of the Precision Medicine Initiative announced in the State of the Union address on January 20, 2015 (White House, 2015), and in

the perspective article by Drs. Francis Collins and Harold Varmus, in which precision medicine was described as "prevention and treatment strategies that take individual variability into account" (Collins & Varmus, 2015). Sex is the most basic, fundamental individual difference. Thus, NIDA is pleased to present examples of our research that are consistent with the Precision Medicine Initiative.

Almost all of NIDA's scientific advances highlighted in this report reflect the goals of the NIH Strategic Plan for Women's Health Research (http://orwh.od.nih.gov/research/strategicplan/index.asp). The advances largely fall under Goal 1, "Increase sex differences research in basic science studies," or Goal 3, "Actualize personalized prevention, diagnostics, and therapeutics for girls and women."

The Women and Sex/Gender Differences Research Program Leadership at NIDA

NIDA's Women and Sex/Gender Differences Research Program was established in 1995. The Coordinator and Deputy Coordinator, along with NIDA's Women & Sex/Gender Research Group (WGRG), lead the scientific efforts at NIDA to promote research that is specific to or prominent in women and that investigates sex/gender differences in drug abuse. The WGRG has membership from all of NIDA's divisions and offices, representing research areas that span from molecular biology and genetics to risk and protective factors, prevention, consequences, and treatment and services for drug abuse, as well as the dissemination of research findings. The overarching goal of NIDA's Women and Sex/Gender Differences Research Program is to infuse this research throughout all areas of drug abuse research, to disseminate resultant findings, and to target the next generation of drug abuse researchers. The program is using a variety of strategies, including funding opportunity announcements, travel awards, development and sponsorship of symposia and meetings, scientific presentations, publications, and NIDA's Web site.

NIDA's Women and Sex/Gender Differences Research Program Coordinator and Deputy Coordinator represent NIDA on the ORWH Coordinating Committee for Research on Women's Health and partner with ORWH in various ORWH programs, including the Specialized Centers of Research (SCOR) on Sex Differences and Building Interdisciplinary Research in Women's Health programs. They also serve as liaisons and committee members in NIH-wide efforts, the HHS Office on Women's Health, other HHS agencies, and the White House, as well as scientific organizations.

Featured Research Programs

NIDA is pleased to partner with ORWH in its SCOR program. The SCOR program consists of research centers across the country that integrate basic, clinical, and translational research approaches with a sex-based focus. Three of the ORWH SCORs are administered by NIDA and are located at the Medical University of South Carolina, the University of Minnesota, and Yale University. Each has at least three highly integrated, synergistic research projects. All three are studying nicotine addiction and two are studying cocaine addiction. Each is translational, having at least one preclinical project and at least two clinical projects. And each is taking a precision medicine perspective, studying factors such as stress and impulsivity that may impact the effectiveness of a potential medication and may do so differentially in males and females.

The SCOR at the Medical University of South Carolina, led by Dr. Kathleen Brady, focuses on three neuropeptides—oxytocin, orexin, and corticotrophin-releasing factor—as potential mechanisms underlying the stress response in cocaine-dependent men and women, and as potential targets for sex-based medications for the treatment of both cocaine addiction (for which there are no Food and Drug Administration [FDA]–approved medications) and nicotine addiction. The SCOR contains two clinical projects and two animal model projects. One set of clinical studies is investigating oxytocin as a potential cocaine medication for stress-based relapse. Oxytocin is a hypothalamic neuropeptide that has been shown to mediate behavioral responses to stress and to play a role in neuroadaptations that occur following long-term drug use. Other clinical studies are examining the influences of sex hormone and oxytocin administration on the relationships among stress, craving, and smoking resistance. A set of preclinical studies is examining orexin and oxytocin as neuropeptide substrates that may underlie sex and estrous cycle-dependent differences in cocaine taking and reinstatement of cocaine seeking. Another set of preclinical studies are focused on

the role of norepinephrine and the corticotrophin-releasing factor in stress reactivity in cocaine self-administration. The sex-based and stress-based focus of this SCOR has potential to lead to sex-based treatments for both nicotine and cocaine addiction. **[Objectives: 1.5, 1.6]**

The SCOR at the University of Minnesota, led by Dr. Marilyn Carroll, focuses on interactions among sex differences, hormonal status, impulsivity, and drug-motivated behavior to study potential treatments for nicotine and cocaine addiction. Three medications that have been shown to reduce impulsivity are being examined: progesterone, atomoxetine, and varenicline. A preclinical project is studying sex differences in an animal model of nicotine and cocaine relapse, and in an animal model of impulsivity for nicotine or cocaine in rats treated with progesterone alone and in combination with atomoxetine or varenicline, which is FDA approved for nicotine cessation. This preclinical project will determine whether medications that reduce impulsivity will also reduce drug seeking and will also consider hormonal factors including naturally occurring hormonal fluctuations in pregnancy and post partum. A clinical study is investigating sex differences in the effect of exogenous progesterone on impulsivity and smoking cessation, and another clinical study is investigating sex differences in the effect of exogenous progesterone combined with atomoxetine on impulsivity and on preventing relapse to cocaine abuse. **[Objectives: 1.5, 1.6]**

The SCOR at the Yale University School of Medicine, led by Dr. Sherry McKee, is aimed at developing effective smoking cessation treatments, especially for women. In preliminary human laboratory studies and a small smoking-cessation efficacy trial, Dr. McKee has demonstrated that guanfacine can effectively reduce smoking rates in both men and women—but via different mechanisms. In males, guanfacine appears to modulate nicotine reinforcement, whereas in females, the drug appears to mitigate negative affect and stress. Going forward, the Yale SCOR is studying sex differences in the drivers of smoking and relapse, both behavioral and neurobiological, via an animal model project and a human brain imaging project linked to a human laboratory project and larger Phase 2 smoking cessation trial with guanfacine. Together, these projects will probe the noradrenergic system's effects on stress-reactivity and nicotine reinforcement, testing the hypotheses that different brain systems modulated by noradrenergic activity are activated by smoking in women and men, and that guanfacine, an α-2a noradrenergic agonist, can preferentially target these sex-sensitive systems to improve smoking cessation outcomes. On December 10, 2014, a study published by Yale SCOR researchers showed for the first time profound sex differences in the brain release of the neurotransmitter dopamine in smokers while undergoing PET brain imaging (Cosgrove et al., 2014). This study, which received widespread media attention, shows that differential brain mechanisms are involved in nicotine addiction in males and females. **[Objectives: 1.5, 1.6, 2.6]**

As described above, all three of NIDA SCORs have clinical projects that address nicotine addiction and medications to treat it. Together, they hold promise for the development of sex-based smoking cessation treatments and for developing better treatment options for both men and women. A meta-analysis underway by one of the SCORs is aimed at surveying the clinical literature on sex differences in response to available FDA-approved smoking cessation medications with the goal of determining the best option for men, the best option for women, and the rank-ordering of the remaining medication options for men and for women.

Progress in medications research made by NIDA SCORs was highlighted at the annual meeting of the College on Problems of Drug Dependence, June 14–19, 2014, in San Juan, Puerto Rico, in a symposium, "Medications for Drug Addictions: Sex Differences in Outcomes in Animal and Human Laboratory Studies and in Clinical Trials." The symposium featured presentations from researchers from each of the three SCORs, including each of the principal investigators. **[Objectives: 1.9, 4.5]**

Research Accomplishments

Nicotine and Smoking

Differences in smoking between men and women are well documented, including the health consequences, nicotine dependence, quit success, barriers to treatment, and success with nicotine replacement treatments. The research described below describes studies exploring mechanisms that may contribute to these sex differences and studies on two subpopulations of women smokers: those who use oral contraceptives and those who are seriously mentally ill and have posttraumatic stress disorder.

Sex Differences in Resting State Neural Networks of Nicotine-Dependent Cigarette Smokers. Although many sex differences in nicotine dependence have been identified, the underlying neural mechanisms underlying these sex differences are not well understood. The present study examines sex differences in resting-state brain activity using an arterial spin labeling perfusion imaging technique. Sated nicotine-dependent cigarette smokers underwent perfusion functional magnetic resonance imaging during the resting state. Using functionally defined hippocampus/amygdala (HIP/AMY) seed regions, researchers observed sex differences in correlation strength between the HIP/AMY and the bilateral anterior insula, rostral anterior cingulate cortex, and inferior parietal lobule with females showing stronger functional coupling than males. These sex differences in the pattern of synchronous variations in dynamic cerebral blood flow in smokers provide a novel perspective on the neural mechanisms that may contribute to sex differences in nicotine dependence (Wetherill, Jagannathan, Shin, & Franklin, 2014). **[Objectives: 1.5, 1.6, 2.6]**

Sex Differences in the Brain's Dopamine Signature of Cigarette Smoking. Researchers have developed a technique allowing them to quantify dynamic changes in the brain's release of the neurotransmitter dopamine during smoking and create real-time "movies" showing bursts of dopamine release. The quantitative analysis and movies revealed distinct sex differences. In males but not females, consistent and rapid dopamine release occurred in the right ventral striatum, which is associated with drug reinforcement. In females, dopamine release occurred rapidly in the right dorsal putamen, which is associated with habit formation, whereas in males the rise in dopamine release was slow and moderate if at all. These findings accord with other studies indicating that smoking in men is due to reinforcement provided by nicotine, whereas in women smoking occurs for other reasons such as mood and emotion regulation and reactivity to cues. Follow-up research by the researchers is aimed at using this new real-time method of imaging dopamine to evaluate the effects of smoking cessation treatments in males and females (Cosgrove et al., 2014). **[Objectives: 1.5, 1.6, 2.6]**

Cue-Elicited Craving Is Greater in Adolescent Female Smokers than Male Smokers. Smoking initiation usually begins in adolescence, but how and for whom nicotine dependence emerges during this period is unclear. The cue-reactivity laboratory paradigm is well suited to examine one marker of dependence: craving-related stimulus control, that is, the ability of environmental cues to elicit craving to smoke. Researchers examined the effects of level of smoking involvement (daily versus occasional smoking) on reactivity to both smoking and alcohol cues in adolescents 16–20 years of age. Daily smokers exhibited higher levels of tonic (i.e., non–cue-elicited) craving than did occasional smokers. Both groups showed significant increases in craving in response to cues (i.e., cue-elicited craving), with little evidence that cue-elicited craving differed between groups. Females were more reactive to both the alcohol and smoking cues than males. Cue-elicited craving may be one mechanism that contributes to the maintenance of smoking behavior and perhaps to the development of nicotine dependence within early stage smokers. These findings could be particularly important for the development of smoking cessation treatment programs for females (Carpenter et al., 2014). **[Objectives: 1.5, 1.6]**

Potential Effect of Oral Contraceptive Use on Smoking Cessation. Approximately 27 percent of premenopausal women who smoke report using oral contraceptives (OCs), but little is known about how their use may influence smoking cessation outcomes. An exploratory study examined the difference in smoking-related symptomatology during acute smoking abstinence between women on a standardized combination OC compared with women not on OCs. The women were 18–40 years old, smoked at least 5 cigarettes/day, and reported regular menstrual cycles. During acute smoking abstinence, women who were on OCs experienced several notable differences in symptomatology as compared with women not on OCs. OC users had lower levels of positive affect during smoking cessation. Additionally, smoking satisfaction and psychological reward varied by OC use and menstrual cycle, and OC users had more menstrual cycle variation in negative affect. The results suggest that women on OCs may have different patterns of smoking-related symptomatology during short-term smoking abstinence as compared with women not on OCs. Additional work is needed to examine how this may affect smoking cessation efforts (Hinderaker et al., 2014). **[Objectives: 1.6, 3.1]**

PTSD Symptomatology and Readiness to Quit Smoking Among Women with Serious Mental Illness. People with

posttraumatic stress disorder (PTSD) smoke more heavily, experience more severe withdrawal symptoms, and have lower quit rates than those without PTSD. Most research on PTSD and smoking has been conducted with men, particularly combat veterans, and little is known about the association among women. In a sample of 374 adult women smokers aged 18–73 with serious mental illness, researchers found that nearly half the sample screened positive for PTSD, which was associated with poorer mental health functioning, greater illicit drug use, and a greater prevalence of drug use disorders. A positive screen for PTSD was unrelated to severity of nicotine dependence, and notably, a greater desire to quit smoking compared with women who screened negative for PTSD. These findings have implications for interventions practices that concurrently address trauma recovery and tobacco cessation (Young-Wolff et al., 2014). **[Objectives: 1.5, 1.6]**

Cannabis—Male-Female Differences

Prior research indicates that although the severity of a cannabis use disorder is higher for men, women proceed to cannabis use disorder more quickly after first use. The first two studies below explore mechanisms that may play a role in this sex difference and the third study explores how cannabis might differentially impact neurocognition in male and female users.

Sex-Dependent Subjective Effects of Smoking Cannabis. Women exhibit an accelerated progression from first cannabis use to cannabis use disorder (CUD). Findings from a laboratory study may shed light on this faster progression in females. The study compared the subjective effects of smoking cannabis in men and women matched for current cannabis use. Women reported higher ratings of abuse-related effects relative to men but did not differ in ratings of intoxication. The results suggest that when matched for cannabis use, women are more sensitive to the subjective effects related to cannabis' abuse liability relative to men, which may contribute to their enhanced vulnerability to developing CUD. Thus, sex is an important variable to consider when assessing the development of CUD (Cooper & Haney, 2014). **[Objectives 1.5, 1.6]**

Sex Differences in Tolerance to THC's Pain-Relieving Effects. In rodent studies, sex differences in the behavioral effects of cannabinoids have been reported. Those studies found that females are more sensitive than males to the reinforcing, anxiogenic, spatial memory-impairing, hypothermic, and sedative effects of cannabinoids. They are also more sensitive than males to the antinociceptive (pain-relieving) effects of cannabinoids. In a recent study of the effects of delta-9-tetrahydrocannabinol (THC) on pain relief, researchers have now found—using two different tests of pain sensitivity—that female rodents become more quickly tolerant than males to THC's antinociceptive effects. Given the importance of drug tolerance in the development of drug dependence, these results suggest that females may be more vulnerable than males to developing dependence after chronic cannabinoid exposure (Wakley, Wiley, & Craft, 2014). **[Objectives 1.4, 1.5, 1.6]**

Preliminary Evidence for a Sex-Specific Relationship Between Amount of Cannabis Use and Neurocognitive Performance in Young Adult Cannabis Users. Accumulating evidence suggests that cannabis use can cause neuropsychological deficits. However, few studies have examined how cannabis use may differentially impact neurocognition in male and female cannabis users. To explore this issue, researchers examined potential sex differences in associations between amount of cannabis use (across several time frames) and neurocognitive performance among young adult regular cannabis users. Consistent with previous studies, more cannabis use was generally associated with poorer episodic memory and decision-making but not other measures of inhibitory control. Patterns of results suggested sex-specific dissociations. In particular, more cannabis use was more consistently associated with poorer episodic memory performance in females than males. Conversely, more cannabis use was associated with poorer decision-making performance for males, but not females. These results provide further evidence for residual cannabis-associated neurocognitive deficits and suggest the importance of examining the impact of cannabis on neurocognition separately for males and females (Crane, Schuster, & Gonzalez, 2013). **[Objectives 1.5, 1.6]**

Clinical Studies—Implications for Treatment Strategies

The clinical studies described below add to a growing body of research, both clinical and preclinical, showing that research on cocaine, other stimulants, and opioids often

finds different outcomes in men and women. The first study examined whether cocaine differentially affected grey matter volume in men and women, while the second study examined in real time whether male and female cocaine and heroin users responded differently to drug triggers. Impulsivity is a risk factor for addiction, and the third study focused on sex differences in impulsivity among stimulant users and the differential role of physical abuse. Taken together, these studies suggest different treatment targets—behavioral or pharmacologic—for men and women.

Sex Differences in Decreased Limbic and Cortical Grey Matter Volume in Cocaine Dependence: A Voxel-Based Morphometric Study. Structural neuroimaging studies find evidence of differences in local brain volume between cocaine-dependent and healthy control individuals. While sex differences in etiology, course, and brain dysfunction associated with chronic cocaine abuse are previously documented, evidence of sex-specific differences in brain volume has not been examined thus far. This study examined sex-related differences in grey matter volume between cocaine-dependent and healthy control subjects using voxel-based morphometry. High-resolution T1 structural scans were obtained from 36 inpatient, 3-week abstinent, cocaine-dependent (CD) individuals and 50 control subjects. CD patients were found to have less grey matter volume in anterior prefrontal cortex, including frontopolar and orbitofrontal cortices, and a posterior region surrounding the parietal-occipital sulcus. Female CD patients had less grey matter volume than female controls in left inferior frontal gyrus, insula, superior temporal gyrus and hippocampus—which include regions related to emotion and stress. Male CD patients had less grey matter in a superior cortical region that included the precentral gyrus and the mid-cingulate—which include cognitive control regions. These sex differences in lower grey matter volume add to the evidence from functional neuroimaging for sex-specific differences in the neurophysiological changes associated with chronic cocaine use (Rando, Tuit, Hannestad, Guarnaccia, & Sinha, 2013). **[Objectives: 1.5, 1.6, 2.6]**

Sex Differences in Cocaine/Heroin Users: Drug-Use Triggers and Craving in Daily Life. Past clinical studies of people with drug use disorders have shown that women and men experience and respond to drug cues differently. To better understand differing responses to drug cues as they occur in real time, researchers at NIDA's Intramural Research Program used a method called ecological momentary assessment to capture the drug behavior and transient mental states of a sample of cocaine and heroin abusers. For up to 25 weeks, outpatients in a methadone maintenance program reported their current mood, drug-related cravings, and other information several times a day when randomly prompted via a personal digital assistant; they also recorded this information whenever they used or found themselves craving drugs, even if not prompted. Men and women did not differ in the average amount of cocaine or heroin used per episode of drug taking, nor did they differ in how much they enjoyed it. However, they did report divergent patterns of responding to drug cues. Women reported greater recent exposure to drug cues or being tempted to use and more craving in response to those cues than men did. After using drugs, women were more likely than men to report using more than they had meant to, feeling guilty, and having used despite trying not to. Regarding triggers for drug use, women were more likely than men to say that they were testing their self-control; men were more likely than women to indicate that they took a drug because they felt uncomfortable or in pain, an interesting finding given men's previously reported higher tolerance for pain. These findings provide real-time behavioral evidence that women respond differently than men to exposure to drug cues and to drug use, consistent with laboratory and brain-imaging findings. This information may be useful for the development of sex-specific treatment strategies (Kennedy, Epstein, Phillips, & Preston, 2013). **[Objectives: 1.5, 1.6]**

Sex Differences in Disinhibition Among Stimulant-Abusing Individuals and the Role of Physical Abuse. Research suggests that impulsivity is a vulnerability factor for developing stimulant dependence, that women develop dependence more quickly than men, and that physical abuse can increase impulsivity and may have greater adverse health consequences in women. This study sought to tie these findings together by evaluating (1) sex differences in disinhibition prior to lifetime initiation of stimulant abuse and (2) the relationship between physical abuse and disinhibition in stimulant-dependent patients. In this multisite study, 118 stimulant-dependent participants were assessed with the Frontal Systems Behavior Scale (FrSBe) and Addiction Severity Index. The proportion reporting

clinically significant disinhibition was significantly higher in women than in men, with no significant difference on the other FrSBe scales. Physical abuse in women, but not men, was associated with worse functioning, with physically abused women (relative to non-abused women) having a significantly greater proportion with clinically significant disinhibition and total neurobehavioral abnormalities. These findings suggest that women may have significantly greater disinhibition than men prior to lifetime initiation of stimulant abuse and that physical abuse in women is associated with greater disinhibition (Winhusen & Lewis, 2013). **[Objectives: 1.5, 1.6]**

Prescription Opioid Use and Opioid Receptors

Research indicates that women and men often report different reasons for abusing prescription and illicit opioids and that they may be differentially sensitive to some of their effects. These studies below explored clinical correlates of prescription opioid use as well as sex differences in neurotransmitter mechanisms underlying opioid use.

Women with Prescription Opioid Dependence Show Greater Functional Impairment and Psychiatric Severity than Men. The aim of this study was to examine sex differences in clinical characteristics and treatment outcomes in a large clinical trial for prescription opioid dependence. Despite no pretreatment differences in opioid dependence severity, women reported significantly greater functional impairment, greater psychiatric severity, and higher likelihood of using opioids to cope with negative affect and pain than men. Women were also more likely than men to have first obtained opioids via a legitimate prescription and to use opioids via the intended route of administration. Men reported significantly more alcohol problems than women. There were no significant sex differences in medication dose, treatment retention, or opioid outcomes. Thus, despite the presence of pretreatment sex differences in this population, once the study treatment was initiated, women and men exhibited similar opioid use outcomes (McHugh et al., 2013). **[Objectives: 1.5, 1.6]**

Clinical Correlates of Prescription Opioid Analgesic Use in Pregnancy. A 2012 committee opinion from the American College of Obstetricians and Gynecologists highlights the considerable increase in opioid addiction in recent years, yet little is known about clinical correlates of prescribed opioids among pregnant women. This study examined clinical and demographic factors associated with the use of opioid analgesics in pregnancy. Data were derived from a prospective cohort study of pregnant women. Participants were administered the Composite International Diagnostic Interview to identify depressive and anxiety disorders, and data on medication use were gathered at three assessment points and classified according to the Anatomical Therapeutic Chemical (ATC) classification system, ATC code N02A. Participants included 2,748 English- or Spanish-speaking pregnant women. Six percent (n = 165) of women used opioid analgesics at any point in pregnancy. More pregnant women using opioids met diagnostic criteria for major depressive disorder (16 percent versus 8 percent for non-users), generalized anxiety disorder (18 percent versus 9 percent for non-users), posttraumatic stress disorder (11 percent versus 4 percent for non-users) and panic disorder (6 percent versus 4 percent for non-users). Women who reported opioid use were also significantly more likely than non-users to report using illicit drugs and almost three times as likely to report smoking cigarettes in the second or third trimester of pregnancy (4 percent and 23 percent, respectively) as compared with non-opioid users (0.5 percent and 8 percent). The use of opioids in pregnancy was associated with higher levels of psychiatric comorbidity and use of other substances as compared with non-opioid users (Smith, Costello, & Yonkers, 2014). **[Objectives: 1.5, 1.6, 3.4]**

Chronic Morphine Regulates Two Different Subtypes of the Mu-Opiate Receptor in the Spinal Cord Differently in Males and Females. The gene encoding the mu-opioid receptor (MOR) generates a remarkable diversity of subtypes; the functional significance of each of these remains largely unknown. However, pain reduction via MOR differs in males and females, with males being more responsive to MOR than females. Researchers have now determined the influence of sex, stage of estrus cycle, and chronic systemic morphine on levels of two MOR splice variant mRNA and found that chronic morphine doubled the numbers of two splice variants of the receptors and their mRNA in males but had no effect on their densities in females. The signaling consequences of the unique composition of the variants could point the way to defining the molecular components of sex-dependent tolerance and

withdrawal mechanisms and the control of pain (Verzillo, Madia, Liu, Chakrabarti, & Gintzler, 2014). **[Objectives: 1.4, 1.5, 1.6]**

Females Are Less Sensitive than Males to the Depressive-Like Effects of Kappa Opiates. Dynorphin, an endogenous ligand that binds to kappa opioid receptors (KORs), produces depressive-like effects and contributes to addictive behavior in male nonhuman primates and rodents. A recent study examined how likely that kappa opiate stimulation would alter the perception of reward by treating male and female rats with a kappa opiate agonist and then allowing them to self-administer rewarding brain stimulation. As expected, increasing the dose of the kappa opiate reduced the amount of rewarding stimulation that the animals sought, consistent with a hypothesized role of kappa opiate stimulation in the maintenance of depression. However, males were more sensitive to the increased doses of the agonist than females, regardless of estrous cycle stage in females or gonadectomy in males. Sex differences in the neural activation were pronounced in corticotrophin releasing factor-containing neurons of the paraventricular nucleus of the hypothalamus and primarily in non-corticotrophin releasing factor-containing neurons of the bed nucleus of the stria terminalis. These data suggest that the role of KORs in motivated behavior of rats is sex-dependent, which has important ramifications for the study and treatment of mood-related disorders, including depression and drug addiction in people (Russell et al., 2014). **[Objectives: 1.4, 1.5, 1.6]**

Prenatal Drug Exposure

Research shows that pregnant women should not use any tobacco, alcohol, or illicit substances, as these can have severe health consequences for infants. This is because many substances pass easily through the placenta, so anything that the pregnant woman ingests is taken in to some degree by the baby. Studies below describe impairments in children with prenatal exposure to cigarettes or cocaine, outcomes that often differ in boys and girls. A final study addresses treatment of drug-using pregnant women and the role of family discord in treatment outcomes.

Male Infants Are More Sensitive to the Effects of Prenatal Exposure to Cigarettes than Female Infants. Researchers examined the association between prenatal cigarette exposure and physiological regulation in infants at 9 months of age and explored the possibility that postnatal environmental tobacco smoke (ETS) exposure could be factor. Respiratory sinus arrhythmia (RSA) was obtained from 206 (142 exposed and 64 non-exposed) infants during a baseline period and during procedures designed to elicit both positive and negative affect. There was a significant suppression of RSA during a negative affect task for non-exposed infants but not for exposed infants. Postnatal ETS exposure did not moderate this association; however, sex did moderate this association such that boys with prenatal cigarette exposure had a significant increase in RSA rather than the suppression seen among both non-exposed boys and girls. These results provide additional support for the idea that boys are particularly vulnerable to the effects of prenatal cigarette exposure and help to inform the development of targeted interventions (Schuetze, Eiden, Colder, Gray, & Huestis, 2013). **[Objectives: 1.5, 1.6, 3.4]**

Prenatal Cocaine Results in More Executive Functioning Deficits in Girls than Boys. This study assessed differences in caregiver reported executive function in 12-year-old children who were prenatally exposed to cocaine (PCE) compared with children who were not prenatally exposed to cocaine (NCE). One hundred and sixty-nine PCE and 169 NCE, primarily African-American children, participated in a prospective longitudinal study. The Behavior Rating Inventory of Executive Function (BRIEF) parent form was administered. Two broadband BRIEF scores—Behavioral Regulation Index and Metacognition Index (MI) and a summary Global Executive Composite (GEC)—were computed. Multiple and logistic regression analyses were used to assess the effects of the amount of PCE on executive function, controlling for a number of relevant covariates. After adjustment for covariates, amount of PCE was associated with the GEC and two MI subscales (Plan/Organize and Monitor) with heavier exposure associated with more problems of executive function. An amount of PCE by sex interaction revealed amount of PCE effects in other remaining subscales of the MI (Initiate, Working Memory, and Organization of Materials) only among girls. Assessment and targeted interventions to improve metacognitive processes are recommended for girls who were prenatally exposed to cocaine (Minnes et al., 2014). **[Objectives: 1.5, 1.6, 3.4]**

Adolescent Risk-Taking: The Interaction Between Prenatal Cocaine Exposure and Sex. This study examined the effects of cocaine and biological sex on adolescent risk-taking while controlling for early environmental risk. Adolescents (n = 114, mean age = 16) were grouped according to high and low risk-taking propensity as measured by the Balloon Analogue Risk Task. Prenatal cocaine exposure was assessed at birth, while environmental risk was assessed at three points during early childhood. Males were 3.5 times more likely than females to be high risk takers. Biological sex and prenatal cocaine exposure interacted such that exposed males were most likely to be high risk takers while exposed females were the least likely to be high risk takers. This pattern held after controlling for prenatal alcohol exposure and early environmental risk. Early environmental risk did not predict adolescent risk-taking. These findings complement and extend earlier research demonstrating that prenatal cocaine exposure interacts with biological sex in domains related to inhibitory control, emotion regulation, antisocial behavior, and health risk behaviors during preadolescence (Allen, Bennett, Carmody, Wang, & Lewis, 2014). **[Objectives: 1.4, 1.5, 1.6, 3.4]**

Family Discord Is Associated with Increased Substance Use for Pregnant Substance Users. Childhood abuse and partner violence are associated with prenatal substance abuse, but the potential impact of current family discord, which reflects broader family relationships and encompasses problems less severe than violence, has had little evaluation in pregnant substance users. Using data from 196 pregnant substance users, researchers examined the relationship of baseline family discord to substance use and treatment session attendance. Family discord was assessed using items from the Addiction Severity Index. Substance use was assessed by self-report and urine drug screens (UDS). Women with family discord were more likely to report living with a problematic substance user, reported a higher percentage of substance use days throughout each study phase, had a greater proportion of positive UDS over the 4-month study period, and attended more weeks of treatment during the first month. As hypothesized, women with family discord reported more days of substance use relative to women without family discord during each study phase (Denton, Adinoff, Lewis, Walker, & Winhusen, 2014). **[Objective 3.4]**

Preventing High-Risk Sexual Behavior in Youth and Young Adults

Drug use is associated with an increased likelihood of risky sexual behaviors. These two studies below describe successful prevention efforts aimed at decreasing risky sexual behaviors. The first intervention targeted foster care girls, and the second was a family-centered intervention.

Long-Term Impact of the Middle School Success Intervention on Health-Risking Sexual Behaviors Among Foster Care Girls. Researchers examined the effects of the middle school success intervention, a program to promote healthy adjustment in foster girls, on their health-risking sexual behavior, using a randomized controlled trial design. As hypothesized, girls in the intervention condition showed significantly lower levels of health-risking sexual behavior than did girls in the control condition at 36 months post baseline. Further path analysis indicated that this intervention effect was fully mediated through its effects on girls' tobacco and marijuana use. Findings highlight the importance of providing preventive intervention services to foster girls during early adolescence (Kim, Pears, Leve, Chamberlain, & Smith, 2013). **[Objective: 3.9]**

Family Intervention Delivered to Youth in Adolescence Reduces High-Risk Sexual Behavior in Adulthood. This study examined the long-term effects of the Family Check-Up (FCU) intervention, a brief family-centered intervention, on high-risk sexual behaviors (HRSB) in adulthood (age 22). Study participants were youth (and their families) who were assigned to FCU in sixth grade and offered multilevel and more intensive services/intervention as needed. Although results indicated no direct effect of the FCU on HRSB, families that participated in FCU demonstrated improved family relationship quality compared with control families, and an improved family relationship resulted in lower levels of HRSB in early adulthood. The effect of family relationship quality on HRSB was mediated by differences in parental monitoring and early sexual activity, and these effects varied by sex and ethnicity. With respect to sex, the effect of the FCU on change in family relationship quality was smaller for males than for females, and the effect of change in family relationship quality on HRSB was mediated by sexual activity and parental monitoring for males, whereas it was

mediated only by monitoring for females. These findings have potential implications for informing understanding of mechanisms and for enhancing the impact of family-centered interventions (Caruthers, Van Ryzin, & Dishion, 2014). **[Objective: 1.6]**

Interventions for Women and Girls in the Criminal Justice System

Compared with their male counterparts, female inmates are more likely to have mental disorders such as depression or anxiety, to be HIV positive, and to have been physically or sexually abused. Effective treatment during incarceration and upon release should address these issues. Studies below examined specialized treatment needs of HIV-positive women leaving the criminal justice setting and a prevention program to reduce at-risk traits in young girls involved in the juvenile justice system.

Treatment Needs for HIV-Positive Women Leaving Criminal Justice Settings. Women represent a significant and growing segment of jail detainees and persons living with HIV. Two separate studies explored the unique treatment needs of HIV-positive women leaving the criminal justice system. Data from each study were from the largest multisite prospective cohort study of HIV-infected released jail detainees (n = 1,270): the Enhancing Linkages to HIV Primary Care and Services in Jail Setting Initiative, January 2008 and March 2011, which had 10 sites in 9 States. The first study examined sex differences in health status, care and social service needs, and care engagement among jail releases with HIV. Compared with men, more women reported homelessness, reduced adherence to prescribed ART, worse health, more severe substance use disorders, and more chronic health conditions. Men and women generally reported different needs post-release. As the number of expressed needs increased, women were more likely to drop out of care. These findings suggest that effective and sex-specific strategies are required to identify needs, link services between jails and communities, and sustain retention of women with HIV in programs after release from criminal justice settings (Williams et al., 2013). The second study assessed baseline and 6-month HIV treatment outcomes and found that compared with men, women were more likely to be younger, non-Hispanic White, married, homeless, and depressed but were similar in recent alcohol and heroin use. By 6 months post-release, women were significantly less likely than men to experience optimal HIV treatment outcomes, including (1) retention in care, (2) antiretroviral therapy prescription or optimal antiretroviral therapy adherence, and (3) viral suppression. In multiple logistic regression models, women were half as likely as men to achieve viral suppression. HIV-infected women transitioning from jail experience greater comorbidity and worse HIV treatment outcomes than men. These outcomes suggest that future interventions that transition people from jail to community-based HIV clinical care should be sex-specific (Meyer et al., 2014). **[Objectives: 1.6, 3.9]**

MTFC Intervention Reduces Drug Use Trajectories, Depressive Symptoms, and Suicidal Thinking in Females with Prior Juvenile Justice System Involvement. Two studies explored the effects of a prevention intervention, Multidimensional Treatment Foster Care (MTFC), in reducing later drug use and comorbid mental health disorders. The first study delivered MTFC during adolescence to girls with juvenile justice system involvement. The study found that the prevention intervention delivered during adolescence (to girls ages 13–17) had effects on young adult drug use trajectories (7–9 years after the study began). While partner drug use was significantly associated with the girls' drug use, the findings revealed that girls who participated in the MTFC intervention were more resilient to partner drug use than those in the control condition (Rhoades, Leve, Harold, Kim, & Chamberlain, 2014). The second study included girls of mean age 15.3, who were randomized to receive MTFC or group care (treatment as usual). Nine years later, girls assigned to MTFC showed significantly greater decreases in depressive symptoms across the long-term follow-up period than girls who received group care (treatment as usual). MTFC also decreased suicidal thinking. These results suggest that behavior-focused intervention that targets reducing delinquency in chronic offending populations may also be useful in reducing depression. (Kerr, DeGarmo, Leve, & Chamberlain, 2014). **[Objective 3.9]**

Treatment Medications for Drug Addictions

Studies of medications to treat drug addiction sometimes obtain results that differ in women and men, as reported in the studies below, which investigate medications for

smoking, cocaine, and opioid addictions. Some studies found sex-specific outcomes—both positive and negative. The final study reports that a specific gene variant in women could predict opioid treatment success in women, but not men.

Sex Differences in Response to Reduced Nicotine Content Cigarettes. Very low nicotine content (VLNC) cigarettes appear to lead to a reduction in the number of cigarettes smoked, toxicant exposure, withdrawal symptoms, and dependence as compared with smoking the usual cigarette brand. There are sex differences in the trajectory of nicotine addiction. However, it is not known if there are sex differences in responses to VLNC cigarettes. This study analyzed data from a randomized trial of 235 participants (58 percent females) and compared the effects of VLNC cigarettes, nicotine patch, and the two combined. Results showed that the combination was more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males than females, whereas females were equally responsive to VLNC cigarettes with and without the nicotine patch. Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the VLNC cigarettes; however, males were more likely to quit smoking in the nicotine patch alone condition than females. These results indicate sex of the smoker as an important determinant of effects of VLNC cigarettes and nicotine patch. Future large randomized trials to confirm these results are needed (Vogel et al., 2014). **[Objective: 1.6]**

Sex-Specific Effects in Combination Treatment with Varenicline and Bupropion in Smokers Unlikely to Achieve Quit Success with the Nicotine Patch. The efficacy and safety of combination treatment with varenicline and sustained-release bupropion was assessed for smokers who, based on an assessment of initial smoking reduction prior to the quit date, were deemed unlikely to achieve abstinence using nicotine patch treatment. Smokers were randomly assigned to receive 12 weeks of varenicline plus bupropion or varenicline plus placebo. The primary outcome measure was continuous smoking abstinence at weeks 8–11 after the target quit date. The combination treatment of varenicline plus bupropion was more efficacious than varenicline alone for male smokers, but not for female smokers, and was more efficacious for highly nicotine-dependent smokers than in smokers with lower levels of dependence (Rose & Behm, 2014). **[Objective: 1.6]**

Sex Differences in Guanfacine Effects in Cocaine-Dependent Individuals. Currently, there is no FDA-approved medication for the treatment of cocaine use disorder, and women appear to be more at risk for the consequences of cocaine addiction. Guanfacine is an alpha-2 adrenergic agonist that is being investigated as a pharmacological treatment for cocaine addiction. Abstinent, treatment-seeking, cocaine-dependent males and females were randomly assigned to receive either daily placebo or guanfacine (2 mg or 3 mg) for 3 weeks, and the effects on cocaine-related stress, craving, negative emotion, anxiety, and cardiovascular function were evaluated. Guanfacine significantly attenuated cocaine craving, alcohol craving, anxiety, and negative emotion in females, but not in males. These findings highlight sex-specific effects of guanfacine on drug craving, anxiety, and negative mood, with significant effects in women and not men. Further evaluation of the sex differences in the safety and efficacy of guanfacine in the treatment of cocaine use disorder is warranted (Fox, Morgan, & Sinha, 2014). **[Objective: 1.6]**

Buspirone May Worsen Outcomes for Cocaine-Dependent Women, but Not for Men. This is a study to evaluate the potential efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. Adult crack/cocaine-dependent individuals were randomized to buspirone titrated to 60 mg/d or placebo. All participants received psychosocial treatment as usually provided by the treatment programs. Outcome measures included maximum days of continuous cocaine abstinence, proportion of cocaine use days, and days to first cocaine use during study weeks 4–15, assessed by self-report and urine testing. There were no significant treatment effects on maximum continuous days of cocaine abstinence or days to first cocaine use. In the female participants, there was a significant increase in cocaine use by those receiving buspirone, relative to placebo, early in the outpatient treatment phase. A similar effect was not detected in the male participants (Winhusen et al., 2014). **[Objective: 1.6]**

Genetic Variation and Response to Opioid Treatment in Females, but Not in Males. Two commonly prescribed treatments for opioid addiction are methadone and buprenorphine. However, treatment response varies among individuals, and it is likely that genetic factors have a role in determining treatment outcome. This study analyzed the pharmacogenetic association of six polymorphisms

in OPRD1, the gene encoding the delta-opioid receptor, on treatment outcome in 582 opioid-addicted individuals randomized to methadone or buprenorphine over the course of a 24-week clinical trial. Treatment outcome was the number of missed or positive urines over the 24 weeks. In the total sample, no single-nucleotide polymorphisms (SNPs) in OPRD1 were significantly associated with treatment outcome in either treatment arm. However, sex-specific analyses revealed two intronic SNPs (rs581111 and rs529520) that predicted treatment outcomes in females treated with buprenorphine. Females with the AA or AG genotypes at rs581111 had significantly worse outcomes than those with the GG genotype when treated with buprenorphine. For rs529520, females with the AA genotype had a significantly worse outcome than those with the CC genotype. No significant associations were detected in males (Clarke et al., 2014). **[Objective: 1.6]**

Health Disparities

Below are three examples of NIDA-supported published research focusing on racial/ethnic subgroups. Also described below is ongoing research funded under a NIDA HIV/AIDS request for applications seeking research specific either to Black/African-American women or Black/African-American men who have sex with men. Additionally, the section on STEM activities contains descriptions of programs that target advancing the research careers of minority investigators.

Racial/Ethnic-Specific Gender Differences Should Be Considered in the Development of Culturally Competent, Comprehensive Substance Abuse Treatment. This study examined gender differences within Black, Latino, and White subgroups in the utilization of comprehensive services and their relation to post-treatment substance use. Survey data were collected during the National Treatment Improvement Evaluation Study, a prospective, longitudinal, multisite study of substance abuse treatment programs and their clients in the United States. The analytic sample consisted of 1,812 Blacks (734 women and 1,078 men), 486 Latinos (147 women and 339 men), and 844 Whites (242 women and 602 men) from 59 service delivery organizations. Results related to service utilization indicated that compared with men, women in all racial and ethnic groups needed and received more services targeted to their needs and reported more positive relations with service providers. Gender was a significant moderator of the relationship between service receipt and treatment outcomes for all racial and ethnic groups, but especially for the Latino subsample. Findings point to the need to consider racial/ethnic-specific gender factors in the development of culturally competent, comprehensive substance abuse treatment (Guerrero, Marsh, Cao, Shin, & Andrews, 2014). **[Objective 1.6, 3.9]**

Paraprofessional-Delivered Home-Visiting Intervention Improves American Indian Teen Mothers' Parenting Outcomes and Infant Outcomes. The high rate of maternal substance abuse among American Indians underscores the importance of testing and disseminating effective prevention interventions. This study examined the effectiveness of Family Spirit, a paraprofessional-delivered, home-visiting pregnancy and early childhood intervention, in improving American Indian teen mothers' parenting outcomes and mothers' and children's emotional and behavioral functioning 12-months post partum. The study sample included 322 pregnant American Indian teens from four southwestern tribal reservation communities who were randomly assigned to the Family Spirit intervention plus optimized standard care or to optimized standard care alone. At 12-months post partum, mothers in the intervention group had significantly greater parenting outcomes and fewer externalizing behaviors, and the infants of these mothers had fewer externalizing problems. In a subsample of mothers with a history of substance, children who received the Family Spirit intervention had few externalizing and dysregulation problems and fewer scored in the at-risk range for externalizing and internalizing problems. The 12-months findings suggest that the Family Spirit intervention improves parenting and infant outcomes that predict lower behavioral and drug use risk for teen mothers and their children. This provides a viable prevention program model for American Indian populations, for whom culturally appropriate preventive interventions are lacking (Barlow et al., 2013). **[Objective 1.6, 3.3, 3.9]**

Discrimination Generally Associated with Risk for Substance Use, with Increased Risk of Alcohol/Cannabis and Hard Drug Use Among Young Latina Women. Based on a stress-coping framework, the present study investigates the relationship between discrimination and substance use, and the moderating effects of gender.

This cross-sectional study analyzes data from Latina/o young adults aged 18–25 (n = 401) from Brooklyn, NY. Discrimination was significantly associated with increased odds of substance use adjusting for covariates (e.g., age, education). Gender was a moderator. Discrimination was associated with increased risk of alcohol/cannabis and hard drug use among young Latina women. However, discrimination was associated with decreased risk of alcohol/cannabis use and increased risk of hard drug use among young Latino men. These findings suggest that discrimination is generally associated with risk for substance use and, further, that the outcomes vary by gender. Future research should explore gender-specific dimensions of discrimination and their associations with other outcomes (Otiniano Verissimo, Gee, Iguchi, Ford, & Friedman, 2013). [**Objective 1.6, 3.9**]

A Multimedia HIV/STI Intervention for Drug-Involved Black Women on Probation. Under this in-progress grant—1R01DA038122-01, Louisa Gilbert (contact), Nabila El-Bassel, (principal investigator)—a randomized controlled trial is rigorously evaluating the effectiveness and cost-effectiveness of delivering a multimedia evidence-based intervention and streamlined HIV testing to prevent HIV and other sexually transmitted infections with Black women drug users in probation sites in New York City, compared with streamlined HIV testing alone. This grant was funded under the NIDA funding opportunity announcement (FOA), "HIV/AIDS and Substance Use Among Black/African-American Women and Young MSM." This FOA, issued as a Request for Applications (RFA) sought grant applications (1) to conduct research that expands our understanding of the intersection between substance use and HIV among Black/African-American women (BAAW) and young Black/African-American men who have sex with men (YBAAMSM), and (2) to develop and test interventions that improve HIV prevention and care among BAAW and YBAAMSM, with attention to substance use and its consequences. **[Objective 1.6, 3.9]**

STEM Efforts

Special programs at NIDA targeting junior investigators and aimed at nurturing their research careers have been very successful in attracting women. In addition, NIDA and the National Institute on Aging (NIA) have formed a partnership to support women intramural scientists at the NIH Biomedical Research Center, located at its research facilities in Baltimore, MD.

Women & Sex/Gender Differences Research Junior Investigator Travel Award at CPDD. To promote entry of junior investigators into drug abuse research on women and sex/gender differences, beginning in 2000 NIDA has sponsored a travel award program to assist awardees in defraying the cost of attending the annual meeting of the College on Problems of Drug Dependence (CPDD). Award applicants must be first author on their research submission to CPDD, and the research must focus on women or include a sex/gender analysis of data. CPDD has been in existence since 1929 and is the longest standing group in the United States addressing problems of drug dependence and abuse. In 2013, 86 percent of the applicants were women, and in 2014, 82 percent were women. In both 2013 and 2014, 27 awards were made of which 22 (88 percent) went to women. **[Objective: 4.5; Goal 6]**

NIDA Director's Travel Award at CPDD. The NIDA Director's Travel Award Program partially defrays the cost of travel for NIDA-supported National Research Service Award fellows, trainees, and NIDA diversity-supplement recipients to attend the annual CPDD meeting. In 2013, 13 of the 20 awards (65 percent) went to women; in 2014, 15 out of the 20 awards (75 percent) were made to women. **[Objective: 4.5]**

Grant-Writing and Career Workshop at CPDD. NIDA's Grant-Writing and Career Workshop, held in conjunction with CPDD, capitalizes upon the expertise gathered for the CPDD meeting to provide young investigators with the tools and resources necessary to become successful substance abuse researchers. This workshop demonstrates our continued commitment to the next generation of these researchers. In 2013 and 2014, more than 60 percent of the participants (attendees) were women. **[Objective: 4.5]**

NIDA Mini-Convention: Frontiers in Addiction Research. The 1-day NIDA Mini-Convention: Frontiers in Addiction Research is a satellite to the Society for Neuroscience (SfN) annual meeting. The mini-convention includes several symposia and an invited poster session for early career investigators, which showcases their research and provides an opportunity for young investigators to interact with the symposia speakers, NIDA staff,

and NIDA-supported training program directors and researchers. NIDA provides travel awards to many of the poster presenters, which help defray the cost of travel for the mini-convention and the SfN meeting. In 2013, 36 of the 70 participants (51 percent) in the poster session were female. The mini-convention for 2014 was cancelled because of the government shutdown. However the poster presenters who had been provisionally invited included a similar proportion of females. **[Objective: 4.5]**

Early Career Investigators Poster Session and Social Hour at APA. This event sponsored by NIDA, the National Institute on Alcohol Abuse and Alcoholism, and Divisions 28 (Psychopharmacology and Substance Abuse) and 50 (Society of Addiction Psychology) of the American Psychological Association (APA) is held at the annual APA convention. Most of the presenters receive competitive travel awards to assist in defraying costs associated with attending the convention. In 2013, 24 of the 41 presenters were women (59 percent), and in 2014, 41 of the 78 presenters (53 percent) were women. **[Objective: 4.5]**

NIDA's Asian American Pacific Islanders Internship Program for Future Addiction Scientists. This multisite summer internship program for high school and college students is aimed at broadening public awareness about research advances in drug abuse and addiction and promoting interest in addiction science. The program creates and supports a virtual community through several participating institutions across the continental United States as well as Hawaii, connected online through a common core curriculum. Under the mentorship of well-established researchers and health professionals, interns interact and participate with other students in programs across the country (typically housed at six to eight major universities) in the areas of health and addiction science, and engage in site-specific research projects. Interns then present their work and research topics in the format of a seminar with direct faculty involvement as moderators. In 2013, 60 percent of the 34 interns were female, and in 2014, 55 percent of the 13 interns were female.

NIDA's Office of Diversity and Health Disparities. Three STEM efforts focusing on underrepresented racial/ethnic populations were sponsored by NIDA's Office of Diversity and Health Disparities (ODHD).

- **NIDA Summer Research Internship Program.** This program provides research internships for high school and undergraduate students with a goal of recruiting underrepresented racial/ethnic students into research. Internships include a paid 8-week intensive, hands-on drug abuse and addiction research experience that provides students with the opportunity to gain an understanding of the research process. The experience may include laboratory experiments, formal courses, data collection activities, data analysis, patient recruitment, manuscript preparation, literature reviews, and library research. The program exposes students to drug abuse research and encourages them to pursue careers in biomedical and behavioral research. Internships are conducted with NIDA-funded investigators across the country. In 2013, NIDA ODHD awarded 64 internships, of which 42 were to women (66 percent). In 2014, 54 internships were awarded, of which 42 were to women (78 percent).
- **Administrative Supplements to Improve Diversity.** Through the award of administrative supplements to active NIDA research grants, this diversity supplement program was established to improve diversity in the scientific research workforce by supporting and recruiting undergraduate students, predoctoral and postdoctoral fellows, and investigators from groups that have been shown to be underrepresented in the sciences, including disabled individuals. In 2013, NIDA ODHD funded 30 diversity supplements, of which 22 of them (74 percent) were awarded to women. In 2014, 32 diversity supplements were funded, of which 17 were awarded to women (53 percent).
- **Grant Writing and Research Development Workshop.** This two-part workshop targets underrepresented postdoctoral and early-stage investigators conducting drug abuse research, though all race/ethnicities can apply. It is designed to increase understanding of the NIH grant funding and review process from proposal development, through peer review, to award. The Part I Workshop: Research Development Seminar exposes participants to the competitive research funding process and critical information related to research design, methods, scientific writing, the peer review process, and grant application preparation. For the Part II Workshop:

Mock Review, the part I participants are invited to write draft research grant applications, which are then evaluated by a mock review panel using a process that mirrors the NIH peer review system. Through this two-part workshop, NIDA ODHD aims to increase the number of successful applications from underrepresented minority investigators. In 2013, 23 early stage investigators participated in the part I seminar, of which 18 (78 percent) were women; and in the part II mock review, 7 of the 10 participants were women (70 percent). In 2014, there were 19 early stage investigators in the part I seminar, of which 17 were women (89 percent); in the part II mock review, 11 of the 13 participants were women (85 percent).

NIDA/NIA Women Scientist Advisors and Its Awards Program. The NIDA/NIA Women Scientist Advisors (WSA) meet on a regular basis to support women intramural scientists at the NIH Biomedical Research Center located at its research facilities in Baltimore, MD. The group supports and fosters women actively working in science through an exchange of ideas and annual awards for women scientists: WSA Investigator Award, WSA Staff Scientist Award, and WSA Fellows Award.

Other Activities

NIDA's Clinical Trials Network (CTN), http://www.drugabuse.gov/about-nida/organization/cctn/ctn, is a national consortium of drug abuse researchers and providers who cooperatively conduct clinical trials in order to develop, validate, refine, and deliver new treatment options to patients in community-level clinical practice settings. Currently, CTN consists of 13 regional centers at academic medical centers affiliated with approximately 60 academic institutions and more than 240 health care clinics (including hospitals) throughout the United States and Puerto Rico. During the years 2013–2014, CTN has conducted several analyses on gender differences of multiple trials, publishing more than 40 manuscripts from this work, such as (1) exploratory results regarding genetic variation and response to opioid treatment, (2) gender differences in HIV risk behaviors and HIV testing, (3) gender differences in a clinical trials using a medication for cocaine dependent individuals, and (4) gender differences in prescription opioid dependence. One group of researchers plans to conduct a multistudy secondary analysis titled "Gender differences in the interrelationships between sexual abuse, risky sexual behavior, and anxiety/depression in treatment efficacy and drug use over time among individuals with substance use disorders." In addition, investigators are planning gender analyses for nine ongoing multisite trials. CTN established a Gender Special Interest Group, which has played a key role in the overall gender research across the CTN studies and in identifying substance abuse research areas that could benefit from additional attention to gender-related outcomes. This group presented one symposium in 2013 and another one in 2014, showcasing some of the recent findings from the CTN studies. For this period, six datasets were added to the Web site https://datashare.nida.nih.gov; a total of 33 datasets are now available. NIDA encourages researchers (including early career investigators) to take advantage of these datasets for addressing gender-specific questions. In addition, as new trials are planned, NIDA invites scientists to work with the trial investigators to plan ancillary or platform studies that can provide needed information on issues that can affect women in drug abuse treatment. **[Objective 1.6]**

NIDA-Issued FOAs on Women and Sex/Gender Differences

- Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence, PA-14-038 (R01), PA-14-036 (R21), PA-14-037 (R03), re-released December 12, 2013.
- HIV/AIDS and Substance Use among Black/African American Women and Young MSM, RFA-DA-14-010 (R01), RFA-DA-14-009, RFA-DA-14-012 (R21), RFA-DA-14-007 (U10), released June 10, 2013.
- Drug Abuse Dissertation Research, PAR-13-182 (R36), re-released April 5, 2013.

NIDA Staff: Invited Presentations

[Objective 1.9]

- "Epidemiology of Drug Use and Disorders: Sex/Gender Differences," Winter Brain Conference, Breckenridge, CO, January 28, 2013.
- "The Ubiquity of Sex/Gender Differences in Drug Abuse," Women's Health Research Day, Medical University of South Carolina, Charleston, SC, April 18, 2013.

- "Sex Differences in Drug Abuse," Society for Women's Health Research (SWHR) Conference, "What a Difference an X Makes—The State of Women's Health Research," Washington, DC, July 18–19, 2013.
- "Sex/Gender Matters in Drug Abuse," Behavior Change, Health, and Health Disparities Conference, Burlington, VT, September 26–27, 2013.
- Panel discussant. Global Perspectives on Women and Addiction panel, International Women's and Children's Health and Gender (InWomen) Conference, San Juan Puerto Rico, June 13, 2014.
- "Sex/Gender Matters in Drug Abuse Research," NIDA Office of Diversity and Health Disparities Research Development Seminar Series Part II Workshop, Rockville, MD, June 26–27, 2014.
- "Drug Abuse and Addiction: A Major Contributor to Women's Rising Mortality Rates?" Congressional briefing sponsored by Women's Policy, Inc., Rayburn House Office Building, Washington DC, July 15, 2014.
- Panel member, "HHS Commitment to Advance Preventive Services for Women." International Conference & Summit on Violence, Abuse and Trauma, "Linking Research, Practice, Advocacy and Policy: Collaboration and Commitment for Change," San Diego, CA, September 7–10, 2014.
- "Training, Career Development & New Investigators." Behavior Change, Health and Health Disparities Conference, Burlington, VT, Oct 2–3, 2014.

NIDA Staff: Symposia, Workshops, Roundtables, and Panels

[Objective 1.9]

- Symposium, Gender Differences Research in the Clinical Trials Network: What's New? Clinical Trials Network Steering Committee, Gaithersburg, MD, March 2013.
- Roundtable, High Risk Girls in High Risk Settings: What Have We Learned? What's Next? Society for Prevention Research, Washington DC, May 27–30, 2014
- Workshop, Animal Models of Sex Differences & Drug Abuse: Mind the Gaps. College on Problems of Drug Dependence, San Diego, CA, June 15–20, 2013.
- Symposium, Sex Hormone Modulation of Nicotine Reward: Effects on Urges, Affect, Physiological Response, and Brain Activation. College on Problems of Drug Dependence, San Diego, CA, June 15–20, 2013.
- Symposium, Gender Differences & Substance Abuse Treatment: The Lab, the Clinic & Health Care Reform. American Psychological Association, Honolulu, HI, July 31–August 4, 2013.
- Symposium, Behavioral Economics and Maternal-Infant Health Among Substance Abusers. American Psychological Association, Honolulu, HI, July 31–August 4, 2013.
- Symposium, Medications for Drug Addictions: Sex Differences in Outcomes in Animal and Human Laboratory Studies and in Clinical Trials. College on Problems of Drug Dependence, San Juan, PR, June 14–19, 2014.
- Symposium, Cognitive and Affective Factors in Substance Abuse in Men and Women. American Psychological Association, Washington, DC, August 7–10, 2014.
- Symposium, Empowerment: Giving Women Their Voices. American Psychological Association, Washington, DC, August 7–10, 2014.
- Symposium, Gender Differences in SUD Treatment: Recent Findings from the Clinical Trials Network. American Psychological Association, Washington, DC, August 7–10, 2014.
- Symposium, Intimate Partner Violence Screening and Counseling Research. Rockville, MD, December 9, 2013.

Publications

- *Mini-Program: Focus on Women & Sex/Gender Differences.* (2013; 2014). Retrieved from http://www.drugabuse.gov/sites/default/files/nidaprogrambook.pdf. NIDA has prepared this publication for distribution at the CPDD annual conference since 1999. Excerpted from the CPDD program book, this mini-program contains only those program listings related to women and sex/gender differences. It also contains information about the Women & Sex/Gender Differences Research Junior Investigator Travel Awardees, the announcement of the travel award

program for the following year CPDD meeting, and information on current NIDA funding opportunities relative to women and sex/gender differences. **[Objective: 4.5]**

- University of Michigan. (2013; 2014). Monitoring the Future National Results on Adolescent Drug Use [Web page]. Retrieved from http://www.monitoringthefuture.org. Published yearly, this report provides a summary of drug use trends from a survey of 8th, 10th, and 12th grade students nationwide, including analysis by sex. It also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.
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National Institute of Environmental Health Sciences

Executive Summary

"Your environment is your health." This statement summarizes why it is important to understand the ways in which our environment plays a role in our health and biology. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to discover how the environment affects people's health to promote healthier lives. NIEHS investigators conduct studies to better understand how women are affected by environmental exposures, how exposures and disease progression may impact women and men similarly or differently, and how an individual's sex and gender may influence both susceptibility to disease and the eventual outcome. The scope of women's health research has become a dynamic, multidisciplinary area of study within environmental health sciences. There are striking sex and gender differences in the prevalence, progression, and outcome of numerous conditions, including diabetes, obesity, cardiovascular diseases, substance abuse disorders, depression and brain disorders, infectious diseases, cancer, and autoimmune diseases. Certain health conditions including menopause and pregnancy are unique to women; diseases such as endometriosis, ovarian cancer, and cervical cancer occur only in women; breast cancer is overwhelmingly found in women; and certain autoimmune diseases and osteoporosis occur to a greater extent in women compared with men. Many or most of these conditions and diseases may be environmentally mediated. These disparities between women and men are influenced by biological sex and gender identity and by developmental, cultural, environmental, and socioeconomic factors. Therefore, women's health and sex differences research encompasses not only clinical studies but also a full spectrum of scientific investigations, such as molecular, genetic, and other basic and laboratory studies and investigations into healthy lifestyles and behavior, risk reduction, and disease prevention. With this information in hand, women can better determine how to alter the lifestyle factors that lead to these exposures and diseases and provide better protection for themselves and their children.

On a wider scale, society can better define standards that protect women from the environmental triggers of these diseases and develop better gender-specific and sex-specific interventions and therapies.

Accomplishments and Activities

NIEHS Uterine Fibroid Study

The NIEHS Uterine Fibroid Study enrolled randomly selected 35- to 49-year-old women who were members of an urban health plan between 1996 and 1999. One of the variables assessed in the women was their Vitamin D status, assessed by radioimmunoassay and by questionnaire data on sun exposure. When the Vitamin D data were compared with the women's fibroid history, the study found that women with sufficient vitamin D had an estimated 32 percent lower chance of fibroids compared with those with vitamin D insufficiency. The association was found in both black women and white women in the study (Baird, Hill, Schectman, & Hollis, 2013).

Safety of Flu Shots for Pregnant Women

Scientists at NIEHS and the Norwegian Institute of Public Health initiated a study following the 2009 H1N1 influenza pandemic, during which questions had been raised about vaccine safety; media reports of pregnancy losses after flu shots caused some expectant mothers to forgo vaccination. The researchers combined data from obstetrical visits, birth records, and vaccination registries to investigate whether the influenza vaccination posed a risk to pregnancy. The study found that influenza infection increased the risk of fetal loss up to twofold. Influenza vaccination did not increase the risk of loss. Instead, the results suggest that vaccination reduces the risk of fetal loss (Håberg et al., 2013).

Obesity and Sex-Specific Differences at an Imprinted Genetic Locus

In an NIEHS-funded study of Mexican-American children, researchers observed a significant difference in the frequency of a specific mutation between boys and girls among the children who were overweight or obese, but not between the lean boys and girls. They also found that children with lower DNA methylation status at that specific mutation site had higher birth weights than did children with higher methylation. The report suggests that DNA methylation at that specific site may be associated with childhood obesity in Mexican-American children in a sex-specific manner (Hernández-Valero, Rother, Gorlov, Frazier, & Gorlova, 2013).

Variations in Pregnancy Length

Researchers at NIEHS studied 125 pregnancies from the North Carolina Early Pregnancy Study. They found a much broader range in the length of human pregnancies than is usually considered average. Their results could lead to a different way of assigning due dates to pregnancies in the future. The authors found that the median time from ovulation to live birth was 268 days, or 38 weeks and 2 days, but that this time ranged from 208 to 284 days. Most surprising was the 37-day range of gestational length among term births within a relatively select group of otherwise healthy, normal births. One fundamental problem that has historically plagued pregnancy length studies is the inability to accurately determine when gestation began; physicians typically use a combination of the onset of the woman's last menstrual period and ultrasound measurements to determine a pregnancy's due date. In this study, for the first time, levels of hormones found in daily urine samples were used to determine when the subjects ovulated. By accounting for cases where medical interventions were used to shorten the length of pregnancy, the researchers were able to determine a range of gestation lengths in normal births. The fact that normal pregnancy can have such a wide range in length suggests that development rates are individualized. Indeed, the researchers found that the length of a pregnancy tends to correlate with other pregnancy lengths from the same woman, supporting this notion. In addition to the start of ovulation, the number of days between fertilization and implantation was determined using the rise in the level of the hormone human chorionic gonadotropin. They found that the longer the time between fertilization and implantation, the longer the gestation tended to be. In addition, later rises in the hormone progesterone were associated with nearly 2 weeks shorter gestations than those with an early rise. These findings could indicate that each pregnancy has an intrinsic developmental pace. This study, and future studies, could be used to change the way obstetricians assign a due date for pregnancies. Giving a range of dates may be better, as many women who reach their assigned due date are often distressed if that date passes (Jukic, Baird, Weinberg, McConnaughey, & Wilcox, 2013).

Pregnant Women's Levels of PBDEs

Polybrominated diphenyl ethers (PBDEs) are persistent chemicals that have been widely used as flame retardants in furniture, carpet padding, car seats, and other consumer products during the past three decades. Prenatal exposures to PBDEs can harm neurodevelopment in humans and animals. After some specific PBDEs were banned in California in 2003–2004, a 2013 report compared levels of serum PBDEs and their metabolites in second trimester pregnant women recruited from a San Francisco clinic, one group in 2008–2009 and the second in 2011–2012. Serum concentrations of PBDEs decreased 65 percent between the two cohorts, which is likely due to regulatory action (Zota et al., 2013). In a separate study (the HOME Study), scientists examined whether in utero exposure to PBDEs is associated with child cognitive function and behavior. In this prospective birth cohort, they measured maternal serum concentrations of several PBDEs in 309 women at 16 weeks of gestation and followed their children in Cincinnati. They measured cognitive and motor abilities, intelligence, and children's behaviors at multiple years of age. They found that high levels of one particular PBDE congener, termed BDE-47, was associated with a 4.5 decrease in Full-Scale IQ and an increase in the hyperactivity score at age 5 (Chen et al., 2014).

Maternal Exposure to Nanomaterials and Fetal Microvascular Function

In a rat model, exposing pregnant rats to inhaled engineered nanoparticles (titanium oxide) led to severely impaired uterine microvascular reactivity and also severely impacted fetal vascular reactivity. Longer gestational exposures to the nanoparticles led to reductions in the size and number of offspring. This was the first report that maternal inhalation of nanoparticles creates a hostile gestational environment capable of impacting fetal health (Stapleton et al., 2013).

Effects of Prenatal Exposure to Low Dose Bisphenol A

Exposure of rodent fetuses to low doses of the endocrine disruptor bisphenol A (BPA) causes subtle morphological changes in the prenatal mammary gland and results in precancerous and cancerous lesions during adulthood. NIEHS-supported scientists showed that when mice were exposed to either BPA or a steroidal estrogen in utero, the exposures resulted in altered gene expression in the fetal mammary tissue of genes involved in cell adhesion, adipogenesis, and cell death. An independent study of prenatal BPA exposure in sheep demonstrated alterations in fetal ovarian gene expression relevant to gonadal differentiation and development (Veiga-Lopez, Luense, Christenson, & Padmanabhan, 2013; Wadia et al., 2013).

Identification of DNA Methylation Changes in Newborns Related to Maternal Smoking During Pregnancy

NIEHS scientists, partnering with Norwegian investigators in the Norway Facial Clefts study, conducted an epigenome-wide association study investigating alterations in DNA methylation across the entire genome in infants exposed in utero to maternal tobacco smoke. They identified 10 genes with newly established links to maternal smoking. They also noted differences between smoking related changes in DNA methylation seen in newborns versus adults, suggesting possible distinct effects of direct versus indirect tobacco smoke exposure (or possibly age). The methylation changes identified in newborns may mediate the association between in utero maternal smoking exposure and later health outcomes (Markunas et al., 2014).

Prenatal Exposure to Air Pollution, Maternal Psychological Distress, and Child Behavior

In a longitudinal birth cohort study, 248 children of nonsmoking white women in the coal-burning region of Krakow, Poland, were followed from in utero until age 9. The goal was to evaluate potential interactions between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs), pollutants generated by combustion of fossil fuels and other organic material, and maternal psychological distress during pregnancy, and their combined effects on subsequent behavioral problems in children. Significant interactions between maternal demoralization and PAH exposure (high versus low) were identified for several types of behaviors in the children as measured by the researchers (anxious/depressed, withdrawn/depressed, social problems, aggressive behavior, internalizing problems, and externalizing problems). The effects of demoralization on syndromes of anxious/depressed, withdrawn/depressed, rule-breaking, aggressive behavior, and the composite internalizing and externalizing scores were seen only in conjunction with high PAH exposure. Fewer significant effects with weaker effect sizes were observed in the low-PAH-exposure group. Maternal demoralization during pregnancy thus appears to have a greater effect on child neurobehavioral development among children who experienced high prenatal PAH exposure (Perera et al., 2013).

Genetic Control of Estrogen-Related Responses in Mouse Uterus

Scientists at NIEHS identified distinct estrogen-regulated signatures of gene expression associated with uterine tissue from different strains of mice. These insights into the mechanisms underlying the genetic control of tissue sensitivity to estrogen have great potential to advance understanding of individualized effects in physiological and disease states (Wall et al., 2013).

National Toxicology Program: Pregnancy Outcomes Following Chemotherapy During Pregnancy

In 2013, the National Toxicology Program (NTP) issued a draft monograph of pregnancy outcomes following

chemotherapy treatment for cancer during pregnancy. The goal of the monograph was to summarize the peer-reviewed literature documenting the effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for the clinical and patient communities. Of the approximately 110 cancer chemotherapeutic agents currently in use, the NTP monograph included data on 52 agents that were used in more than 1,250 pregnancies for which pregnancy outcomes were documented. The NTP monograph focuses on five health outcomes:

1. Major congenital malformations;
2. Spontaneous fetal death, including spontaneous abortion and stillbirth;
3. Spontaneous preterm birth;
4. Small for gestational age; and
5. Adverse health effects at follow-up evaluation.

In addition, the NTP monograph provides background materials on individual cancer chemotherapeutic agents (e.g., evidence for placenta and breast milk transport of agents, developmental toxicity in animals) and a brief review of the prevalence and prognosis of seven frequently diagnosed cancers in women during pregnancy. Finally, the NTP monograph identifies the challenges in interpreting the health outcomes from this observational literature base and discusses possible actions to improve the understanding of the developmental effects of chemotherapy treatment for cancer administered during pregnancy (NTP, 2013).

Breast Cancer and the Environment: Prioritizing Prevention

The Breast Cancer and Environmental Research Act established the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC), which has examined research on the current state of breast cancer and the environment. The Committee was charged with making recommendations for eliminating any knowledge gaps in this area. Based on its review of the state of the science, current programs and investments by Federal agencies and nongovernmental organizations, and relevant communication efforts and policies, the IBCERCC published a comprehensive report in February 2013 summarizing its findings and listing seven recommendations to highlight the need for coordinated, targeted efforts to identify and mitigate the environmental causes of breast cancer. The seven recommendations are to (1) prioritize prevention, (2) transform how research is conducted, (3) intensify the study of chemical and physical factors, (4) plan strategically across Federal agencies, (5) engage public stakeholders, (6) train transdisciplinary researchers, and (7) translate and communicate science to society (IBCERCC, 2013).

Estrogenic and Anti-Estrogenic Activity of Off-the-Shelf Hair and Skin Care Products

Use of personal care products is widespread in the United States. Of special concern is the possible hazard of absorption of chemicals with estrogenic activity (EA) or anti-estrogenic activity (AEA) in these products. Such exposure may have adverse health effects, especially when it occurs during developmental windows (e.g., prepubertally) when estrogen levels are low. NTP and NIEHS researchers assessed the ethanol extracts of eight commonly used hair and skin products popular among African-Americans for EA and AEA using a cell proliferation assay with the estrogen-sensitive MCF-7:WS8 cell line derived from a human breast cancer. Four of the eight personal care products tested (oil hair lotion, extra-dry skin lotion, intensive skin lotion, petroleum jelly) demonstrated detectable EA, whereas three (placenta hair conditioner, tea-tree hair conditioner, cocoa butter skin cream) exhibited AEA. These data indicate that hair and skin care products can have either estrogen-mimicking or estrogen-blocking activity; they suggest that laboratory studies are warranted to investigate the in vivo activity of such products under chronic exposure conditions as well as epidemiologic studies to investigate potential adverse health effects that might be associated with use of such products (Myers et al., 2014).

Counseling Patients on Preventing Prenatal Environmental Exposures

To determine the attitudes, beliefs, and practices of U.S. obstetricians on the topic of prenatal environmental exposures, a group of NIEHS-funded scientists undertook a national online survey of American Congress of Obstetricians and Gynecologists fellows and three focus groups of obstetricians. The majority (78 percent) of respondents agreed that they can reduce patient exposures to environmental health hazards by counseling patients. However, 50 percent reported that they rarely take an

environmental health history, less than 20 percent reported routinely asking about environmental exposures commonly found in pregnant women in the United States, and only 1 in 15 reported any training on the topic. Barriers to counseling included a lack of knowledge of and uncertainty about the evidence, concerns that patients lack the capacity to reduce harmful exposures, and fear of causing anxiety among patients. Thus, U.S. obstetricians in the study recognized the potential impact of the environment on reproductive health and the role that physicians could play in prevention, but they reported numerous barriers to counseling patients. Medical education and training, evidence-based guidelines, and tools for communicating risks to patients are clearly needed to support the clinical role in preventing environmental exposures that threaten patient health (Stotland et al., 2014).

Agricultural Health Study

The Agricultural Health Study (AHS), funded by NIEHS, the National Cancer Institute (NCI), the Environmental Protection Agency, and the National Institute for Occupational Safety and Health, works to understand how agricultural, lifestyle, and genetic factors affect the health of farming populations. More than 89,000 farmers and their spouses in Iowa and North Carolina have been involved in the AHS since 1993. Several AHS reports of particular relevance for women's health were published during FY 2013 and FY 2014. Among the findings:

- Sun exposure was associated with a reduced risk of breast cancer among wives of pesticide applicators, in agreement with earlier reports that vitamin D may confer protection. The AHS report attempted to look also at the interaction of levels of sun exposure with gene variants in vitamin D receptor; that portion of the study was inconclusive (Engel et al., 2014).
- Use of any of five pesticides was positively associated with incident diabetes in farmers' wives (Starling et al., 2014).
- Self-reported incident depression in farmer's wives was positively associated with diagnosed pesticide poisoning (Beard et al., 2013).

NIH Strategic Plan for Women's Health Research

NIEHS funds a large array of studies that explore variations due to sex as an integral part of the search for knowledge across the entire research spectrum, beginning at the most basic laboratory level. NIEHS research regarding sex differences encompasses diverse fields, including genetics, immunology, endocrinology, developmental biology, cell biology, epidemiology, microbiology, biochemistry, toxicology, and the behavioral and social sciences. Below are examples of NIEHS research activities that further knowledge in this area. The activities support the implementation of the ORWH Strategic Plan Goal 1: "Increase sex differences research in basic science studies."

Endocrine Disruptors

NIEHS is funding numerous human studies examining the health effects on the developing fetus of prenatal exposures to environmental chemicals. Many studies to date have reported small but significant changes as it relates to reported sexually dimorphic behaviors. In some studies, pregnant women exposed to a specific class of endocrine disruptors show changes in girls and not in boys as it relates to depression, yet play behavior changes are reported in boys and not girls. Larger studies are being conducted to see whether specific endocrine disruptors like phthalates and BPA perturb the developing fetal endocrine system and increase the risk for behavioral disorders. This effect may be related to changes in the gestational sex steroid milieu as noted in animal studies. Outcomes to be addressed include but are not limited to visual and spatial abilities and determining whether males or females are more vulnerable to specific chemicals. *Supports ORWH Strategic Plan Objectives 1.2, 1.7, and 1.8.*

National Toxicology Program

The general toxicology assessments conducted by NTP usually involve exposures of rats and mice of both sexes to test articles for periods of 14 days or 13 weeks. Assessments almost always performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and

mice (B6C3F1 hybrid) with three exposure concentrations plus untreated controls in groups of 50 animals for 2 years. Both sexes are evaluated to determine whether there are differences in outcome caused by gender differences. *Supports ORWH Strategic Plan Objectives 1.2, 1.4, and 1.7.*

NIEHS Sister Study

The Sister Study is a landmark research effort created by NIEHS scientists to find causes of breast cancer. More than 50,000 women across the United States and Puerto Rico, who were between ages 35–74 and whose sister had breast cancer, joined this effort between 2004 and 2009. Because of their shared environment, genes, and experiences, studying sisters provides a greater chance of identifying risk factors that may help us find ways to prevent breast cancer. The Sister Study is currently tracking the health of women in the cohort. Research in the Sister Study focuses on causes of breast cancer and other health issues in women and on factors that influence quality of life and outcomes after a breast cancer diagnosis. Results from the Sister Study have been accumulating every year. Several groundbreaking studies appeared in 2013 and 2014. For example, a report published in May 2014 found that the women who worked with organic solvents prior to their first full-term birth had an increased risk for hormone receptor-positive breast cancer (Ekenga, Parks, D'Aloisio, DeRoo, & Sandler, 2014). Another study of DNA methylation in blood samples from the Sister Study women showed promise as biological markers of breast cancer detection and prediction of risk (DeRoo et al., 2014). Overweight or obese women are at increased risk of developing and dying from breast cancer; researchers looked at a group of incident cases and non-cases from the Sister Study to see whether obesity-driven inflammation would drive higher levels of prostaglandin-mediated estrogen biosynthesis in breast tissue. They found evidence that metabolites of prostaglandin had promise as a biological marker of breast cancer in postmenopausal women that could potentially have useful implications for the development of preventive strategies (Kim, Taylor, Milne, & Sandler, 2013). *Supports ORWH Strategic Plan Objectives 1.1, 1.2, 1.7, 1.8, and 1.9.*

Household Air Pollution and Cookstove Research

Chronic exposure to smoke from traditional cooking practices causes a range of health effects, including heart disease, stroke, and acute respiratory infections. Most deaths occur in low- and middle-income countries (LMICs), with women and children overwhelmingly disproportionately exposed. The NIEHS Household Air Pollution program takes a multipronged approach to understanding the global health impact of cookstoves, including research to assess exposures and determine health outcomes and supporting improved cookstove design and intervention trials along with training and capacity building to support these efforts. NIEHS currently supports both research and capacity-building grants, including public-private partnerships, in 17 different countries. NIEHS partners with the Fogarty International Center on the International Hubs of Interdisciplinary Research and Training in Global Environmental and Occupational Health (GEOHealth) funding program. GEOHealth supports paired consortia—led by an LMIC institution and a U.S. institution—to develop research, research training, and curriculum development activities that address and inform priority national and regional environmental and occupational health policy issues. Four GEOHealth hubs—in Bangladesh, Colombia, Chile, and Ghana—support research on indoor air pollution. The NIEHS–World Health Organization Collaborating Centre for Environmental Health Sciences includes indoor air pollution associated with biomass burning as one of the five focus areas of environmental health concern. Global environmental health, including a focus on cookstoves and indoor air pollution, is identified as a priority research area for NIEHS in the 2012–2017 Strategic Plan. NIEHS is a lead IC for NIH in the Global Alliance for Clean Cookstoves. In August 2014, NIEHS and NTP hosted a Symposium on Assessing Exposures and Health Effects Related to Indoor Biomass Fuel Burning that brought together exposure scientists, toxicologists, epidemiologists, engineers, and public policy experts to discuss the state of the science and future directions. *Supports ORWH Strategic Plan Objectives 4.1, 4.2, 4.4, and 4.6.*

Women's Health and the Environment Across the Entire Lifespan

Concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. Through their effects on hormonal pathways, environmental chemicals can differentially affect females, particularly at critical and sensitive periods across the life span. These critical periods include stages of particular vulnerability, such as fetal development and among the elderly; major life transitions, such as during midlife and into late life; and stages of rapid cell proliferation and growth, such as during fetal development, puberty, and lactation. Public and scientific concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. The Women's Health and Environment Across the Entire Lifespan program at the University of Rochester Medical Center (URMC) trains junior faculty to conduct outstanding interdisciplinary research that will help identify environmental agents that can adversely affect women's health at all stages of life, thus addressing these concerns. Results of this research will provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health. *Supports ORWH Strategic Plan Objectives 1.2, 1.4, and 1.7.*

Inclusion

NIEHS supports very few clinical trials. However, NIEHS and NTP conduct a great deal of animal research, almost all of which is analyzed by sex.

Science, Technology, Engineering, and Mathematics Efforts

Building Interdisciplinary Research Careers in Women's Health

NIEHS has primary assignment of one Building Interdisciplinary Research Careers in Women's Health K12 Career Development Program at URMC, with Dr. Deborah A. Cory-Slechta as the program director. The purpose of this award is to foster career development of junior faculty whose research interests are focused on the role of environmental chemical exposures on women's health across the life span. The long-term objectives are to graduate scholars who go on to successful careers in interdisciplinary research in women's environmental health, establish a successful and sustainable training program in women's health research, create an environment at URMC conducive to interdisciplinary research in women's health, develop researchers who provide positive feedback to the research environment and the fields of women's health research, and build in continuing mechanisms to effectively translate results of women's health research to health professionals and the broader community. Results of this research provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health.

Female Tenure Track Investigators Program

The NIH Women Scientist Advisors Committee and the Intramural Committee of the NIH Working Group on Women in Biomedical Careers have developed a new program for basic and clinical tenure track investigators and assistant clinical investigators. NIH program coordinators have agreed to help coordinate and develop a tenure track investigators program at NIEHS. Female senior scientists serve as mentors for this program.

Office of Fellows' Career Development

The first "MOMDADDOCS" meeting was recently held at NIEHS. The goal of MOMDADDOCS is to provide an informal mentoring, support, and networking program for NIEHS fellows balancing a career and family. The program is open to all, but it is particularly helpful for women looking to share advice and support as they strive for a work/life balance. Also, another intramural program, the NIEHS Brown Bag Lunch Program, has assisted with female career development in the sciences. The Brown Bag Lunch Program highlights a different set of Ph.D. careers each month to provide fellows the opportunity to meet scientists with firsthand experience. The lunch provides an informal and intimate atmosphere for fellows to ask questions and hear about potential career options. In FY 2013 and FY 2014, the program brought in 28

professionals, 80 percent of whom were women. During Postdoc Appreciation Week in 2013, the Office gave away approximately 100 books to help women further their careers, including "A Place at the Bench: Women in Biomedical Research" (available at http://www.bwfund.org/sites/default/files/media/files/wis.pdf). These efforts have specifically provided female trainees with a unique career development opportunity to learn about the role of women in a broad range of scientific fields.

Funding Initiatives, Workshops, and Conferences

Funding Initiatives

Administrative Supplements for Research on Sex/Gender Differences

ORWH developed a program to catalyze exploratory research on sex and gender differences by providing administrative supplements to ongoing NIH-funded research. NIEHS is currently funding three supplements under this program.

Mechanisms of Asthma-Dietary Interventions Against Environmental Triggers. This program at the Johns Hopkins University School of Medicine is using well-controlled mouse-model studies to better understand the relationship between dietary intake and asthma. The supplement will allow sex differences to be examined for all parameters of the project's population-based study and will compare the effects of air pollution and diet on asthma in female and male mice.

Children's Environmental Health and Disease Prevention Research Center at Dartmouth. This center is conducting an ongoing study of pregnant women in New Hampshire who rely on well water in their homes to ascertain molecular changes and child health outcomes from placental exposure to arsenic that may contaminate wells. The supplement will analyze sex-specific differences in identified molecular markers of arsenic exposure. Environmental lead exposure and prenatal stress are co-occurring risk factors for impaired cognition in children, and they also increase risk for adulthood disease.

CNS Glucocorticoid Epigenetic Changes of Lead Stress Effects. This study at URMC is examining chemical changes to DNA and proteins in the brains of mice as a result of lead and stress exposure. The supplement will assess sex-specific effects within these molecular changes in the brain.

The Role of Environmental Exposures in the Development of Autoimmune Disease (R21)

Autoimmune diseases result from an immune response directed against the body's own tissues. There are more than 80 different autoimmune diseases. Although many individual autoimmune diseases are rare, autoimmune diseases collectively afflict approximately 24.5 million Americans, with women disproportionately affected. The causes of autoimmune disorders remain largely unknown. Genetic risk factors have been and continue to be studied and account for a portion of the risk for autoimmune disorders. It is becoming clear from human studies, as well as animal model and in vitro research, that the etiology of autoimmune disease is multifactorial, involving both genetic and environmental influences. This announcement encourages exploratory research applications aimed at investigating the role environmental exposures play in the development and/or the exacerbation of autoimmune disease. Examples of research addressed in this funding opportunity announcement (FOA) include research to understand the interplay between environmental exposures and the hormonal milieu in mediating sex differences in disease incidence and research examining the functional consequence of the timing of exposure on disease formation, including characterization of critical windows in the timing of specific environmental exposures—such as during the fetal, perinatal, prepubertal, pubertal, adult, and aged periods—in relation to the sensitivity to the development of autoimmune disease, and others.

Environmental Influences During Windows of Susceptibility in Breast Cancer Risk (U01) and Coordinating Center for the Breast Cancer and the Environment Research Program (U01)

The overarching goal of the NIEHS Breast Cancer and the Environment Research Program (BCERP) is to support integrated scientific research to enhance our knowledge of environmental and genetic factors underlying breast cancer

risk. Projects and the coordinating center funded under two complementary FOAs together constitute BCERP. One funding opportunity supports transdisciplinary research projects to investigate the influence of environmental exposures during specific time windows of susceptibility on breast cancer risk. These transdisciplinary projects should be designed to address one or more potential windows of susceptibility and facilitate the integration of experimental model and human studies to accelerate understanding of the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies, and they must include community-academic partnerships with defined community-engagement activities. Collectively, the BCERP will form a consortium of multidisciplinary teams that will work collaboratively to conduct high-quality, transdisciplinary research focused on the impacts of environmental exposures during specific windows of susceptibility on breast cancer risk. The BCERP Consortium will also develop and implement strategies to translate and communicate these research findings to appropriate stakeholders.

Workshops and Conferences

Women's Environmental Reproductive Health Consortium. On January 30, 2013, NIEHS and the Collaborative on Health and the Environment cohosted the second annual meeting of the Women's Environmental Reproductive Health Consortium, whose goal is to advance research and facilitate collaboration to move the field of women's environmental health forward. Speakers described research including the use of artificial reproductive technology to study the impact of environmental chemicals on very early human development, work in a mouse model to show how a high-fat diet and BPA exposure during pregnancy affects the mother's reproductive health, a multigenerational study using pregnancy as a maternal sensitive window for environmental exposure, and the continued usefulness of diethylstilbestrol as a model for estrogen exposure. Clinicians from the American Congress of Obstetricians and Gynecologists spoke about integrating environmental health concepts into preconception and prenatal care. The workshop included discussion of the need for outreach and communication efforts between scientists and clinicians to ensure research findings are translated into practice.

Gordon Research Conference on Environmental Endocrine Disruptors. NIEHS provided support for the Gordon Research Conference on Environmental Endocrine Disruptors held in May 2014 in Lucca, Italy. The goal of the meeting was to link observations in wildlife with mechanistic laboratory studies using model systems and human clinical and epidemiological studies to provide an integrated view of how endocrine-disrupting chemicals affect health. Session topics included reproductive health, thyroid disruption, obesity/metabolism, and immunity, each of which has unique consequences for women.

ENDO 2013: The Endocrine Society's Annual Meeting and Expo. ENDO 2013, the 95th annual meeting of the Endocrine Society, was held in San Francisco in June 2013 with NIEHS support. The meeting included more than 200 scientific sessions on the latest breakthroughs in understanding the endocrine system and its function as well as the mechanism, prevention, diagnosis, and treatment of endocrine diseases. Specific topics of relevance for women's health included diabetes and metabolism, hormone-responsive cancers, bone diseases such as osteoporosis, vitamin D metabolism, endocrine disruptors, reproduction, puberty, aging, neuroendocrinology, and thyroid function.

2013 California Breast Cancer Research Symposium. NIEHS and NCI provided support for the May 17–18, 2013, California Breast Cancer Research Program (CBCRP) breast cancer research symposium to commemorate the 20th anniversary of the CBCRP. The symposium brought together scientists, advocates, clinicians, and policymakers to inspire collaborations between people with diverse experiences with breast cancer and provide a venue where they could share their knowledge about the disease. The goal of the symposium was to support scientifically based changes in public and health policy and practice that will impact the incidence and mortality of breast cancer. Specific objectives included facilitating contributions of advocacy to conducting breast cancer research and setting research priorities; providing tools for influencing breast cancer research, policy, and patient care directions; promoting discussion and collaborations among researchers clinicians, advocates, legislators, and the public about critical issues in breast cancer research; and showcasing achievements made in biological, epidemiological, clinical, and sociocultural breast cancer research. Topics covered in the symposium

included the environment and breast cancer (early life exposures, development of biologically relevant testing for chemicals that could affect breast cancer, and lessons from large cohort studies; training for conducting community-based participatory research and incorporating advocates in research studies to affect change; and hands-on demonstrations of tools for engaging in breast cancer research and advocacy.

Mammary Gland Biology Gordon Research Conferences 2013 and 2014. NIEHS support helped to bring together developmental biologists, experts in breast cancer risk and prevention, stem cell biologists, lactation physiologists, breast pathologists, endocrinologists, cancer biologists, and oncologists at the Mammary Gland Biology Gordon Research Conference to tackle important issues in mammary biology and breast cancer prevention and treatment in both 2013 and 2014. The goals of the program series were to inspire important insights, energize new scientists, and foster creative collaborations that will deepen our understanding of normal breast physiology and accelerate the eradication of breast cancer. The 2013 conference focused on the influence of diabetes/obesity on mammary development, lactation physiology, and breast cancer; a better understanding of signaling pathways that regulate both normal development and carcinogenesis; emerging controversies in stem/progenitor cell specification and in tumor-initiating cells; the epigenetic regulation of breast cell differentiation and breast cancer; and breast cancer invasion and metastasis. The 2014 conference focused on outstanding questions and recent discoveries related to breast cancer risk and prevention, mammary niche and reprogramming, pubertal and pregnancy hormones, lactation and involution, tumor heterogeneity and resistance to therapy, as well as dormancy and metastasis.

Household Air Pollution from Solid Fuel Combustion Smoke and Global Health Equality. Household solid fuel smoke is the most important environmental risk factor for the global burden of disease, affecting 2.8 billion people—mainly women and children—who constitute 40 percent of the world population. Household solid fuel smoke is not simply a problem for developing countries. Limited data suggest that wood smoke is a risk factor for asthma and chronic obstructive pulmonary disease in the United States, and the attributable risk for cardiopulmonary disease from wood smoke exposure in the United States is likely to increase. This scientific workshop, funded by NIEHS and the National Heart, Lung, and Blood Institute and held in New Mexico in November 2014, aimed to address critical gaps in research related to the health effects of household air pollution.

Health Disparities

Health Disparities from the 2010 Deepwater Horizon Gulf Spill

The NIEHS-led Deepwater Horizon Research Consortia supports community-university partnerships aimed at addressing the health effects stemming from the 2010 Deepwater Horizon oil spill in the Gulf of Mexico to help improve community preparedness and response to disasters and minimize disaster-related health impacts such as stress, exposure to contaminants, and diet changes. There are two studies within the consortia that focus on women and children being conducted at Louisiana State University and Tulane University and that involve minority or ethnic populations:

- **Women and Their Children's Health Study (5U01ES021497-04).** Goal: Determine mid- and long-term physical, behavioral, social, and economic effects on women and children's well-being
    - Two sub-studies are being conducted on resiliency (association between resilience, social capital, and emotional health and association between subjects' exposure and their emotional and physical health) and a child impact study. These studies include women from low-income communities, from Vietnamese subsistence communities, and among Houma Nation (Native American) communities.
- **Transdisciplinary Research Consortium for Gulf Resilience on Women's Health.** Goals: Assess mental and reproductive health outcomes and interactions of environmental and social disparities among women who are pregnant or of reproductive age and characterize women's exposures to select contaminants
    - Two sub-studies are being conducted on Lifetime Adversity and Reproductive-Aged Women and Real and Perceived Exposures in Reproductive-Aged Women. These studies also involve low-income communities and ethnic minorities as noted above.

Study of Environment, Lifestyle, and Fibroids

NIEHS intramural scientists are studying a variety of diseases that affect women. One epidemiological study, called the Study of Environment, Lifestyle, and Fibroids, is being conducted among African-American women ages 23 to 34 in the Detroit area (1ZIAES049013-19). Fibroids are more common in black women than white women, and fibroids are the leading indication for hysterectomy. The reason for the health disparity is not known. This NIEHS study is a prospective cohort study with enrollment of women before they are diagnosed with fibroids and follow-up for at least 5 years to document new fibroid development with ultrasound examinations at approximately 20-month intervals. Researchers will examine a wide range of potential risk factors for the condition to evaluate their associations with appearance of new fibroids and growth of existing fibroids.

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National Institute of General Medical Sciences

Executive Summary

The National Institute of General Medical Sciences (NIGMS) supports basic research that increases understanding of biological processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS-funded scientists investigate how living systems work at a range of levels, from molecules and cells to tissues, whole organisms, and populations. The Institute also supports research in certain clinical areas, primarily those that affect multiple organ systems. Studies supported by NIGMS do not target particular diseases or conditions but rather encompass fundamental research in a range of fields including cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics, and computational biology.

In FY 2013 and FY 2014, the work of a number of NIGMS-supported investigators is related to the interests of ORWH and focused on women's health conditions. These projects range from research using model organisms to behavioral studies evaluating stereotype threat interventions. As a result, NIGMS-supported research aligns with a variety of goals and objectives within the NIH Strategic Plan for Women's Health Research.

Several projects support Goal 1 of the NIH Strategic Plan for Women's Health Research. One investigates the mechanisms that control sexual dimorphism in brain structure and function. This research will help inform efforts to develop new treatments for certain neurological and neuropsychiatric disorders that are attributed to the sex-specific bias disorders.

Several NIGMS-funded projects align with Objective 2.7 of the Plan. One such project investigates novel targets in mitochondria for treatment of breast cancer. Other investigators are utilizing pharmacogenomics to determine the efficacy of antiestrogen therapies in breast cancer. NIGMS-supported investigators are also identifying new drug molecules to treat platinum-resistant ovarian cancer.

Through the Trans-NIH Coordinating Committee on Women's Health (CCWH), NIGMS awards supplemental funding to NIH-funded researchers to encourage the consideration of sex and gender factors in their ongoing research. NIGMS staff members actively participate in the NIH Working Group on Women in Biomedical Careers, and in 2014 NIGMS cosponsored with ORWH the Advancement of Women in Biomedical Careers Workshop.

Accomplishments and Activities

NIH Strategic Plan for Women's Health Research

The following accomplishments support the NIGMS and NIH strategic plan goals and objectives for women's health research.

Lower Susceptibility of Female Mice to Acetaminophen Hepatotoxicity. Acetaminophen overdose causes severe liver injury in animals and humans. However, researchers have not been able to clarify the mechanisms underlying the gender differences in susceptibility to acetaminophen overdose in mice. NIGMS-funded scientists found that a dose of 300 mg/kg of acetaminophen causes severe liver injury in male mice but 69 to 77 percent lower injury in females (Du, Williams, McGill, & Jaeschke, 2014). They did not find differences in gender regarding the biological transformation or metabolic activation of acetaminophen. The scientists found that hepatic glutathione (GSH), an intracellular peptide produced by the liver that protects against liver damage, was rapidly depleted in both genders. However, GSH recovery in female mice was 2.6 times higher in the mitochondria at 4 hours and 2.5 and 3.3 times higher in the total liver at 4 hours and 6 hours, respectively. The researchers demonstrated that in comparison to male mice, the lower susceptibility of female mice was achieved by the improved detoxification of reactive oxygen due to accelerated recovery of mitochondrial GSH levels. These findings provide some insight on gender- and sex-related differences in liver detoxification mechanisms. The research supports NIH Strategic Plan for Women's Health Research Goal 1 and Objectives 1.4 and 1.6.

NEET Proteins as Promising Mitochondrial Targets for Breast Cancer Therapy. Mitochondria are emerging as important players in the transformation process of cells, maintaining the biosynthetic and energetic capacities of cancer cells and serving as one of the primary sites for the regulation of cell death (apoptosis) and cell self-destruction (autophagy). Several avenues of cancer therapy have focused on mitochondria; nonetheless, progress in developing mitochondria-targeting anticancer drugs has been slow. There are a limited number of known mitochondrial target proteins that link metabolism with cell self-destruction or cell death. Recent studies have demonstrated that two members of the newly discovered family of NEET proteins, NAF-1 (CISD2) and mitoNEET (mNT; CISD1), could play such a role in cancer cells. Researchers found that NAF-1 is a key player in regulating cell self-destruction, and mNT mediates iron and reactive oxygen homeostasis in mitochondria (Sohn et al., 2013). Researchers showed that the protein levels of NAF-1 and mNT are elevated in human epithelial breast cancer cells. They found that by suppressing the level of these proteins using short hairpin RNA, or shRNA, they can significantly reduce cell proliferation and tumor growth and decrease mitochondrial performance, uncontrolled accumulation of iron and reactive oxygen in mitochondria, and activation of cell self-destruction. These results highlight NEET proteins as promising mitochondrial targets for cancer therapy including breast cancer. The research supports NIH Strategic Plan for Women's Health Research Goal 2 and Objective 2.7.

Does Chronic Pain Following Childbirth, Including Cesarean Delivery in Women, Exist? Physical injury, including surgery, can result in chronic pain, yet chronic pain following childbirth, including cesarean delivery in women, is rare. Scientists have not yet explored the mechanisms involved in this protection by pregnancy or delivery. NIGMS-funded scientists examined the effect of pregnancy and delivery on hypersensitivity to mechanical stimuli of the rat hindpaw induced by peripheral nerve injury (spinal nerve ligation) and after cerebrospinal fluid injection (intrathecal) of oxytocin, atosiban, and naloxone.

Additionally, they determined the concentration of oxytocin in the cerebrospinal fluid (Gutierrez, Liu, Hayashida, Houle, & Eisenach, 2013).

They found that spinal nerve ligation performed at mid-pregnancy resulted in similar hypersensitivity in nonpregnant controls but that the hypersensitivity partially resolved beginning after delivery. Removal of pups after delivery prevented this partial resolution. The cerebrospinal fluid concentrations of oxytocin were greater in rats with a normal postnatal period and prior to weaning. They examined the effect of injury at the time of delivery rather than during pregnancy, and they performed a spinal nerve ligation within 24 hours of delivery. This resulted in acute hypersensitivity that partially resolved over the next 2 to 3 weeks. Weaning of pups resulted only in a temporary return of hypersensitivity. The injection of oxytocin in the cerebrospinal fluid effectively reversed the hypersensitivity following separation of the pups. The postnatal resolution of hypersensitivity was transiently abolished by injection of the oxytocin receptor antagonist atosiban in the spinal fluid. These results suggest that the postnatal period rather than the pregnancy period protects against chronic hypersensitivity from peripheral nerve injury and that this protection may reflect sustained oxytocin signaling in the central nervous system during this period. The research supports NIH Strategic Plan for Women's Health Research Goal 3 and Objective 3.3.

Forms of Stereotype Threats and the Ways Interventions Work to Reduce Them. To date, stereotype threat interventions have been considered interchangeable. Across four experiments, NIGMS-funded scientists demonstrated that stereotype threat interventions need to be tailored to the specific form of experienced stereotype threat to be effective. The Multi-Threat Framework (Shapiro & Neuberg, 2007) distinguishes between group-as-target stereotype threats, or concerns that a stereotype-relevant performance will reflect poorly on the abilities of one's group, and self-as-target stereotype threats, or concerns that a stereotype-relevant performance will reflect poorly on one's own abilities. Researchers conducted a series of four experiments that focused on the performance of black college students on diagnostic intelligence tests and the interest and performance of women in science, technology, engineering, and math (STEM) (Shapiro, Williams, & Hambarchyan, 2013). Across the four experiments, scientists randomly assigned participants to experience either a group-as-target or self-as-target stereotype threat. Experiments 1 and 2 revealed that role model interventions were successful at protecting only against group-as-target stereotype threats, and Experiments 3 and 4 revealed that self-affirmation interventions were successful at protecting only against self-as-target stereotype threats. The present research provides an experimental test of the Multi-Threat Framework across different negatively stereotyped groups (black and female students), different negatively stereotyped domains (general intelligence and STEM), and different outcomes (test performance and career interest). This research suggests that interventions should address the range of possible stereotype threats to effectively protect individuals against these threats. Through an appreciation of the distinct forms of stereotype threats and the ways in which interventions work to reduce them, this research aims to facilitate a more complete understanding of stereotype threat. The research supports NIH Strategic Plan for Women's Health Research Goal 6 and Objective 6.3.

Chaetoglobosin K (ChK) Was Shown to Have a More Potent Growth Inhibitory Effect than Cisplatin on Two Cisplatin-Resistant Ovarian Cancer Cell Lines. Ovarian cancer is one of the leading causes of cancer-related death among the gynecologic malignancies in the Western world. Platinum drugs, such as cisplatin and its analogues, have been most frequently used for treatment of human cancer, including ovarian cancer. However, the obvious drawbacks of these agents, the normal tissue toxicity and acquired resistance to conventional platinum-based chemotherapy, are driving the development of more selective drugs that target cancer-specific defects. Increasing the susceptibility of cancer to apoptosis (cell death) is one of the potential strategies to overcome drug resistance in ovarian cancer cells. Recently, NIGMS scientists conducted studies that demonstrated that chaetoglobosin K (ChK) induced cell death through a p53-dependent caspase-8 activation extrinsic pathway and caused G2 cell cycle arrest in ovarian cancer cells (Li et al., 2015). Therefore, ChK would be a potential compound for treating platinum-resistant ovarian cancer. The research supports NIH Strategic Plan for Women's Health Research Goal 2 and Objective 2.7.

The CYP2D6 Genotype in Breast Cancer Patients Does Not Correlate with Tamoxifen-Endoxifen Metabolism Activity. Tamoxifen has been a mainstay

drug for antiestrogen therapies for the treatment of breast cancer and other estrogen receptor (ER)–positive cancers. Tamoxifen can be considered a prodrug in that the active antitumor agent is a metabolite named endoxifen, which is formed after tamoxifen is metabolized by the enzyme CYP2D6. CYP2D6 exists in several variant forms. Some forms demonstrate less enzymatic activity than others, and certain variant CYP2D6 forms correlate with decreased plasma concentrations of this metabolite. This concept is important because there are two major drug treatment regimens for breast cancer. The first is drugs classified as selective estrogen receptor modulators, which include the drug tamoxifen. The second is aromatase inhibitors, which block the formation of estrogen in the body. This is critical in deciding drug treatment for a cancer patient because 60 to 70 percent of newly diagnosed breast cancers are ER-positive, but of these only 60 percent of these cancers respond to therapy. An NIGMS-supported scientist published studies confirming his earlier research (Rae et al., 2012) that showed that the CYP2D6 genotype in breast cancer patients does not correlate with tamoxifen-endoxifen metabolism activity (Rae et al., 2013). The research supports NIH Strategic Plan for Women's Health Research Goal 2 and Objective 2.7.

Antagonistic Co-Evolution of Males and Females. In some insect and worm species, the mere presence of a female can shorten the life span of a male and vice versa. Scientists have investigated the molecular basis for this effect in the roundworm *C. elegans*, where it is known that males accelerate aging and reduce the life span of hermaphrodites. Males usually make up less than 1 percent of a worm population, and the rest are hermaphrodites, which can either self-fertilize their eggs or mate with a male (Maures et al., 2014). Using the genetic and molecular tools available for this model organism, they were able to determine that pheromones produced and excreted by the males, a mixture of small molecules called ascarosides, are responsible for the phenomenon and alter female physiology to increase male fitness. It is possible that sexually antagonistic coevolution has shaped interacting sensory pathways in males and females that in turn evolved to impact life span and fitness. As a result, the aging process in humans might similarly be influenced not only by genetic factors and individual behavior but also by social interactions between males and females. The research supports NIH Strategic Plan for Women's Health Research Goal 1 and Objective 1.8.

What Fish Can Teach Us About Sexual Fate and Reproductive Disorders. Genetics influence sexual determination in mammals. As we are learning, environmental factors influence in utero development, including that of the gonad. In fact, certain reproductive disorders such as testis dysgenesis and polycystic ovary disease likely originate from environmental factors acting on genetic factors during development in the womb. In zebrafish, both genetic and environmental mechanisms determine the sex of the individual. The zebrafish, with its finely tuned sex determination program, is a powerful model for discovering how environmental factors integrate with genetic pathways to tip the balance of sex determination between male and female and to gain insight into the development of human congenital disorders. An NIGMS-funded scientist recently determined the genetic locus for sex determination in native zebrafish, which had been lost from widely used laboratory strains (Howe et al., 2013). This is a significant finding because prior to this discovery, it was thought that environmental factors solely determined whether a testis or ovary formed in zebrafish. The discovery of a genetic locus for sex determination makes the genetically tractable zebrafish an excellent model for studying the interplay between genes and environment during gonad development. Moreover, it provides the potential to reintroduce the sex determination locus into laboratory stocks to achieve more balanced sex ratios, which is important for all biological studies using male and female zebrafish. Additional studies are being conducted to work out the larger genetic network that determines sex and how this network is "tweaked" by environmental factors, such as nutrition, that may ultimately affect gonad fate. The research supports NIH Strategic Plan for Women's Health Research Goal 2 and Objective 2.2.

Compound from Sponge May Lead to Treatments for Breast Cancer. A series of marine natural products isolated from the sponge of *Verongida* have been shown to have interesting bioactivity and cytotoxic properties in tumor cell lines. The compound, 11-deoxyfistularin-3, is cytotoxic against the estrogen-dependent human breast carcinoma cell line MCF-7. This project is to synthesize derivatives of this compound that will have submicromolar activity against MCF-7 breast cancer cells (Das, Valente, & Hamme, 2014). Studies are ongoing to synthesize the natural product and to produce analogues that will be tested for their ability to bind to estrogen receptors and to

kill MCF-7 breast cancer cells. The research supports NIH Strategic Plan for Women's Health Research Goal 2 and Objective 2.7.

RNA Splicing Regulation in Brain Sexual Differentiation. The developmental process of brain sexual differentiation is critical for the establishment of dimorphism in neural function and behaviors between the sexes, and the role that sex steroids (estrogens and androgens) have is not clearly understood. An NIGMS-supported investigator has identified an RNA splicing factor, suppressor of white-apricot homologue (*Drosophila*) Sfswap, also known as splicing factor arginine/serine-rich 8, as one of the many candidate genes differentially expressed in the neonatal mouse cortex. The investigator has proposed the novel hypothesis that sex steroids and their receptors regulate transcription of the Sfswap gene in the developing cortex, which leads to sex differences in brain structures and behaviors (Armoskus, Mota, Moreira, & Tsai, 2014).

Among their findings in 2013–2014, this investigator has reported that Sfswap expression is higher in the female cortex and hippocampus than in males after birth (Armoskus et al., 2014). The investigator has identified 55 male-biased genes and 35 female-biased genes, which included sexually dimorphic expression of eight sex chromosome genes, three located on the X chromosome (Xist, Eif2s3x, and Kdm6a), three on the Y chromosome (Ddx3y, Eif2s3y, and Kdm5d), and two in the pseudoautosomal region of the X and Y chromosomes (Erdr1 and Mid1). In addition, five autosomal genes (Cd151, Dab2, Klk8, Meg3, and Prkdc) were shown to have sexually dimorphic expression in the neonatal mouse cortex/hippocampus. Their microarray data has been deposited in the NIH Gene Expressing Omnibus database. A better understanding of the mechanisms that control sexual dimorphism in brain structure and function will enhance our understanding of the underlying causes of the sex-specific bias in certain neurological and neuropsychiatric disorders and assist in the development of new treatments for these disorders. The research supports NIH Strategic Plan for Women's Health Research Goal 1 and Objectives 1.5 and 1.7.

Activities

NIGMS is actively involved in the CCWH and is taking part in the Administrative Supplements for Research on Sex/Gender Differences (http://grants.nih.gov/grants/guide/pa-files/PA-15-034.html), which seeks to provide supplemental funding to NIH-funded researchers to encourage the consideration of sex and gender factors in their ongoing research. This activity supports NIH Strategic Plan for Women's Health Research Goal 5 and Objective 5.2.

NIGMS participates in the NIH Working Group on Women in Biomedical Careers and cosponsored with ORWH a workshop on Advancement of Women in Biomedical Careers. The report from the workshop is available at http://orwh.od.nih.gov/career/pdf/advancingwomenscareersworkshopsummary.pdf. These activities address NIH Strategic Plan for Women's Health Research Goal 6 and Objective 6.3.

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National Institute of Mental Health

Executive Summary

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders and eating disorders than boys, while boys are more likely to suffer from autism spectrum disorder and attention deficit-hyperactivity disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder (PTSD). There are also differences in the course and severity of mental disorders between men and women. Additionally, some women are at increased risk of depression during certain times of reproductive change, such as in the perinatal and perimenopause periods.

Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender differences in mental health and mental illness. NIMH has also advanced knowledge in the area of specific mental disorders that either affect women exclusively (e.g., perinatal depression), or predominantly (e.g., eating disorders). Through crosscutting efforts such as the Women's Mental Health Team, NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, and services, and the prevention of mental disorders in women. Through initiatives in global mental health, efforts to promote research on mental health disparities, and increased training in both areas, NIMH is laying the groundwork for accelerated research in

global health and mental health disparities. This research captures the needs of women from diverse socioeconomic backgrounds, racial and ethnic groups, and geographic contexts. This report for FYs 2013 and 2014 highlights NIMH offices and groups designated to focus on women's mental health, published findings on sex differences and women's mental health research, specific workshops and initiatives to promote research in the areas described above, as well as efforts on behalf of special populations of women. Research highlights, initiatives, and workshops are grouped by relationship to the NIH Strategic Goals for Women's Health and Sex Differences Research, with relevance to specific NIH objectives described in each goal section. Separate sections are demarcated on sex steroids, women and trauma, women and aging, sexual minorities, and pregnancy. Findings regarding adolescents, low-income women, rural women, and mental health disparities are featured throughout the research highlights.

Offices and Groups Designated to Focus on Women's Mental Health

The Women's Mental Health Program is located organizationally in the Office for Research on Disparities and Global Mental Health (ORDGMH) within the Office of the NIMH Director. The Women's Mental Health Program was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational focal point for women's mental health science communication and liaising with ORWH and other governmental and nongovernmental organizations interested in women's issues. The program chief of the Women's Mental Health Program serves on a number of NIMH, NIH, and other Federal working groups and committees, which are detailed under Goal 4, in order to contribute to NIH and Federal collaboration on women's mental health research. In FY 2013–FY 2014, the ORDGMH coordinated NIMH activities that serve to fulfill the congressional mandate for tracking the inclusion of women and minorities in clinical research. In the future, the NIMH Office of Clinical Research will take over these duties.

The Women's Mental Health Team serves as the focal point for coordination of NIMH scientific activities related to women's health and sex/gender differences research. Members of the team include representatives from all four extramural research divisions and the Division of Extramural Activities, as well as the Office of Science Policy, Planning, and Communications; the Office of Constituency Relations and Public Liaison (OCRPL); and the Office of Clinical Research. Team members work together across disciplinary boundaries to plan workshops, prepare/review science reports, and develop funding opportunities related to women's mental health.

Accomplishments and Activities

Goal 1: "Increase Sex Differences Research in Basic Science Studies."

Research on Sex Differences in Brain and Behavior

Many mental disorders have striking gender disparities in prevalence, as shown in population-based epidemiology studies of U.S. adults. For example, adult women experience major depression at almost twice the rate of adult men. Sex differences can be due to a variety of factors, including the effects of sex-linked genes, sex hormones, and differences in environmental stressors that impact brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental illnesses. The following examples of NIMH-supported study findings illustrate the Institute's efforts in this area, which are closely related to many of the objectives of Goal 1 of the NIH Strategic Goals. The basic and translational research findings on the effects of trauma upon women are summarized separately below.

Recent findings:

NIMH-funded studies include these published examples, which follow several objectives of this goal:

Objective 1.1: "Encourage genetic and epigenetic studies to identify sex differences in gene expression."

Objective 1.4: "Include sex parameters in the design of experiments using animal models."

Objective 1.5: "Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric and substance abuse disorders."

Epigenetic Predictors of Postpartum Depression (PPD). Changing estrogen levels associated with pregnancy and the postpartum period have been associated with mood changes in some women. Using a cross-species design, NIMH-funded researchers found DNA methylation changes that predicted the development of PPD with over 80 percent accuracy. This small, but innovative, study is the first to be able to identify predictive biomarkers of PPD. (Guintivano, Arad, Gould, Payne, & Kaminsky, 2014) (PMID: 23689534)

Maternal Depression Leads to Increased Stress and Aging in Daughters. Major depression has been associated with increased rates of medical illness, abnormal stress response, and signs of aging (shortened telomere length). However, it is not known if these changes are the result of depression itself or a marker of risk. NIMH-funded researchers are examining this question through a study of normal girls, some of whom have mothers who have depression. Daughters of depressed mothers were found to have an abnormal stress response and showed signs of accelerated aging (shortened telomere length). This may have important implications, as this sign of aging may predispose these daughters not only to an increased risk for depression but also for other medical illnesses. (Gotlib et al., 2014) (PMID: 25266121)

Sex Differences in Neuropeptide Systems and Social Behavior. The neuropeptides oxytocin (OT) and vasopressin (VP) act centrally to change social behavior. Animal research on these neuropeptides has suggested that OT acts primarily in females to increase affiliative (prosocial) behaviors, whereas VP acts primarily in males to increase aggressive behaviors. To date, most translational research in humans has focused on the potential therapeutic benefits of these neuropeptides as prosocial agents. Many of the translational studies, however, have studied only adults, only males, and/or only OT. The following three recent NIMH-funded studies have extended and refined our understanding of these systems by studying both of these neuropeptides, including female animals or study participants, and investigating sex differences.

Sex-Specific Modulation of Juvenile Social Play by Vasopressin. Peer interactions are critical for the development of normal social and emotional skills, but this has been an under-investigated area within social neuroscience. In this study, researchers tested the hypothesis that OT and VP have sexually dimorphic effects on peer-to-peer social play in juvenile rats. The actions of OT and VP were manipulated pharmacologically via intracerebral injections of antagonists. Notably, OT antagonists caused no substantial change in social play behavior in either males or females. When targeting the lateral septum specifically, the investigators found that VP blockade had opposite effects in males and females: It increased social play in male rats, while decreasing play in females. This is the first report of VP-mediated changes in social play behavior in juvenile rats. Most important, these findings highlight how the behavioral impacts of OT and VP are mediated by the specific neuropeptide system targeted, the injection location, and the sex of the animal. (Veenema, Bredewold, & DeVries, 2013) (PMID: 23838102)

Sex Differences in Response to Intranasal Oxytocin and Vasopressin. Studies using intranasal delivery of neuropeptides to healthy individuals have underscored the importance of considering sex as a factor in translational research. In a previous study with men only, researchers showed that OT and VP caused different patterns of fMRI BOLD responses and cooperative behaviors. In this current study, which involved a parallel study with women, researchers found substantially different results in women as compared to those seen in men. In women, VP had very little behavioral impact at all; post-OT fMRI signals were either absent or in the opposite direction. Together, this work demonstrates the complexity and sex-dependence of both brain and behavioral responses to OT and VP neuropeptides. (Rilling et al., 2014) (PMID: 24157401)

Sex Moderates the Effect of Oxytocin on Social Judgments. In a similarly themed study, researchers investigated the effects of intranasal OT on social judgments of faces. They used a continuous flash suppression task in which the rapid, simultaneous presentation of two different faces led to the expression on one face influencing the perception of the other. They found that intranasal OT caused men to perceive neutral faces more negatively, whereas the same treatment caused women to have more positive social judgments. Due to the presumption that it has uniformly prosocial effects, OT has been considered a potential treatment for a variety of mental health disorders with social deficits. As the authors note, "If the effects of oxytocin are different in men and women,

it is possible that its efficacy as a treatment might differ by gender." These considerations are critical to take into account prior to the adoption of OT more widely. (Hoge et al., 2014) (PMID: 24911580)

NIMH, in both its extramural and intramural programs, supports research on naturally occurring sex steroids and their effect upon development and vulnerability to mental illness.

> **Objective 1.7:** "Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs."
>
> **Objective 3.5:** "Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span."

Estrogen Protects Against Detrimental Effects of Repeated Stress on Glutamatergic Transmission and Cognition. Male and female animals show different responses to stress; however, the mechanism underlying this difference is not understood. In this study, NIMH-funded investigators found that young female rats exposed to repeated stress did not show any negative effects on temporal order recognition memory mediated by glutamatergic neurons located in the prefrontal cortex (PFC). This repeated stressor produced a different effect in young male rats that showed a profound impairment in this type of memory. The detrimental effects of repeated stress on memory were unmasked in female animals when estrogen receptors were inhibited in the PFC. Conversely, when males were administered estrogen, they were protected from the adverse effects of the stressor. These results suggest that estrogen protects against the detrimental effects of repeated stress on glutamatergic transmission and PFC-dependent cognition. (Wei et al., 2014) (PMID: 23835908)

Short-Term Hypogonadism Does Not Adversely Affect Cognitive Performance. Gynecology clinic-based studies have consistently demonstrated that induced hypogonadism (a temporary menopause-like state that can be produced by certain treatments) is accompanied by declines in cognitive test performance. This study examined the effects of induced hypogonadism on cognitive performance in healthy women. Women were also tested during estradiol and progesterone add-back. The battery of cognitive tests assessed verbal and visual memory, visual special ability, verbal fluency, motor speed and dexterity, and attention and concentration. With the exception of improved performance on mental rotation during estradiol, there were no significant effects of estradiol or progesterone on measures of attention, concentration, or memory compared with hypogonadism. (Schmidt et al., 2013) (PMID: 23188540)

These findings relate to these objectives listed under Goals 1 and 3:

> **Objective 1.6:** "Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract and sexually transmitted infections."
>
> **Objective 3.5:** "Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span."

Intimate Partner Violence Impedes the Impact of HIV/STI Prevention Interventions. In many HIV and sexually transmitted infection (STI) preventive intervention trials conducted among women, condom negotiation and communication skills are major components of the intervention. However, the role of intimate partner violence (IPV) within personal relationships is often overlooked. Compared to Caucasian women, African-American women are 2.5 times more likely to experience IPV and are disproportionately impacted by HIV and other STIs. Based on principles from social cognitive theory and the theory of gender and power, this study aimed to examine the moderating role of IPV on the efficacy of an HIV/STI risk reduction intervention among 848 African-American women. Data were collected longitudinally over 12 months. Investigators found that lifetime report of IPV was associated with inconsistent condom use and having a risky sexual partner. Results also indicated that for women with a history of IPV, certain core skills that are taught in HIV/STI preventive interventions, such as condom use, may not be beneficial for women who potentially lack control in their relationships. Therefore, HIV/STI interventions for women who have experience IPV should go beyond improving skills in self-efficacy and female empowerment to focus on the IPV and help them avoid or terminate abusive sexual relationships. (Seth, Wingood, Robinson, Raiford, & DiClemente, 2014) (PMID: 25399033)

Examination of the Role of Mental Disorders and Cognitive Decline in the Nurses' Health Study. PTSD is a pervasive and debilitating mental disorder that is particularly common in women. PTSD is characterized by changes in the normal endocrine response to stress. In animal studies, these changes have been associated with changes in cognitive processes, brain structure and function. Understanding the relation of PTSD and cognitive health in women could inform interventions aimed at reducing any risks PTSD may pose on cognitive health. Previous studies in this area have used small samples of specific populations, such as veterans or Holocaust survivors. This study presents a unique opportunity to study a large (54,282) group of women aged 48 to 65 who have been part of a sub-cohort followed since 1989 with detailed data on PTSD. The primary aim of this study is to evaluate if PTSD, independent of depression, is associated with worse cognition in middle-aged women and to collect preliminary data on cognitive changes. As a secondary aim, this study will evaluate specific elements of any relation of PTSD to cognitions, including factors acting as mediators and effect moderators that could be targeted for interventions. (R21MH102570-01A1)

Goal 2: "Incorporate Findings of Sex/Gender Differences in the Design and Application of New Technologies, Medical Devices, and Therapeutic Drugs."

Research on Sex Differences and Disorders in Women Using Neuroimaging

Recent findings:

Many NIMH-funded published findings make use of advanced neuroimaging techniques that also lead to further development of these approaches. The examples below are illustrative of the following objectives:

> **Objective 2.6:** "Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery."

> **Objective 3.5:** "Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span."

Abnormalities of Dorsolateral Prefrontal Function in Women with Premenstrual Dysphoric Disorder (PMDD). Using positron emission tomography and fMRI scans and a working memory task, NIMH intramural investigators found that women with PMDD exhibited abnormal working memory activation in the dorsolateral prefrontal cortex of the brain compared to women without PMDD. The degree to which this abnormal activation was increased correlated with several measures including disability (as measured by the global assessment of functioning score), age of onset of PMDD symptoms, duration of PMDD, and differences in symptoms pre- and post-menses. (Baller et al., 2013) (PMID: 23361612)

Impact of Puberty on Evolution of Cerebral Perfusion During Adolescence. Using a large sample of 922 youths ages 8–22, researchers studied the developmental differences in cerebral blood flow. Patterns of cerebral blood flow were similar between boys and girls during early puberty, but diverged markedly by midpuberty. Girls showed increased perfusion, whereas boys showed overall decreased cerebral perfusion in areas associated with executive functioning and mood. Further research may help elucidate whether these changes may be linked to the greater risk for mood disorders in females and the lower risk for schizophrenia. (Satterthwaite et al., 2014) (PMID: 24912164)

Goal 3: "Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women."

Translational and Clinical Research on Disorders in Women: Risk Factors, Etiology, Course of Illness, and Therapeutics

Recent findings:

NIMH intramural and extramural research focuses on risk factors for mental disorders, the etiology and course of these disorders, and intervention research, following these objectives:

> **Objective 3.1:** "Conduct developmental and developmentally framed research to understand the

role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span."

Objective 3.9: "Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions."

Initiatives and findings on pregnant women, perinatal disorders, women and aging, and sexual minority issues are highlighted separately below at the end of this section, with their respective objectives.

Sex Differences in Fear-Potentiated Startle Across Puberty. Puberty is a time period associated with acute changes in physiology and intense emotional experiences. It is also a time when sex differences emerge in certain kinds of psychopathology. NIMH Intramural investigators prospectively examined the startle reflex in a group of boys and girls ages 10–13. The startle reflex is a reflex response to an abrupt and unexpected stimulus that is potentiated by fear and anxiety. The investigators found that girls showed stronger fear potentiation than boys over the course of puberty. Prospective studies of adolescents have established links between increased rates of mood disorders and panic attacks with changes in reproductive hormones across puberty. This study provided the first evidence on increased fear-potentiated startle in girls across puberty. (Schmitz, Grillon, Avenevoli, Cui, & Merikangas, 2013) (PMID: 24334108)

Menopause and Cognition in HIV-Infected Women. In a sample of 708 HIV-infected and 278 uninfected premenopausal, perimenopausal, and postmenopausal women, investigators examined verbal learning and memory, attention/processing speed, and executive function. Symptoms of anxiety, depression, vasomotor issues, and sleep difficulties were also assessed. Elevated anxiety was associated with worse verbal learning in HIV-infected women compared to noninfected women. In both groups, vasomotor, depressive, and anxiety symptoms (but not menopausal stage) were more associated with worse cognitive performance. (Rubin et al., 2014) (PMID: 24496085)

Adult Women with Attention-Deficit Hyperactivity Disorder (ADHD) at High Risk for Self-Harm. NIMH-funded researchers found that adult women with ADHD are at particularly high risk for self-harm and that this risk is linked to impulsiveness. ADHD is more prevalent in boys, and most research on ADHD is conducted with boys and men. This prospective, longitudinal study is focused on girls with and without a diagnosis of ADHD and their long-term outcomes over 10 years. Now young women, individuals in the study with a childhood diagnosis of ADHD were much more likely to exhibit self-harmful behaviors, particularly when symptoms of ADHD persisted throughout the duration of the follow-up period. These findings underscore the importance of thorough and frequent monitoring of self-harmful behavior among girls and young women with ADHD. The authors also note that evidence-based treatment to reduce high levels of impulsivity and comorbid symptoms may help to reduce risk for those at risk. (Swanson, Owens, & Hinshaw, 2014) (PMID: 25436256)

Behavioral Health and Social Correlates of Re-Incarceration Among Hispanic, American Native, and White Rural Women. In order to identify community re-entry needs, the authors of this study examined mental illness, substance dependence and other correlates of re-incarceration in an ethnically diverse, rural population of women prisoners. Of the 98 women interviewed, 85 percent had substance dependence, 50 percent had current mental disorders, and 46 percent had both conditions. All of the women had been exposed to trauma, and 83 percent had experienced physical or sexual trauma. Previous incarceration was associated with precarious housing and with having co-occurring mental illness and substance dependence. These findings support those of similar studies in urban areas and with other ethnic groups. (Willging, Malcoe, St. Cyr, Zywiak, & Lapham, 2013) (PMID: 237286032)

NIMH also supports a number of studies examining aging and mental health. These findings relate to the following objectives:

Objective 3.7: "Explore differences in response to therapeutic interventions among samples of elderly women, including those with comorbid conditions."

Objective 3.8: "Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living,

self-management of symptoms, preservation of cognitive functions, and health-related quality of life."

Menopause Is a Risk Factor for Recurrence of Depression. NIMH-funded researchers recently published a variety of high-impact articles based on their study of mental health in menopausal women. Specifically, they found that menopause was a significant risk factor for experiencing recurrent depression in women with a history of major depression. The risk was even higher for women with a history of an anxiety disorder. In contrast, among women without a history of depression, the risk of depression during the midlife period was substantially lower and not associated with the onset of menopause. For these women, the prominent risk factors were health conditions developed before midlife and their perceptions of their functioning and vasomotor symptoms during midlife. (Bromberger, Schott, Kravitz, & Joffe, 2014) (PMID: 25417760)

The pattern was somewhat different with respect to anxiety. Researchers found that among women without a history of anxiety symptoms, menopause increases the likelihood of experiencing significant anxiety, but that among women with a history of anxiety symptoms, menopause did not further increase this risk. At the same time, anxiety symptoms tended to be a predictor of developing a depressive episode over the ensuing year, particularly among those prone to recurrent episodes of depression. (Kravitz, Schott, Joffe, Cyranowski, & Bromberger, 2014) (PMID: 24467997)

Comorbidity and Midlife. This study found that women with a history of both depression and anxiety as comorbid conditions tend to experience more psychiatric disorders, distress, stressful events, and poor social support during menopause compared with women who had only one of these disorders. Other analyses by these investigators suggested that women from this sample (Study of Women's Health Across the Nation) who reported physical abuse during childhood (as opposed to sexual or emotional abuse) were at increased risk for developing metabolic syndrome, a precursor to heart disease, during midlife. (Midei, Matthews, Chang, & Bromberger, 2013) (PMID: 22775234)

Menopausal Status and Antidepressant Treatment Response. Treatment with serotonin reuptake inhibitors may be affected by a woman's hormonal status. In the Sequenced Treatment Alternatives to Relieve Depression(STAR-D) project, 896 premenopausal and 544 postmenopausal women were treated with citalopram for 12–14 weeks. Baseline demographic and clinical characteristics were used in adjusted analyses of the effect of menopausal statue and use of hormonal contraceptive or menopausal hormone therapy (HT) on outcomes. This study determined that treatment outcome was not affected by menopausal status. Hormonal contraceptives and HT also did not affect the probability of having a good treatment outcome. (Kornstein et al., 2013) (PMID: 23398127)

NIMH participated in the NIH Lesbian, Gay, Bisexual, Transgender, and Intersex (LGBTI) Research Coordinating Committee. NIMH also participated in the National Action Alliance for Suicide Prevention's (NAASP) Lesbian, Gay, Bisexual, and Transgender Populations Task Force, and supports a number of research grants in this area. In order to encourage more research in this area, NIMH participated in the NIH set of Program Announcements (PAs), "Research on the Health of LGBTI Populations," released in 2012:

- http://grants.nih.gov/grants/guide/pa-files/PA-12-111.html
- http://grants.nih.gov/grants/guide/pa-files/PA-12-112.html
- http://grants.nih.gov/grants/guide/pa-files/PA-12-113.html

Several applications from these PAs have been funded, including one examining dimensions of community participation among lesbian, gay, bisexual, and transgender people with schizophrenia (5R03MH100542-02) and a study on risk compensation and pre-exposure prophylaxis to prevent HIV (5R21MH100979-02).

NIMH supports research on mental health during pregnancy and the postpartum period in its intramural and extramural programs. These findings relate to the following objectives:

> **Objective 3.3:** "Encourage research on safe and effective interventions for conditions affecting pregnant women."
>
> **Objective 3.4:** "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."

Objective 3.5: "Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span."

The Patient Protection and Affordable Care Act of 2010 (ACA) called for continued Federal research on postpartum depression. These PAs, titled "Women's Mental Health during Pregnancy and the Postpartum Period," were issued in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute on Drug Abuse and outline research areas of interest that span basic and clinical research, clinical course, epidemiological and risk factors research, and intervention and services research.

- http://grants.nih.gov/grants/guide/pa-files/PA-12-216.html
- http://grants.nih.gov/grants/guide/pa-files/PA-12-215.html

Improving Care for Depression in Obstetrics and Gynecology. Major depression disproportionately affects women, with the highest rates occurring during the reproductive and menopause transition years. Obstetrician-gynecologists are often the only health providers women may see on a regular basis. Collaborative care models in primary care have shown improvement in the quality of mental health care and depression outcomes. This study examined an evidence-based collaborative care intervention adapted to obstetrics and gynecology clinics compared with usual care. The women in the intervention group had greater improvement in depressive symptoms at 12 months, were more likely to have at least a 50 percent reduction in these symptoms at 12 months, and had greater improvement in functioning at 18 months. (Melville et al., 2014) (PMID: 24807320)

Sertraline Effective in Producing Remission of Postpartum Major Depression (PMD). Few randomized double-blind placebo-controlled trials of medication have been conducted among women with PMD (defined as having an onset within the first 4 weeks after childbirth). An NIMH-funded research group found that treatment with sertraline produced a twofold increase in remission of PMD compared with placebo. (Hantsoo et al., 2014) (PMID: 24173623)

Antidepressant Use in Pregnancy Is Not Significantly Associated with Increased Risk of Cardiac Defects in Infants. There have been inconsistent reports associating first trimester use of antidepressants, particularly paroxetine, with heart defects. In this study, NIMH-funded investigators examined a cohort of 949,504 pregnant women in the Medicaid program. After adjusting for depression and a number of other confounding factors, they found no significant increase in the risk for cardiac defects in infants born to women who took antidepressants and those who did not. These findings also did not support earlier studies that found an association between paroxetine and right ventricular outflow track obstruction. (Huybrechts et al., 2014) (PMID: 24941178)

PTSD During Pregnancy Increases the Risk for Preterm Birth. Approximately 8 percent of pregnant women have PTSD. Stressful conditions, including PTSD, have been inconsistently associated with preterm birth. This is important because preterm birth is a major cause of death in newborns. NIMH-funded researchers performed a prospective, longitudinal study of 2,654 pregnant women to determine if PTSD, major depression, or antidepressant or antianxiety medications were associated with risk of early delivery (<37 weeks). They found that PTSD, particularly when coupled with a diagnosis of major depression, increased the risk of preterm birth fourfold. This risk was independent of medication use. (Yonkers et al., 2014) (PMID: 24920287)

Goal 4: "Create Strategic Alliances and Partnerships to Maximize the Domestic and Global Impact of Women's Health Research."

Creation and Maintenance of Alliances and Partnerships

ORDGMH has encouraged the program chief of the Women's Mental Health Program to create and maintain NIH, HHS, and other alliances. Simultaneously, global initiatives undertaken in FY 2013–FY 2014 by ORDGMH and NIMH allow staff to integrate knowledge and opportunities for women's health research with those for global mental health, HIV/AIDS, and mental health disparities research. Pregnancy and maternal and child health research is relevant to each of these areas. Outreach

and collaborations by other NIMH offices as well as the NIMH Division of Intramural Research Programs and funded researchers are also described. ORDGMH convened groups of investigators to stimulate and coordinate research efforts to reduce mental health disparities. These efforts dovetail with Goal 4.

Initiatives and collaborations:

NIMH efforts are described below and have followed a number of Goal 4's strategic objectives:

> **Objective 4.2:** "Establish new ventures and initiatives with a wide cross-section of partners, including NIH institutes, centers, and offices; academia; other Federal agencies; international organizations; private foundations; and industry."
>
> **Objective 4.3:** "Promote an environment that uses multiple avenues and technologies to facilitate continuing input from partners committed to improving women's health and promoting research."
>
> **Objective 4.4:** "Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups."
>
> **Objective 4.5:** "Partner with professional societies to include women's health research issues in national scientific meetings and conferences, including issues involving career training and development."
>
> **Objective 4.6:** "Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries."

Global Grand Challenges. In FY 2011, NIMH published the Grand Challenges in Global Mental Health, a synthesis of the views of more than 400 researchers, advocates, and clinicians working in 60 countries, which led to identification of 40 priorities for mental health research. Research specifically focused on solving these challenges could significantly transform the field and the lives of people with mental disorders. This collaborative initiative coincides with and has led to the prioritization of a number of activities relevant to women's health research. In June 2014, NIMH continued to facilitate new collaborations and research in global mental health by convening the meeting, "Solving the Grand Challenges in Global Mental Health: Partnerships for Research and Practice." The workshop participants discussed topics related to mental health treatment, current research activities, and emerging findings to address six goals identified in the Grand Challenges in Global Mental Health, including topics related to maternal mental health.

In FY 2013, NIMH published a funding opportunity announcement, "Grand Challenges in Global Mental Health: Integrating Mental Health into Chronic Disease Care Provision in Low- and Middle-Income Countries," and funded several projects in Africa and Asia. In FY 2014, Tanzanian and American investigators continued to collaborate in the Healthy Options study to optimize delivery of group psychotherapy for HIV-positive depressed perinatal women.

Global Research Hubs. During FY 2013–FY 2014, ORDGMH continued to fund the Collaborative Hubs for International Research on Mental Health, a set of five regional hubs in South Asia, Sub-Saharan Africa, and Latin America whose aim is to reduce the mental health treatment gap in low and middle-income countries. The hubs conduct research on task-sharing for the delivery of mental health services in low- and middle-income countries; support mental health research capacity-building in countries in their regions; and will utilize the network they form to answer mental health services questions across different health system environments. The South Asian Hub for Advocacy, Research, and Education is developing an innovative, effective, and sustainable approach for the delivery of an established psychological treatment that reduces the burden of depression in mothers in South Asia.

Collaboration and Committees. The Women's Program Chief worked with a number of trans-HHS committees, including the National Action Alliance for Suicide Prevention's Research Task Force, the NIH Lesbian, Gay, Bisexual, Transgender and Intersex Research Coordinating Committee, and the White House Working Group on the Intersection of HIV/AIDS, Violence against Women, and Gender-related Health Disparities. The program chief continued service on the following NIH committees and workgroups: the NIH Coordinating Committee on Research on Women's Health, the Women and Trauma Federal Partners' Committee, the NIMH Steering Committee, and the NIMH Diversity and Re-entry Supplements Committee. All of these contribute to NIH,

HHS, and Federal coordination of women's mental health research issues and related policy.

Outreach to Advocacy Groups. The Office of Constituency Relations and Public Liaison in the Office of the Director, NIMH maintains a robust outreach effort to mental health advocacy groups, including a number of women's health-related groups, which participate in the biannual NIMH Alliance for Research Progress meetings. Women's health groups that are members of the NIMH Alliance and have participated in FY 2013–FY 2014 include Postpartum Support International; the Society for Women's Health Research; the Eating Disorders Coalition for Research, Policy and Action; the National Eating Disorders Association; Families Empowered and Supporting Treatment of Eating Disorders; and the Eating Disorders Coalition.

Educational Outreach Efforts. In 2014, OCRPL and ORDGMH, together with NICHD, entered into a 2-year collaboration with Delta Sigma Theta Sorority, Inc., called the Mental Health Across the Lifespan Initiative. The educational outreach initiative seeks to raise awareness about certain mental health conditions affecting women and their families, including PPD and bullying, as well as about successful aging later in life. The Initiative will harness the power of the organization's membership network to extend the reach of NIH's research-based information directly into the communities served by more than 1,000 Delta Sigma Theta chapters in the United States and abroad. The collaboration will also expand and intensify NIH's efforts to increase awareness about the diagnosis, treatment, and latest research in the area of PPD. Expansion of efforts to increase support, education, and research related to PPD was a key provision of the ACA.

Goal 5: "Develop and Implement New Communication and Social Networking Technologies to Increase Understanding and Appreciation of Women's Health and Wellness Research."

Communication and Social Networking

NIMH has responded to numerous requests for expert information from NIH, HHS, and Congress as well as over a hundred annual requests from investigators on women's health research opportunities. In addition to responding to these requests, NIMH utilizes new media technologies (e.g., Twitter, Facebook, YouTube, RSS feeds) to disseminate research findings and cultivate relationships with advocacy groups. These efforts meet the following objective:

> **Objective 5.1:** "Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues."

In FY 2013–FY 2014, NIMH utilized social media to host several "Twitter chats" on topics related to women's mental health.

- NIMH Twitter Chat on Premenstrual Dysphoric Disorder
- NIMH Twitter Chat on Postpartum Depression
- NIMH Twitter Chat on Borderline Personality Disorder
- NIMH Twitter Chat on Eating Disorders

Goal 6: "Employ Innovative Strategies to Build a Well-Trained, Diverse, and Vigorous Health Research Workforce."

STEM Training Efforts

NIMH continued funding diversity and re-entry supplements, revamped and expanded efforts to provide additional training to early-stage investigators who have received diversity supplements, and conducted outreach to potential and early-stage researchers in global mental health. A number of these grantees and students are pursuing research interests in topics of interest in women's health, such as perinatal depression and maternal and child health. Objectives followed include the following:

> **Objective 6.1:** "Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH."
>
> **Objective 6.2:** "Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage evaluation of mentoring practices."

New Initiatives. In FY 2013–FY 2014, NIMH re-issued Biobehavioral Research Awards for Innovative New Scientists (BRAINS) (RFA-MH-13-110). This program is intended to support the research and research career development of outstanding scientists who are in the early, formative stages of their careers and who plan to make a long-term career commitment to research in specific mission areas of NIMH. While the BRAINS program is not targeted specifically at supporting women in the field, a number of these awards have gone to innovative female scientists since the program's inception.

Training of Diversity Supplement Grantees. In 2014, ORDGMH sponsored an NIMH Workshop for Early Stage Investigators. The workshop was designed to provide investigators currently supported by Diversity and Re-entry Supplements with the tools necessary to continue along the path of competitive research support and the transition to independence. The workshop aimed to communicate the importance of producing innovative research within the overall mission of NIMH to these promising early-career researchers. Content of the workshop emphasized issues relating to grantsmanship and strategies for successfully navigating obstacles and developing solutions on the journey to a successful research career. A number of these grantees and students are pursuing research interests in topics of interest in women's health.

Training of Global Researchers. ORDGMH continued to host the Global Mental Health Careers Listserv to build an ever-growing community of new investigators and engaged with them through bi-monthly publication of the *GlobalTracks* newsletter. The listserv and newsletter are vehicles for the dissemination of training news, upcoming global meetings, and funding opportunity announcements. A number of these grantees and students are pursuing research interests in topics of interest in women's health.

Inclusion Efforts

In FY 2013, NIMH hired an associate director for clinical research to provide more oversight of NIMH-funded clinical trials, including closer examination of the inclusion of women and minority participation in clinical trials. While all clinical trials are encouraged to perform a sex comparison analysis, the following are two examples of large trials that published a separate analysis by sex in FY 2013–FY 2014.

Featured Clinical Trials that Analyzed Data by Sex

Army STARRS. The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) is a multicomponent study designed to generate actionable recommendations to reduce Army suicides and increase knowledge of risk and resilience factors for suicidality. In their investigation of trends and predictors of suicide, the researchers found that increased suicide risk was associated with being male, White race/ethnicity, junior enlisted rank, recent demotion, and current or previous deployment. While women had a consistently lower suicide risk than men, the sex difference narrowed during deployment. (Schoenbaum et al., 2014) (PMID: 24590048)

STOP-PD. The Study of Pharmacotherapy of Psychotic Depression (STOP-PD) is a multicenter, randomized, placebo-controlled trial to assess the risks and benefits of continuing antipsychotic medication in persons with psychotic depression once the depression has responded to treatment. It also examines predictors or moderators of treatment variability, potentially leading to more personalized treatment of psychotic depression. Investigators examined sex differences in this trial and found that women were more likely to have comorbid anxiety disorders, as well as hallucinations and delusions with disorganization. Women were also more likely to have higher cholesterol levels. However, there were no significant sex differences in treatment response. There were also no differences in treatment-associated changes in body mass index. (Deligiannidis et al., 2013) (PMID: 24229753)

Funding Initiatives, Workshops, and Conferences

In FY 2013–FY 2014, NIMH sponsored a number of funding initiatives, workshops, and conferences relevant to women's mental health and sex/gender differences research. They encompass a wide range of scientific interests.

Advancing Eating Disorders Research Through Dimensional Studies of Biology and Behavior (RFA-MH-14-030). This funding opportunity announcement utilizes the elements of the NIMH Research Domain Criteria project's approach to examine neural or other biological mechanisms underlying eating disorders, conditions that disproportionately affect women and girls.

Gut-Microbiome-Brain Interactions and Mental Health (RFA-MH-14-080). This funding opportunity encourages research that investigates mechanisms by which gut microbiota influences prenatal and postnatal development as well as genes, signaling cascades, and brain circuits related to behavioral domains relevant to the mission of NIMH. Included as specific areas of research interests are studies of sex differences in effects of the gut microbiota on the modifiability of neural and circuit function across the life span.

Improving Health and Reducing Premature Mortality in People with Severe Mental Illness (SMI) (RFA-MH-14-060). This funding announcement supports grants that test innovative services interventions designed to reduce the prevalence and magnitude of common modifiable health risk factors related to shortened life span in adults with severe mental illness. Part of the focus of this funding opportunity is to support studies that develop or test strategies that reduce or eliminate racial, ethnic, or gender disparities in the development of medical comorbidities among people with SMI.

Pushing Translational Boundaries: Advances in Developmental Neuroimmunology and Mental Health (May 12–13, 2014). NIMH hosted a workshop to bridge basic and translational research and to define gaps and opportunities in developmental immunology. Discussion topics included, among other things, mechanisms and sex differences underlying risk and resilience.

Role of Relationships in HIV Prevention Among Young Women in Africa (September 4–5, 2014). NIMH and the National Institute of Allergy and Infectious Diseases invited experts in the field to discuss recent findings and gaps within the study of the uptake of and adherence to HIV prevention strategies by young women in sub-Saharan Africa. One talk focused specifically on the role that mental health plays in the use of HIV prevention strategies among young women. The presentations and discussion will be used to inform the writing of a funding opportunity on this topic area.

Advances in Global Mental Health Research and Capacity Building (May 2–3, 2013). NIMH invited key stakeholders from around the world to present study designs and key considerations from mental health services research in low- and middle-income countries. There was discussion of the interface of advocacy, policy, and research and developments in research capacity building. The objectives of this meeting were to disseminate current research activities, structure mentoring of early-career investigators, discuss funding priorities and form new collaborations. Some of these investigators are working in the area of maternal mental health.

Health Disparities

Addressing inequities in mental health is a major focus of ORDGMH. Some racial and ethnic groups bear a greater burden of certain mental health issues, such as suicide. In addition, there are often barriers to mental health care for certain populations of women that may be related to racial/ethnic differences, geographic location, socioeconomic status, or the presence of serious mental illness. In addition to research findings described elsewhere in this report, NIMH has sponsored or participated in several efforts in this area.

Administrative Supplements for Minority Health and Mental Health Disparities Research (PAR-14-238). Among other things, this supplement provides support for subgroup analysis of existing data to enable researchers to examine clinical and functional differences in intervention outcomes, as well as mediators and moderators of outcome variability among diverse racial and ethnic groups, and provides support for additional recruitment of racial and ethnic minority participants in order to increase statistical power for analysis.

Interventions for Health Promotion and Disease Prevention in Native American Populations (PAR-14-260). This program announcement supports applications for both AIDS and non-AIDS research in mental health, including developing culturally appropriate interventions to increase engagement in mental health services and expansion of science-based interventions that preempt or prevent mental disorders, including suicide.

Workshop: Closing the Gaps: Reducing Disparities in Mental Health Treatment Through Engagement (September 12–13, 2011). ORDGMH hosted a meeting to address the significant disparities in mental health care related to race and ethnicity that affect both men and women. Participants included representatives from the NIH

community and other Federal agencies and researchers charged with improving the nation's mental health equity.

Webinars on Advancing Knowledge on Mental Health Disparities (August 13 and 27, 2013). Presentations included topics related to women's mental health, such as advancing knowledge on mental health disparities for perinatal depression through a network-based approach.

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National Institute on Minority Health and Health Disparities

Executive Summary

The National Institute on Minority Health and Health Disparities (NIMHD) promotes and supports research to improve minority health and eliminate health disparities, as well as plans, leads, coordinates, and assesses the efforts of NIH as a whole to reduce and eliminate health disparities. To achieve this mission, NIMHD employs a multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information; promote research infrastructure and training; foster emerging programs; and extend its reach to health disparity communities.

The mission of NIMHD aligns well with the objectives of the NIH Strategic Plan for Women's Health and Sex Differences, with a particular research focus targeting Objective 3.9 ("Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions"). Recent accomplishments in women's health resulting from NIMHD programs and collaborations during FYs 2013 and 2014 that address this objective and others are summarized in the following report. Highlights include a project developing a computer-based HIV prevention program that will allow Spanish-speaking Hispanic women access to vital disease prevention knowledge, a project using telemedicine to give a virtual medical home for transgender women who may avoid more traditional care to the detriment of their health, and an investigation of the intersection between criminal history and health in women of low socioeconomic status. Through these studies and other targeted opportunities, NIMHD actively works to reduce health disparities for women from underserved populations.

Since NIMHD's mission is not disease-specific, NIMHD-supported researchers investigate a broad range of diseases and conditions, including cardiovascular disease, obesity, diabetes, cancer, HIV/AIDS, depression, and substance abuse. Projects involve both research with women-only populations and research that examines differences between men and women or boys and girls. Within these diseases and conditions, researchers conduct research on both biological and nonbiologic factors using various study types and interventions, such as prevention studies; comparative effectiveness studies; and behavioral, educational, and health services interventions. NIMHD also supports many studies using a community-based participatory research approach. NIMHD investigators also provide training to new investigators and engage communities in innovative efforts to improve minority health and to reduce and eliminate health disparities. Central concepts found in many of the NIMHD-supported studies include cultural competency and culturally tailored interventions.

Accomplishments and Activities

Consistent with the NIH Strategic Plan for Women's Health and Sex Differences Objective 3.9 ("Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions"), NIMHD supported a number of projects focused on understanding and addressing the health needs of particularly vulnerable groups of women from health disparity populations, including women living in poverty, those with substance abuse problems, and those involved in the criminal justice system. Another priority area for NIMHD was the use of innovative health information technology approaches to reach high-risk but underserved women from health disparity populations.

Criminal Justice and Health Disparities Among African-American Women Who Use Drugs

This study is examining the extent of criminal justice involvement and its association with unmet health care needs among African-American women who use illicit drugs. The number of African-American women living under the supervision of the criminal justice system is increasing, but little research has investigated the impact being involved in the system has on the health of this vulnerable population. Using a community-based sample of 600 African-American women in Oakland, CA, who use illicit drugs, this 3-year cross-sectional quantitative study will examine the range of involvement in the criminal justice system, compare unmet health care needs among groups of similar women with and without criminal justice involvement, and assess whether associations vary according to frequency, type, and duration of criminal justice involvement. By examining how criminal justice involvement is associated with unmet health care needs among African-American women who use illicit drugs, the proposed study will provide information that can help guide sound correctional and public health policies to reduce health disparities in a vulnerable population.

Developing Computer-Based Sexually Transmitted Infection (STI)/HIV Prevention Interventions for Hispanic Women

Project SAFE (Sexual Awareness for Everyone) is a cognitive-behavioral intervention designed to reduce HIV and other STIs in women from underserved racial and ethnic populations. Project SAFE has demonstrated efficacy in two separate, randomized controlled trials with Hispanic women, and the developer is committed to expanding the intervention's reach by creating updated, computer-delivered versions. This research is developing and testing computer-delivered Spanish- and English-language versions of all three sessions in Project SAFE. In the first phase, the team successfully developed a computer-delivered English version of Project SAFE's first session and created a short demonstration prototype for the Spanish version. Usability testing indicated that the product was well received and demonstrated a significant increase in the testers' HIV-related knowledge. Now, the team is developing a complete, computer-delivered version of Project SAFE in Spanish (C-SEGURA) and in English (C-SAFE) as well as conducting usability tests and implementing a randomized controlled trial to assess C-SAFE and C-SEGURA's efficacy in reducing HIV risk behaviors among 400 Hispanic women at six clinics in California, Texas, and

the Northeast. The project offers many innovations, including the production of the first evidence-based, computer-delivery HIV prevention intervention in Spanish; a mechanism to offer Spanish-language HIV prevention services in clinics and organizations that do not have Spanish-speaking staff; and significant cost reductions in the delivery of HIV prevention interventions. This research promotes community members' participation in HIV prevention activities by permitting sensitive topics to be addressed privately (i.e., one-on-one with the computer) and according to a flexible schedule. Ultimately, the interventions have the potential to reduce sexual risk-taking behavior and HIV infection rates among Hispanic women, who are disproportionately affected by HIV/AIDS.

Mobile Health App to Reduce Diabetes in Hispanic Women with Prior Gestational Diabetes

This study is developing an interactive, culturally and individually tailored, plain-language Spanish/English mobile health intervention for women with recent gestational diabetes. By tailoring this intervention for Hispanic women, the proposed mobile intervention significantly expands the reach of a previously developed online intervention, the Diabetes Prevention Program. The program includes education and skills development for lifestyle behavior change and algorithm-derived, individually tailored educational/motivational text messages. These texts are participant generated; automated based on prior participant-defined schedule; and "just in time," based on real-time participant input about current activities (i.e., two-way text messaging). This study is promoting self-efficacy and behavioral change among Hispanic women with prior gestational diabetes with the goal of preventing type 2 diabetes in these women. The intervention offers the potential of a highly scalable and cost-effective approach to decreasing health disparities and to improving health outcomes in a high-risk yet underserved group.

Modeling Criminal History Effects on Women's Health

This study is examining the complex relationships (both concurrent and dynamic) among criminal histories, welfare use, employment, and health in a national sample of more than 4,500 predominantly disadvantaged women followed over multiple years. Criminal conviction–related collateral consequences disproportionately affect socioeconomically disadvantaged women, as they are more likely to commit the types of crime that result in a criminal conviction rather than incarceration, rely more heavily on the types of jobs and welfare benefits negatively affected by collateral consequences, and have a far higher rate of health problems than the general population of women. This study is performing a secondary analysis of a nationally representative, 9-year longitudinal panel survey data set of 4,898 women from the Fragile Families Study to explore whether the presence, level of severity (charge, conviction, incarceration), or type (drug-, violence-, theft/fraud-, or traffic-related) of a criminal offense history affects employment patterns and health (psychological distress, depression, general health, and limited functioning) for women over time, and the extent to which receiving Temporary Assistance for Needy Families moderates these relationships. These findings could inform public health–oriented interventions to reduce adverse health outcomes for women with a criminal offense history.

Reducing Adolescent Pregnancy and HIV in a DC Public Housing Community

This study is a collaboration of the District of Columbia Housing Authority; African-American residents (adults and adolescents) of the Benning Terrace public housing community in Washington, DC; community-based health, social service, and faith-based organizations; the Urban Institute; and university-based health disparities researchers to reduce adolescent sexual health disparities. Sexual assault and coercion, pregnancy, and HIV/STI are all significantly over-represented among African-Americans in D.C. HIV rates are the highest in the nation, with up to 12 percent of women infected. This 3-year, community-based participatory research (CBPR) process includes a community-driven needs assessment of sexual health disparities; an asset mapping process regarding resources and expertise available for inclusion in a sustainable intervention for sexual health disparities; development of program and evaluation models; and piloting to assess program feasibility, acceptability, perceived efficacy, and outcomes. The use of CBPR in public housing communities

to develop interventions targeting adolescents and their parents may yield more focused techniques for reducing adolescent sexual health disparities in at-risk populations.

Use of Telemedicine to Overcome Barriers to Care Among Transwomen of Color

This pilot study is assessing acceptability and feasibility of telemedicine as a virtual medical home to overcome barriers to utilization of health care services among out-of-care male-to-female transgender persons (transwomen) of color. It will examine telemedicine as a means to overcome unique barriers to care experienced by transwomen of color, which include discrimination, substance abuse, violence, stigma, HIV/STI risk behaviors, and social isolation. This two-phase study will conduct key informant interviews with providers and transwomen themselves to evaluate the acceptability of the telemedicine approach and recruit a sample of 25 out-of-care transwomen for a 3-month comparison period, followed by a 3-month telemedicine/virtual medical home pilot study period. Together, these phases will assess the feasibility of the approach and its association with primary outcomes, including intention to seek care and health care utilization behavior. If successful, telemedicine may offer an innovative strategy for engagement and retention of a medically underserved and vulnerable population in urgent need of health care services.

Using Technology to Prevent Obesity Among African-American Girls

This research is conducting an outcome evaluation on a promising Web-based obesity prevention program for 8- to 10-year-old African-American girls. A pilot study with 80 girls established its feasibility; recruitment goals were met, attrition rates were less than 10 percent, login rates to the online program were nearly 75 percent, and statistically significant increases in fruit and vegetable consumption and time spent being physically active were observed (Thompson et al., 2013). The outcome evaluation will recruit 400 child-parent pairs to examine short- and longer-term effects of the program on obesity risk. At the end of the study, the Web-based program will be hosted on the Children's Nutrition Research Center Web site. Although the use of the Internet as a method for changing health behavior is not new, the use of an Internet program alone, with no face-to-face interaction, is novel. This is one of the first programs to attempt this, particularly in an at-risk population. This work will provide an innovative method for reaching an at-risk population with a culturally competent and developmentally appropriate obesity prevention intervention that can be readily disseminated to the community, thus addressing disparities related to access and obesity risk.

NIH Strategic Plan for Women's Health Research

Strategic Plan for Women's Health Research Highlights

ORWH Strategic Plan Goal 3, Objective 3.4: "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."

Fatty Acids–Mediated Inflammation and Disparities in Pregnancy Outcomes

This study is determining whether free fatty acids in a pregnant woman's bloodstream may increase inflammation and lead to negative pregnancy outcomes such as preeclampsia and preterm delivery. Preterm delivery is a leading cause of infant morbidity and mortality. African-Americans and Hispanics are disproportionately affected by preterm delivery, and the reasons are not fully understood. This research uses existing data and biological specimens from 2,816 healthy, low-income pregnant women from three racial and ethnic groups (African-American, Hispanic, and White) to look at whether low-grade inflammation in women from health disparity populations contributes to preterm delivery and preeclampsia, independent of other factors. In addition, this research is examining whether this inflammation is affected by circulating free fatty acid levels. Circulating fatty acids are good indicators of dietary fat intake. If inflammation is affected by fatty acids, then dietary changes may impact racial and ethnic disparities seen in preterm delivery and preeclampsia.

Epigenetic and Biobehavioral Determinants of Preterm Birth in African-American Women

African-American women disproportionately experience preterm birth, a major cause of infant morbidity and mortality, but the biology behind this phenomenon is not well understood. This study is examining biobehavioral factors like poor nutritional status, stress, and reproductive tract infections, which may influence genes that are linked to preterm birth in African-American women. These factors are known to influence inflammation and gene regulation through epigenetic modification of DNA. Better understanding of the epigenetic differences during pregnancy may lead to increased knowledge about the genetic contribution to racial and ethnic variability in preterm birth rates. One of the unique features of this project is that this research is supported by a multidisciplinary team of investigators that include collaboration of clinicians and basic and translational scientists representing expertise in obstetrical outcomes and maternal-child health, genetics and epigenetics, nutrition, stress, epidemiology, and informatics. This research may provide insight on how poor nutritional status and psychosocial stress impact gene regulation during pregnancy and may contribute to the development of potential blood tests to identify women who are at elevated risk of preterm birth. This may also lead to creating strategies to reduce this risk of preterm birth early in pregnancy.

Preeclampsia: Factors that Confer Risk and Protection

The incidence of preeclampsia is substantially increased in pregnancies complicated by any form of diabetes. This research is identifying preeclampsia risk factors in 300 women from three racial and ethnic groups (American Indian, Hispanic, and White) who have gestational diabetes. Susceptibility for preeclampsia may be modulated through environmental factors (e.g., nutrition), angiogenic factors, metabolic, and genetic factors. This project will also establish repositories for the biospecimens collected to allow them to be used for future genetic studies related to preeclampsia and diabetes. This study is the first time the Oklahoma Chickasaw and Choctaw tribes have agreed to consider genetic studies. This may lead to the development of treatments to prevent or arrest preeclampsia in pregnant diabetic women, particularly from health disparity populations.

ORWH Strategic Plan Objective 3.9: "Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions."

Evidence-Based Demonstration Projects in Immunization

Research indicates that there is a gap in knowledge about vaccines and lower vaccination rates among health disparity populations. In FY 2013, NIMHD partnered with the National Vaccine Program Office to fund six evidence-based demonstration projects to decrease infectious diseases by stimulating immunization rate improvements of children, adolescents, pregnant women, and adults in health disparity populations. Many of these projects are focused on increasing HPV vaccination rates women and girls. One project is being done with a diverse cohort of 6,000 girls and boys who live in low-income communities in Boston; a second is developing a culturally tailored, educational Web site to increase HPV vaccination in adolescent boys and girls in Wisconsin; and a third is educating college-age women in Hawaii who have low knowledge about the role HPV plays in cancer. Other projects are focused on increasing other important vaccination rates. For example, one project is extending a virtual patient advocate system that improves preconception health in young African-American women to include immunization information and another is increasing flu vaccination rates among low-income pregnant women in Puerto Rico. These projects leverage existing community partnerships to increase vaccination rates among women and children from health disparity populations.

Other IC Activities that Support the Implementation of the NIH Strategic Plan for Women's Health Research

ORWH Strategic Plan Goal 1, Objective 1.9: "Incorporate sex/gender considerations into discussions in scientific conferences and meetings."

NIMHD has sponsored scientific presentations relevant to women's health as part of its NIH Health Disparities

Seminar series, which is open to the NIH community and the public.

- "Implementation of Health Reform: Ensuring the Health Needs of Women," March 21, 2013. This presentation discussed work to inform the implementation of the Affordable Care Act and its implications for the health of women based on the report "Ensuring the Health Care Needs of Women: A Checklist for Health Exchanges" (Johnson et al., 2013).
- "Reducing Disparities in Mother and Child Oral Health: Research Needed to Meet Healthy People 2020 Goals," August 15, 2013. This presentation discussed oral health disparities that affect low-income mothers and children, the approach presented by the Affordable Care Act to address these disparities, and the translational community-based research being undertaken at the Northwest Center to Reduce Oral Health Disparities.
- "Native American Health Disparities and 'Native Navigators and the Cancer Continuum,'" November 21, 2013. This presentation provided an overview of current American Indian and Alaska Native (AI/AN) cancer and disparity data and presented results from the Native Navigators and the Cancer Continuum intervention study for AI/AN women with breast cancer.

Specific Position, Office, Branch Designated for Research on Women's Health

While there is no office or branch specifically designated to address research on women's health issues, women's health is an integral part of the NIMHD health disparities scientific research portfolio, which is administered through NIMHD extramural grants; co-funding with other Institutes, Centers, and Offices; and collaborations with other Federal agencies.

Inclusion

Resource-Related Minority Health and Health Disparities Research

Through the Resource-Related Minority Health and Health Disparities Research program, NIMHD funds three cooperative agreements to identify and evaluate strategies to promote greater inclusion of men and women from underrepresented racial and ethnic groups in clinical trials. These projects focus on recruitment into clinical trials related to cancer, stroke, and rare diseases treated in specialty clinics, and they are examining strategies to build trust with communities and individuals, address lack of familiarity with research and clinical trials, and overcome logistical barriers to participation such as transportation and child care.

Preventing HIV/AIDS Among Teens in Juvenile Justice

This project is conducting a randomized clinical trial to test a behavioral intervention to reduce risky sexual behavior, STIs, and substance use in male and female juvenile offenders on probation. The project, which will include equal numbers of boys and girls, is one of the few studies done with juvenile offenders that include girls. There are fewer girls in the juvenile justice system, and they have very different trajectories than boys (e.g., gender-specific diversion programs, programs for pregnant teens), which has made enrollment of girls into the study difficult. NIMHD provided supplemental funds in FY 2014 to enhance identification and referral of girls into the study to ensure that there were enough participants to allow gender comparisons to be conducted.

Science, Technology, Engineering, and Mathematics Efforts

Disparities Research and Education Advancing Our Mission (DREAM)

The NIMHD DREAM program is an intramural research initiative that supports health disparities researchers who meet the NIH criteria for early-stage investigators. The first 2 years are spent within a research laboratory of one of the NIH IC intramural programs, and the final 3 years are spent in an academic setting conducting health disparities research.

NIMHD Loan Repayment Program (LRP)

The NIMHD LRP is another successful program that recruits women into research. This program offers

repayment of educational loans up to $35,000 per year to health professionals with doctorate degrees to conduct health disparities or clinical research in non-Federal research settings. In FY 2013 and FY 2014, approximately 70 percent of the LRP recipients were women.

Funding Initiatives, Workshops, and Conferences

Table 1. NIMHD Initiatives

FOA Number	FOA Title	Objective
RFA-MD-14-004	NIMHD Social, Behavioral, Health Services, and Policy Research on Minority Health and Health Disparities [R01]	To solicit innovative social, behavioral, health services, and policy research that can directly and demonstrably contribute to the elimination of health disparities.
RFA-MD-14-005	NIMHD Basic and Applied Biomedical Research on Minority Health and Health Disparities [R01]	To solicit innovative grant applications on biological and genetic research to explore disease mechanisms or pathways that influence health outcomes in health disparity populations.
RFA-MD-14-003	Limited Competition: NIMHD Exploratory Centers of Excellence Pilot Research Projects [P20]	To support infrastructure and capacity building, building and sustaining novel partnerships, research training, and health disparities research in non–research-intensive institutions.
PAR-13-279	Limited Competition: NIMHD Research Centers in Minority Institutions Infrastructure for Clinical and Translational Research (RCTR) [U54]	To support a center to enhance collaboration across institutions funded by the Research Centers in Minority Institutions program in order to increase the efficiency of the implementation and dissemination of research advances to improve health outcomes.
RFA-MD-14-002	Limited Competition: Transdisciplinary Collaborative Centers for Health Disparities Research Coordinating Center [U54]	To support Transdisciplinary Collaborative Centers' (TCC) consortium activities and increase the efficiency of translational health disparities research by leveraging expertise, infrastructure, and research resources across the TCC sites.
RFA-MD-13-008	NIMHD Basic and Applied Biomedical Research on Minority Health and Health Disparities [R01]	To solicit innovative grant applications on biological and genetic research to explore disease mechanisms or pathways that influence health outcomes in health disparity populations.
RFA-MD-13-006	NIMHD Social, Behavioral, Health Services, and Policy Research on Minority Health and Health Disparities [R01]	To solicit innovative social, behavioral, health services, and policy research that can directly and demonstrably contribute to the elimination of health disparities.
RFA-MD-13-009	NIMHD Technologies for Improving Minority Health and Eliminating Health Disparities [R41/R42]	To stimulate a partnership of ideas and technologies between small business concerns and non-profit research institutes to develop the commercialization of innovative technologies for improving minority health and reducing health disparities.
RFA-MD-13-005	Limited Competition: Revision Applications for Basic Social and Behavioral Research on the Social, Cultural, Biological, and Psychological Mechanisms of Stigma [R01]	To support projects that elucidate mechanisms underlying stigma that are relevant across health conditions or stigmatized statuses.
PA-13-226	Evidence-Based Demonstration Projects in Immunization [Administrative Supplement]	To support evidence-based demonstration projects designed to decrease infectious diseases by stimulating immunization rate improvements of children, adolescents, pregnant women, and adults in health disparity populations.

FOA Number	FOA Title	Objective
RFA-MD-13-002	NIMHD Minority Health and Health Disparities International Research Training [T37]	To provide short-term global research training opportunities for qualified undergraduate, postbaccalaureate, or graduate students in the life, physical, or social sciences; or medical students, dental students, or students in other health-professional programs who have not yet received terminal degrees and who are from populations underrepresented in biomedical, behavioral, clinical, and social sciences research.
RFA-MD-13-003	NIMHD Transdisciplinary Collaborative Centers for Health Disparities Research [U54]	To establish centers that support transdisciplinary coalitions of academic institutions, community organizations, service providers and systems, government agencies, and other stakeholders to conduct health disparities research at the regional level.
PAR-11-132	Research Centers in Minority Institutions Program [G12]	To expand the national capability for research in the health sciences by providing grant support to minority-serving institutions that offer doctorate degrees in the health professions or health-related sciences.

Health Disparities

All of the accomplishments and activities listed under Accomplishments and Activities, NIH Strategic Plan for Women's Health Research, and Inclusion pertain to health disparities.

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National Institute of Neurological Disorders and Stroke

Executive Summary

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. This burden is borne by every age group, by every segment of society, and by people all over the world. Most disorders of the nervous system affect men and women equally, but certain disorders, such as chronic pain, epilepsy, Rett syndrome, stroke, traumatic brain injury, multiple sclerosis (MS), and migraines, disproportionately affect women or have specific health implications for them. NINDS supports basic, translational, and clinical research on these disorders, as well as targeted research to understand sex-based differences in normal development and function of the nervous system, behavior, cognition, and perception.

Chronic pain is caused by the improper function of neuronal pain circuits and results in abnormal pain that persists for weeks, months, or even years. Certain chronic pain conditions like migraine headaches, temporomandibular joint disorders, endometriosis, and fibromyalgia are diagnosed more often or exclusively in women, and women often have more than one of these conditions. Current research is examining the genes involved in familial forms of migraine as well as the influence of the sex hormones estrogen and testosterone.

Epilepsy affects 1 in 26 people during their lifetime, and currently, there are an estimated 2.5 to 3 million individuals with epilepsy in the United States. Although several effective treatments are available, about 30 percent of individuals do not benefit from them. Women with epilepsy face special problems during phases of the menstrual cycle, and those who take certain antiepileptic drugs during pregnancy face higher than normal rates of birth defects in their children. Of importance for the development of future treatments is the need to understand the varying roles of steroid hormones in epilepsy for both males and females.

Rett syndrome is a childhood neurological disease most often caused by mutations in the gene that encodes methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulatory protein. The disorder is almost exclusive to females, affecting about 1 in 10,000, and is characterized by behavior and movement features similar to those found in autism, Parkinson's disease, and dystonia. Research has shown that some features are probably due to dysfunction of neurons and supporting cells rather than to neural degeneration. Symptoms found to be reversible in mouse models could lead to the development of promising new therapies.

Stroke is caused by a rapid disruption in the blood supply to part of the brain as a result of either blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or a sudden, severe headache. Although women in general have a lower risk of stroke than men, because of their longer life expectancy, women account for 60 percent of stroke fatalities in the United States.

MS, a chronic and often disabling disease of the central nervous system, is two to three times more common in women than in men. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to the next. MS affects more than 2 million people worldwide; its cause is still not known. Ongoing research indicates that a combination of several factors may be involved, including immunology and genetics.

Accomplishments and Activities

Research Findings

Chronic Pain

Recommendations for Migraine Treatment in Breastfeeding Women. Breastfeeding has important health and emotional benefits for both mother and infant. While there are some data to suggest migraine may improve

during breastfeeding, more than half of women experience migraine recurrence within 1 month of delivery. Thus, a thorough knowledge base of the safety and recommended use of common acute and preventive migraine drugs during breastfeeding is vital to clinicians treating migraine sufferers. The authors found that ibuprofen, diclofenac, and eletriptan were among acute medications with low levels in breast milk, but studies of triptans are limited. Toxicity was a concern with aspirin due to an association with Reye's syndrome, and sedation or apnea was a concern with opioids. Finally, certain preventive medications, including zonisamide, atenolol, and tizanidine, were not recommended. Thus, many commonly used migraine medications may be compatible with breastfeeding based on expert recommendations. (Hutchinson et al., 2013)

Sex Differences in Peripheral Pain Receptors. Women tend to have lower pain thresholds for many types of pain, yet the biological basis for this is not completely understood. Researchers compared the biophysical properties of peripheral neurons and receptors that sense pain in the gastrocnemius muscle in male and female rats. They confirmed that the behavior of females suggested they were more sensitive to pain in that muscle. However, contrary to their expectation, the neurons and pain receptors in females had higher thresholds for stimulation; that is, it took more force to stimulate the female receptors than the male receptors. Thus, lower pain thresholds in women may be explained by sex differences in the central nervous system, instead of the periphery. (Hendrich et al., 2012)

Epilepsy

Antiepileptic Drug Clearance and Seizure During Pregnancy. The American Academy of Neurology has recommended therapeutic drug monitoring for several antiepileptic drugs during pregnancy, with the goal of maintaining serum levels near preconception baseline. However, insufficient data are available to justify a recommendation for many antiepileptic drugs currently in use. Further, maintaining seizure control during pregnancy and reducing the risk of impaired development of the child exposed to antiepileptic drugs presents a substantial challenge to the mother and physicians. The researchers found that the clearance of lamotrigine and levetiracetam was significantly increased during pregnancy, and thus, the dosage was increased accordingly. Despite the increased dose in most patients, seizures increased in over a third of the participants. Substantial pharmacokinetic changes during pregnancy occur with antiepileptic drugs, and this may increase seizure risk. Further studies are needed for monitoring blood concentrations of these drugs and maintaining seizure control during pregnancy. (Reisinger, Newman, Loring, Pennell, & Meador, 2013)

Multiple Sclerosis

Combination Therapy Trial for MS. Researchers predicted that a single therapy would not be able to manage all of the symptoms of MS and therefore investigated the outcomes of combining two effective drugs with different mechanisms of action. The initial results from CombiRx, a trial using interferon β-1a and glatiramer acetate, showed that the combination therapy did not reduce the risk of relapse in MS more than each individual drug on its own; however, neuroimaging results indicated that the combination of drugs decreased the rate of brain lesions. The trial includes more than 700 subjects, and approximately 70 percent are female. (Lublin et al., 2013)

DNA Methylation in Brain Tissue from MS Patients. Large-scale genome-wide association studies are being used to help identify the mechanisms that lead to MS, though scientists hypothesize that, in addition to genetic sequences, epigenetics may play an important role in MS susceptibility. Researchers examined DNA methylation patterns in tissue taken from pathology-free regions of the brain in MS patients and compared them to control brain tissue from healthy subjects. They found that specific genes that affect the survival of oligodendrocyte cells hypermethylated and expressed at lower levels in MS-affected brains than in controls, while genes related to the breakdown of proteins were hypomethylated and expressed at higher levels. The authors found that age and gender have significant impacts on DNA methylation patterns and therefore accounted for these effects in their analyses. Together, these data suggest that MS is associated with molecular changes in DNA methylation, occurring in genes that affect the vulnerability of brain tissue to damage. (Huynh et al., 2014)

Rett Syndrome

A Female Mouse Model of Rett Syndrome. Rett syndrome primarily affects girls and leads to the loss of purposeful hand skills and language, the onset of anxiety, hand stereotypies, autistic features, seizures and autonomic

dysfunction. To investigate the link between MeCP2 gene dysfunction and Rett pathogenesis, preclinical studies have focused primarily on the molecular and behavioral consequences of the complete absence of MeCP2 in male mice. The lack of studies in females is due to variability caused by X chromosome inactivation effects. A group of researchers characterized the behavior and physiology of female MeCP2(+/–) mice using two different mouse strains. They reported that the female MeCP2(+/–) mice show less anxiety behavior, a lower stress response, motor impairments, sensory abnormalities, and altered social behavior and that some of these characteristics present in adulthood, but not at younger ages. The phenotypes identified in these mice reproduce some, but not all, of the features of Rett syndrome. The characterization of these female mice will improve the design and implementation of future preclinical studies. (Samaco et al., 2013)

Stroke

Sex Differences in Quality of Life After Ischemic Stroke. The quality of life (QOL) of stroke survivors may be influenced by patient factors such as age, socioeconomic status, stroke severity, mood, and sex. Several studies have shown that women have worse QOL after stroke than men, particularly in mental and physical function, but these results may be dependent on the timing of assessment. In a recent report, researchers found several sex differences in the demographics and recovery outcomes following ischemic stroke or transient ischemic attack (TIA). Women were older and more likely to be living alone than the men in the study. Men were more likely to have a history of coronary artery disease, a prior myocardial infarction, or dyslipidemia, while women were more likely to have had a TIA. At 3 months following stroke, women had greater disability, more severe depression, and lower QOL due to problems with mobility, activities, pain, anxiety, and depression. At 12 months, women still had lower QOL, but the magnitude of these sex differences was smaller. Future researched focused on how to improve mobility, pain, anxiety, and depression particularly in women could help increase QOL following stroke. (Bushnell et al., 2014)

Dietary Fat Intake and Stroke in Postmenopausal Women. Trans fat intake is thought to increase incidence of cardiovascular disease, but the data on risk for stroke has been inconsistent or incomplete. Data collected from the Women's Health Initiative Observational Study allowed researchers to prospectively examine intake of total and specific types of fat in relation to incidence of ischemic stroke in postmenopausal women, a group that has greater susceptibility to stroke than younger women. They found a positive relationship between trans fat intake and incidence of ischemic stroke. However, use of aspirin abolished the effect of trans fats. Dietary cholesterol and specific types of foods (red meat, dairy, eggs, and others) did not have an impact on risk of stroke. In a second report, the authors investigated individual serum fatty acids for their association with stroke. They found that certain types of trans, saturated, and monounsaturated fatty acids increased stroke risk, while types of polyunsaturated fats were associated with decreased incidence. Overall, limiting the intake of specific dietary fats and using aspirin may be important for primary ischemic stroke prevention in postmenopausal women. (Yaemsiri et al., 2012, 2013)

Funded Projects

All NIH-funded phase III clinical trials are required to include sufficient numbers of males and females to perform an analysis of sex differences in treatment outcomes, when appropriate to the condition under study. NINDS also supports targeted research to understand sex-based differences in neurological disorders and normal behavior, cognition, and perception. Descriptions of basic and clinical research projects underway are highlighted below:

Chronic Pain

Sex Differences in the Dura Mater Related to Migraine. Migraines affect an estimated 18 percent of women, and the causes are not completely understood. Previous research suggests that the source of the pain in migraine is the neurons in the dura, the layer of tissue underneath the skull that protects the brain. The activity of these neurons is sensitive to stress and may also be influenced by sex, since estrogen is known to regulate the blood vessels and the neurons in the dura. New research proposes that factors related to sex and stress interact in the dura and set the stage for a migraine attack. The experiments will examine multiple components of the dura, including immune cells, nerve fibers, and blood vessels, in male and female adult rats following stress. This research may improve our understanding of the dura and potentially discover novel approaches to preventing migraine attacks. (Gold, 2014)

The Role of Neurosteroids in Migraine. Migraine patients often identify specific migraine triggers, including stress, alcohol, diet, the menstrual cycle, and pregnancy. These triggers are also known to increase levels of neurosteroids in the brain. Neurosteroids can be synthesized directly in the brain or from peripherally produced sex steroids and can influence neuronal excitability through modulation of inhibitory neurotransmitters such as GABA. Increased neuronal excitability has been reported in migraine patients. A recently funded project will investigate the mechanisms by which neurosteroids alter excitability and lead to migraine, which could lead to a better understanding of the causes and potential treatments of migraine. (Anderson, 2014)

Epilepsy

Patient-Specific Factors Involved in Placebo Response to Antiepileptic Drugs. Changes to the way adjunctive antiepileptic drug trials are designed and conducted have led to increased response to placebo over time, with peaks as high as 40 percent. High placebo response rates can confound the true treatment effect size, potentially resulting in failure of investigational anti-epileptic drugs to show efficacy. By collaborating with the International League Against Epilepsy and pharmaceutical companies, researchers will conduct a meta-analysis on the factors associated with response to placebo, including patient-related factors such as sex. The results will help inform whether there are sex differences in the placebo response rates and help in the design of more rigorous studies. (Bagiella, 2013)

Estradiol and Seizure Susceptibility. More than one-third of women with epilepsy have a catamenial seizure pattern in which seizures fluctuate with the menstrual cycle. Catamenial seizures are due, in part, to effects of estradiol and progesterone on brain regions involved in seizures, such as the hippocampus. Researchers have previously found that a 24-hour regimen of estradiol treatment has two simultaneous and opposing effects on seizures: it increases seizure susceptibility and, at the same time, decreases seizure severity. Estradiol appears to decrease inhibition in females, but not males, indicating sex differences in the impact of estradiol on the electrical signaling in neurons. Therefore, the researchers will test whether estradiol has different impacts on seizure susceptibility and severity in male and female rats and will investigate which receptors and neurotransmitters are involved in mediating these differences. (Woolley, 1998)

Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD). The MONEAD study has been ongoing since 2000 and has been investigating whether women with epilepsy have increased seizures during pregnancy and determining the contributing factors for this increased susceptibility. The researchers are also studying the long-term effects of antiepileptic drug exposure in utero or through breastfeeding on verbal abilities and other neurobehavioral outcomes in children, among other maternal and child outcomes. In 2014, a supplement was awarded to the investigators in order to study the metabolomics profiles in umbilical cord blood compared to maternal blood. The goal is to classify these profiles at each trimester and correlate them to type and concentration of antiepileptic drugs. With this information, the researchers will identify potential mechanisms of small-at-gestational-age births. (Meador & Pennel, 2000)

Stroke

The Role of Fetal Cells in Stroke Injury and Recovery. The incidence of stroke in women varies across the life span, and pregnancy is a known risk factor for stroke and vascular disease. Events that occur during pregnancy can have lasting implications for both the mother and fetus, yet how these events affect the risk for stroke and stroke recovery are not well-understood. During pregnancy, a woman exchanges cells with the fetus, and a small number of these fetal cells persist in the mother's bone marrow for many years. Recent experimental work shows that fetal cells can also be found in areas of inflammation, including the brain, and that they differentiate into a variety of cell types. However, it is unknown if these cells contribute to the injury or the repair of tissue. New research will examine whether these cells are present in the maternal mouse brain after ischemic stroke and determine if the number of cells has an impact on the extent of injury and recovery. These studies will increase our understanding of the mechanisms of stroke in women. (McCullough, 2014)

Computational Prediction Models for Sex Differences in Cerebrovascular Disease Risk Factors. Computational models can predict the risk of common cardiovascular and cerebrovascular disease outcomes in men and women, based on patient-specific factors. These models have become

increasingly important for clinicians and patients to make evidence-based care decisions. Researchers have compiled almost 800 prediction models that were published in the last 30 years and found that one-third of them included sex as a risk factor or stratification variable. New analyses will provide a comprehensive summary of sex-related differences in cardiovascular and cerebrovascular health outcomes and a basis for evidence-based clinical strategies to improve outcomes for women. This research has the potential to lessen the sex-based disparities in morbidity and mortality rates. (Kent & Neumann, 2014)

Sex Differences in Genetic Correlates of Atherosclerosis. The risk of stroke or myocardial infarction is higher in individuals with progression of subclinical atherosclerosis compared with those with stable plaque or regression. Atherosclerosis is a complex condition with a substantial genetic contribution, and it does not always correlate with traditional vascular risk factors. Researchers are investigating the genetic correlates of atherosclerosis by comparing individuals with no risk factors to those with a high burden of risk factors. Because of the longer life span of women and the increased risk of atherosclerosis after menopause, identifying the genetic and environmental factors associated with stroke in women is an important public health issue. This project will specifically examine the differences in genetic factors of subclinical atherosclerosis between women and men using cohorts from several ongoing studies, including the Northern Manhattan Study and the Family Study of Stroke Risk and Carotid Atherosclerosis. The research will potentially identify novel genetic associations that could inform interventions to reduce sex disparities. (Rundek & Blanton, 2010)

Multiple Sclerosis

The Role of Estrogen in Neural Protection in an Animal Model of MS. The relapse rate of MS decreases during late pregnancy and also after treatment with pregnancy levels of estriol (a form of estrogen), leading to a decrease in lesions in the central nervous system. Low doses of estrogens also have a protective effect in the animal model of MS, experimental autoimmune encephalomyelitis. Researchers will investigate estrogen-mediated regulation of immune cells that leads to protection of neurons, oligodendrocytes, and microglia in the brain. They hypothesize that chronically activated microglia cause the neuronal and axonal degeneration that occurs in progressive forms of MS and that estrogen may be involved in inhibiting these processes. These mechanisms may provide important information for developing new therapies. (Offner, 2013)

Rett Syndrome

MeCP2 Isoforms in Rett Syndrome. Most researchers using animal models to study Rett syndrome use male subjects due to the complications of X chromosome inactivation that occurs in females. Because the disorder exists almost entirely in females, it is important to understand how the MeCP2 mutation impacts the biochemistry and behavior of female subjects. The gene encodes an epigenetic factor that has at least two isoforms and binds to a variety of DNA targets that have a role in neuron development and activity. New research will focus on the most abundant yet understudied MeCP2 isoform, MeCP2e1, to better understand its function in brain development and behavior, specifically in a female model of Rett syndrome. Moreover, the studies will determine if restoring MeCP2e1 back to normal levels improves specific disease phenotypes in these females. The results are expected to produce critical knowledge needed for understanding Rett syndrome and improving treatments. (LaSalle, 2001)

Chronic Fatigue Syndrome

Sex Differences in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex condition that involves multiple systems within the body, including the immune, endocrine, and cardiovascular systems. The condition affects both women and men, though research indicates that 60 percent to 80 percent of the prevalence is in women. Researchers will profile the neuroendocrine factors, immune cell subtypes, and gene expression activation in men and women with ME/CFS during a rest phase and an exercise challenge, with the goal of identifying the irregularities in immune and neuroendocrine signaling that occur in this condition. The investigators expect that the data will allow them to design treatments specific to men and women that are aimed at bringing these systems back to normal. (Fletcher, 2014)

NIH Strategic Plan for Women's Health Research

Highlights

Social and Behavioral Skills in Children Exposed to Antiepileptic Drugs During Development. Primarily addresses Objective 3.4 ("Expand research on pregnancy-related conditions on the subsequent health of women and their offspring"). Also addresses Objective 3.3 ("Expand research on safe and effective interventions for conditions affecting pregnant women").

Antiepileptic drugs potentially influence fetal development throughout the pregnancy and during breastfeeding. The Neurodevelopmental Effects of Antiepileptic Drugs Study, conducted in the United States and the United Kingdom, reported lower adaptive, emotional, and behavioral functioning in 6-year-old children exposed to antiepileptic drugs in utero. Valproate led to worse outcomes than lamotrigine and phenytoin. Children exposed to valproate were at a significantly greater risk for a diagnosis of attention deficit hyperactivity disorder. Awareness of such signs may promote early identification of children at risk. A series of practice parameters on management of pregnant women with epilepsy, issued in 2009 by the American Academy of Neurology and the American Epilepsy Society, identified multiple areas related to clinical management for which evidence was inconclusive or lacking. These areas included rates of obstetrical complications and changes in the frequency of seizures, adverse perinatal outcomes, and rates of teratogenesis (structural and behavioral) for most antiepileptic drugs (AED); in addition, the guidelines noted insufficient data on changes in AED blood levels during pregnancy and on risks of breastfeeding when taking AEDs. (Cohen et al., 2013)

Risk of Blood Vessel Clots Following Pregnancy. Primarily addresses Objective 3.3 ("Expand research on safe and effective interventions for conditions affecting pregnant women"). Also addresses Objective 3.5 ("Identify and validate sex-specific biomarkers for disease risk and prognosis across the life span") and Objective 3.9 ("Examine health disparities among women stemming from race and ethnicity").

The 6-week period following delivery of a baby, the postpartum period, is associated with an increased risk of thrombosis, or clots in blood vessels. The risk for stroke during this period is 3 to 9 times higher than normal. Researchers were interested in learning how long this heightened risk lasts. They found that the risk for thrombosis in the first 6 weeks after delivery was about 11 times higher than it was 1 year later. They also found the risk during weeks 7 through 12 to be about 2 times higher than it was 1 year later. After 12 weeks, the risk was no longer elevated. There was a higher risk during the first 6 weeks after delivery among women who had undergone cesarean section than among those who had undergone vaginal delivery. Finally, the women who had a thrombotic event in the postpartum period were more likely to be White or Black compared with Hispanic or Asian and were more likely to have risk factors for thrombosis. Current guidelines advise that high-risk patients receive prophylactic anticoagulant therapy until 6 weeks after delivery, yet this research indicates that clinicians should be aware that the risk remains increased for at least 12 weeks. (Kamel et al., 2014)

Women's Health Research Coordination at NINDS

Women's health research at NINDS is covered across a number of extramural research clusters, or teams of program directors organized around scientific and disease areas. The Office of Clinical Research oversees and tracks recruitment of women and minorities in clinical trials. In addition, NINDS actively participates in NIH women's health research initiatives by designating a program director as the Institute's primary representative to the NIH Coordinating Committee on Research on Women's Health.

Inclusion

The following processes are used at NINDS to address inclusion of women in clinical research. During the peer review process for grant applications, the inclusion plan for clinical research is examined. Phase III clinical trials are required to have inclusion analysis plans to inform enrollment targets. Peer reviewers assess the inclusion plans, and prior to each council meeting, program directors examine the reviewers' comments on unacceptable inclusion goals and resolve issues in writing with the investigators. Program directors also review enrollment data submitted in the annual progress reports and determine whether the enrollment targets for gender inclusion are scientifically

appropriate. The NIH Inclusion Monitoring System allows access to Institute records and cumulative reports, enabling program staff to track enrollment data. At NINDS, the Office of Clinical Research provides oversight on gender tracking activities by assisting program staff and grants management as needed, including issues on tracking exemptions, and making any necessary changes to the tracking codes in the population tracking database.

Science, Technology, Engineering, and Mathematics Efforts

Research Findings

Impact of Workplace Culture on Women's Career Success. Workplace culture can have a negative impact on women's career success in academic medicine. Recently, researchers developed a construct to define and measure academic workplace culture and identified four dimensions of the culture that influence career success. The dimensions include equal access, work-life balance, freedom from gender biases, and supportive leadership. The authors developed a tool to measure these dimensions and administered the tool to 133 women assistant professors at the University of Pennsylvania. They found evidence that women within departments/divisions agree on the supportiveness of their units but that substantial differences among units exist. The analyses provided strong evidence for the reliability and validity of their measure. This research provides a tool that future researchers can use to evaluate the effectiveness of interventions designed to increase the supportiveness of the environment for women faculty. (Westring et al., 2012)

Initiatives

NINDS Diversity Research Education Grants in Neuroscience (R25), PAR-13-256. Seeks to support the development and implementation of programs to increase the number of graduate, postdoctoral, and junior-faculty career level research scientists from diverse backgrounds in the neuroscience workforce.

Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Supplement), PA-12-150. These supplements support individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. Sponsored by ORWH and many ICs.

Research Supplements to Promote Diversity in Health-Related Research (Supplement), PA-12-149. These supplements seek to improve the diversity of the research workforce by supporting and recruiting students, postdoctoral fellows, and eligible investigators from groups that have been shown to be underrepresented in health-related research. This supplement opportunity is also available to program director(s) and principal investigator(s) of research grants who become disabled and need additional support to accommodate their disability in order to continue to work on the research project. Sponsored by many ICs.

Funding Initiatives, Workshops, and Conferences

Initiatives

The BRAIN Initiative (U01), RFA-NS-14-007, RFA-NS-14-008, RFA-NS-14-009. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative[SM] is part of a new Presidential focus aimed at revolutionizing our understanding of the human brain. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. NINDS and the National Institute of Mental Health issued funding initiatives for BRAIN that were cosponsored by many ICs and ORWH. In FY 2014, the first grants were awarded in this groundbreaking neuroscience initiative, an investment that will enable studies of not only brain circuit dysfunction in diseases that affect women but also gender differences in brain function.

Mechanisms, Models, Measurement, and Management in Pain Research (R01, R03, R21), PA-13-117, PA-13-118, PA-13-119. Seeks proposals to investigate the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two, as well as proposals that link such understandings to the development of better

approaches to therapeutic interventions. Interdisciplinary and multidisciplinary scientific teams are strongly encouraged, as is research from underrepresented, minority, disabled, or women investigators. Issued by NINR. Co-funded by 11 other ICs in the Pain Consortium.

Neurobiology of Migraine (R01, R21), PA-14-068, PA-14-069. Encourages innovative research that will expand our current knowledge of neurobiological mechanisms underlying migraines, examine the role of neuromodulators, study genetic and environmental influences in migraine susceptibility, and explore new targets for therapy development. Issued by NINDS. Co-funded by 5 ICs.

Chronic Overlapping Pain Conditions (R01, R21), PA-14-243, PA-14-244. Encourages epidemiological, clinical, and translational research that will increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors responsible for the presence of multiple chronic pain conditions. Issued by the NIH Pain Consortium.

Workshops and Conferences

Society for Academic Emergency Medicine Conference: Gender-Specific Research in Emergency Care: Investigate, Understand, and Translate How Gender Affects Patient Outcomes, May 13, 2014, Dallas, TX. This conference convened a diverse group of researchers, clinicians, health care providers, patients, and representatives of Federal agencies and policymakers. The main aims were to (1) summarize and consolidate current data related to sex- and gender-specific research for acute care and identify critical gender-related gaps in knowledge to inform an emergency medicine research agenda; (2) create a consensus-driven research agenda that advances sex- and gender-specific research in the prevention, diagnosis, and management of acute diseases and identify strategies to investigate them; and (3) build a multinational interdisciplinary consortium to disseminate and study the sex and gender medicine of acute conditions. NINDS supported this conference (R13NS087861).

http://www.saem.org/research/meetings/past-annual-meetings/2014-aem-consensus-conference

The consensus-building workshops at the conference developed recommendations for priority research in seven clinical domains identified as key to gender-specific emergency care: cardiovascular, neurological, trauma/injury, substance abuse, pain, mental health, and diagnostic imaging. The results of the conference, including the research priorities, were published in a special issue of the journal *Academic Emergency Medicine* (Vol 21, Issue 12, Dec 2014).

8th Annual NIH Pain Consortium Symposium on Advances in Pain Research: Integrated Self-Management Strategies for Chronic Pain, May 29–30, 2013, NIH, Bethesda, MD. The symposium discussed the current state and future challenges for self-management (SM) of pain conditions. The focus areas were community health care settings, tailored strategies for patients and caregivers, and predictors of outcomes in integrated SM strategies.

9th Annual NIH Pain Consortium Symposium on Advances in Pain Research: Biological and Psychological Factors that Contribute to Chronic Pain, May 28–29, 2014, NIH, Bethesda, MD. The symposium focused its sessions on depression, sleep disorders, and inflammation, and the intersection of these disorders with pain.

Health Disparities

Research Findings

Perceptions of Emergency Medical Care for Stroke. African-Americans receive acute stroke treatment less often than non-Hispanic Whites, indicating cultural or race-related barriers to seeking care. Researchers used a community-based participatory approach to conduct a qualitative study exploring perceptions of emergency medical care and stroke among urban African-American youth and adults. The focus group participants were primarily women (64 percent of youth and 90 percent of adults). Three themes emerged: (1) recognition that stroke is a medical emergency, (2) perceptions of difficulties within the medical system in an under-resourced community, and (3) need for greater stroke education in the community. These findings help to identify the barriers to calling 9-1-1 and can inform the design of behavioral interventions to increase stroke literacy, preparedness, and use of emergency care. (Skolarus et al., 2013)

Racial Disparities in Pain Perception and Empathy. Previous studies suggest that African-Americans receive less treatment for pain than European-Americans, and

this may be related to bias in the clinician perception and response to the patient. Researchers examined whether bias was explicit or implicit by using a technique called racial priming, in which the subject is rapidly shown a Black or White face prior to testing. They also tested whether the race of the perceiver played a role in response to another person's pain. European-American subjects had a greater response and empathy towards European-Americans than African-Americans when the race of the "patient" was implicit (i.e., not consciously detectable). When the race of the patient was explicit, European-Americans responded more favorably towards African-Americans. Female participants perceived and responded more to the pain of all patients compared with male participants. These data contribute to our understanding of how patient race-relevant cues may trigger clinicians' consciously held beliefs and automatic associations, which may differentially affect perception, diagnosis, and treatment of pain. (Mathur, Richeson, Paice, Muzyka, & Chiao, 2014)

Post-Stroke Cognitive Decline in Mexican-Americans. Following stroke, cognitive outcomes may be worse in women than men, and it is unknown whether this gender difference is dependent on race. Researchers examined Mexican-Americans prior to and following stroke to assess blood pressure and cognitive function. Among a population of older Mexican-Americans in the Sacramento area, researchers found dramatic declines in global cognitive scores after stroke in both women and men, but the magnitude of change did not differ by gender. There was no influence of blood pressure on post-stroke cognitive decline in women or men. (Levine et al., 2013)

Reasons for Geographic and Racial Differences in Stroke (REGARDS). The NINDS-funded REGARDS study is an observational study with more than 30,000 participants, 59 percent of them women, that is exploring the role of geographic differences in determining the prevalence of risk factors for stroke, stroke incidence, and stroke mortality. The study is also exploring race, gender, genetics, and lifestyle choices as risk factors for stroke. In the 2013–2014 period, the REGARDS investigators published more than 90 reports on the cohort; most of the publications included male/female analysis. Recent analyses in REGARDS showed that intake of trans fatty acids increase the risk of stroke in men, but not women, in contrast to the studies cited above from the Women's Health Initiative. Other reports on risk factors for stroke and cardiovascular outcomes revealed sex- and race-specific findings. For example, refractory hypertension and inadequate blood pressure control, both risk factors for stroke and coronary heart disease (CHD), were more common in males and blacks. Furthermore, the incidence of CHD was higher in men than women and higher in Blacks than Whites. (Kiage et al., 2014; Calhoun et al., 2014; Cummings et al., 2013; Safford et al., 2012)

Funded Projects

Stroke Literacy and Intent to Call 9-1-1 in Adult Black Women. Researchers developed a behavioral intervention designed to improve stroke literacy and behavioral intent to call 9-1-1 in a population of Black, churchgoing adults. The intervention is 12-minute video that also addresses other stroke-related behaviors, including medication compliance, diet, and physical activity. Due to previous research suggesting sex disparities in stroke symptoms, arrival time at the hospital, and recovery outcomes, the researchers hypothesized that women may require tailored interventions. Therefore, they created a supplemental 6-minute film targeted specifically to women and will analyze the impact of the targeted film relative to the original, gender-neutral designed film. The findings will identify women-specific barriers to calling 9-1-1 for acute stroke. (Ogedegbe & Williams, 2012)

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National Institute of Nursing Research

Executive Summary

The National Institute of Nursing Research (NINR) supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and enhance end-of-life and palliative care. Confronting these issues requires a shift to a patient-provider partnership paradigm that is increasingly person-centered rather than disease-oriented, that focuses on preventing the development of chronic illness rather than treating it, and that features the person as an active participant in his or her own health. The Institute's multi- and interdisciplinary scientific approach unites the biological and behavioral sciences to better understand the complex interactions between the physiological factors of health and disease and the knowledge, beliefs, and behavior of the individual, family, and community. Across all scientific programs, NINR's research addresses the special needs of at-risk, vulnerable, and underserved populations with particular emphasis on eliminating health disparities and promoting health equity.

NINR's research portfolio is ideally suited to explore some of the most important challenges affecting the health of women, including the following:

- Growth of an aging female population faced with chronic diseases requiring complex management;
- Growth of diverse populations of women from different racial and ethnic backgrounds and the associated issues of health disparities in these at-risk, underserved populations;
- Symptom management for chronic conditions such as diabetes;
- Health promotion and disease prevention through management of physical activity and obesity; and
- The need to build a cadre of next-generation scientists in women's health research.

In advancing the science of women's health, NINR funds and co-funds programs of research with specific attention to issues surrounding pregnancy, aging and menopause, chronic conditions, health disparities, and the promotion of women in research. Central to the themes within its strategic plan, NINR seeks to strengthen research specific to women, whether as patients, caregivers, or community members. The Institute actively ensures that diverse populations of women are represented in its studies and that disparities experienced by women in minority, rural, immigrant, and other

underserved populations are addressed. NINR-supported investigators have contributed to new knowledge by addressing women's health across the life span. Numerous findings during FYs 2013 and 2014 have furthered understanding of issues uniquely relevant to women's health, including the following:

- Chronic and life-limiting conditions, including irritable bowel syndrome and cancer;
- Promotion of healthy physical and dietary lifestyles to prevent obesity, diabetes, and heart disease;
- Aging and menopause;
- Pregnancy, perinatal period, preterm birth, and postpartum depression; and
- HIV risk reduction in adolescent girls and young women.

Today's challenges in the field of women's health present opportunities for NINR to further expand its impact on the health of the Nation. The Institute will continue to support innovative studies in areas highlighted in its strategic plan, and results from these studies will inform future strategies that will advance women's health in the future.

NINR and Women's Health

NINR is committed to supporting science that addresses women's health. The Institute has supported a wide range of women's health research that has led to scientific advances in our understanding and treatment of conditions and diseases that impact women primarily and others that affect women in different ways than men. This research occurs through grants to individual researchers, collaborative groups, multi-site projects, and research centers, as well as through training grants, all working to develop not only the evidence base for improvements in women's health but also the body of researchers examining symptoms and conditions that affect women across the United States and the world.

For example, NINR is funding the University of Michigan's participation in the long-term, multi-site Study of Women's Health Across the Nation (SWAN). In addition to collecting data for SWAN studies, the University of Michigan site serves as the project's central hormone laboratory and biorepository. This longitudinal, prospective, epidemiological study of the menopausal transition, which is co-funded by the National Institute on Aging and ORWH, has been examining and tracking the health changes in a multi-ethnic cohort of middle-aged women for 20 years as they age and experience menopause. The current phase of the project extends the investigation to late menopause. SWAN is the most comprehensive analysis of the health and the physiological and psychosocial changes of women from pre- to postmenopause in community-based samples, providing a broad and deep perspective of the aging process in women.

Accomplishments and Activities

NINR's research portfolio emphasizes clinical research on promoting health and quality of life for individuals across the life span, from the perinatal period to the end of life. This is illustrated by the following recent research accomplishments and activities.

Chronic and Life-Limiting Conditions

Characterization of Symptom Clusters in Breast Cancer May Guide Treatment Strategies. Treatment of concurrent and interrelated symptoms (symptom clusters) as a group may yield better outcomes than targeting individual symptoms. Over the course of radiation and chemotherapy in breast cancer treatment, five temporal patterns of five symptoms (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) emerged. These patterns included, for example, moderately stable levels of symptoms, gradually increasing levels, and decreasing levels from a high baseline. Characterization of these patterns may facilitate personalized interventions. (Kim, McDermott, & Barsevick, 2014)

A Tool to Measure Breast Cancer Literacy Could Mitigate Some Health Disparities. Breast cancer patients from minority populations may face disparities in health care due to difficulties in understanding complex health information. Current measures of health literacy to bridge these gaps are not sensitive to cultural and language differences among the target populations. A new tool has been developed and tested in African-American, Arab American, and Latina cohorts and has been shown to be effective for measuring functional health literacy, specific to breast cancer, in a diverse community sample. (Williams, Templin, & Hines, 2013)

The Effects of Alcohol Consumption on Irritable Bowel Syndrome Symptoms. Irritable bowel syndrome (IBS) is a debilitating, chronic condition that affects approximately 20 percent of the U.S. population, with a significantly higher prevalence in women than men. Patients frequently adjust their diets to reduce the occurrence of IBS symptoms; however, a study of alcohol consumption showed no differences between drinking habits of women with IBS and those who did not have the condition. Moderate and light drinking did not result in a marked change in IBS symptoms the following day. However, there was a strong association between binge drinking and subsequent IBS symptoms, which may be linked to gut physiology changes in patients who are habitual heavy drinkers. (Reding, Cain, Jarrett, Eugnio, & Heitkemper, 2013)

NINR grant activities in chronic and life-limiting conditions in 2013–2014 included the following:

- R21NR014318: Integrating Palliative Care Into Self-Management of Breast Cancer
- R00NR012232: Investigating the Role of a Lifestyle Intervention on Novel Estrogen Biomarkers
- K01NR013478: Social Context and Inflammatory Risk for Stroke in African-American Women
- F31NR014066: Development and Validation of a Measure of Self-Advocacy in Female Cancer Survivors
- F31NR014754: Emotion Regulation in African-American Women with Heart Failure
- F31NR014399: Predictors of Disability in Older African-American Women with Osteoarthritis

Aging and Menopause

As part of its research portfolio that focuses on the entire life span, NINR devotes significant efforts to studying the needs of the aging population, including issues specific to women. Some of the recent research accomplishments and efforts arising from SWAN study include the following highlights.

Modifiable Factors Can Affect the Menopausal Age and Health. Women who experience their final menstrual periods at a later age than the median 52.5 years have longer life spans and lower rates of all-cause mortality, cardiovascular disease, and orthopedic conditions, such as osteoporosis and fractures, but higher rates of breast, ovarian, and endometrial cancer. The older age of the final menstrual period is not linked to race or ethnicity, but it is associated with social determinants and modifiable factors such as more formal education, prior oral contraceptive use, better self-reported health, continued employment, more alcohol consumption, not smoking, and lower levels of physical activity. (Gold et al., 2013)

A Complex Picture of the Influence of Obesity on Fracture Risk. A lower risk of fractures has been predicted for obese pre- and perimenopausal women because the greater weight they bear contributes to higher bone mineral density (BMD); however, their higher rates of type 2 diabetes and chronic inflammation are associated with higher risk of fracture and reduced bone strength. The increased force impact of falls in obese women may outweigh the protective potential of higher BMD, but soft tissue padding may cushion falls and absorb impact. (Ishii et al., 2014)

The Association of Hot Flashes with Weight Can Vary Over Menopausal Stages. Many women entering menopause are overweight or obese, so vasomotor symptoms such as hot flashes and night sweats have been linked to their adipose (fat) tissue and the interplay of molecular messengers produced by adipose tissue. These messengers, known as adipokines, include adiponectin (which is found at lower levels in obese women) and leptin (which is found at higher levels in obese women). In premenopausal and early menopausal women, higher levels of adiponectin are associated with a lower risk of hot flashes, and higher levels of leptin are associated with a higher risk of hot flashes. Hot flashes are more common in overweight and obese women in the early stages of menopause. These associations between weight or adipokines and hot flashes were not seen in the later stages of menopause or postmenopause, although extra weight may be protective against hot flashes in late menopausal stages. (Thurston, Chang, Mancuso, & Matthews, 2013)

Beyond SWAN, NINR also supported other research programs on aging and menopause, as detailed below.

Factors Associated with Midlife Onset of Urinary Incontinence in Women. The incidence of urinary incontinence increases in older adults, but certain groups of healthy women in their 40s and early 50s develop urge incontinence (resulting from a full bladder) or stress urinary incontinence (accompanying coughing or

sneezing). Worse perceived health and a history of three or more live births were common characteristics in these women. In addition, Caucasian women in this age group were more likely to have stress urinary incontinence than African-American women. Older age and high body mass index were associated with an increased risk for urge incontinence. (Mitchell & Woods, 2013)

Factors Affecting Balance Confidence in Older Women. Falls in older adults can have severe health consequences, but fear of falling, including balance confidence, can lead older women to curtail their activities, with debilitating effects on their physical, functional, and psychological condition. Identification of contributors and predictors of decreasing balance confidence will inform interventions to mitigate falls and disability. Declines in balance confidence over 2 years were associated with poor balance and hip flexion strength, urological disorders, increasing mobility limitations and activity restrictions, and decreasing physical activity and social networks. (Talley, Wyman, Gross, Lindquist, & Gaugler, 2014)

In 2013 and 2014, NINR funded the following grants:

- R01NR012256: Comparing Interventions to Improve the Well-Being of Custodial Grandfamilies
- K23NR014008: Cognitive Behavioral Therapy for Insomnia and Nocturnal Hot Flashes in Menopause
- R01NR012011: Translating Unique Learning for Incontinence Prevention: The Tulip Project
- R01NR013959: Behavioral Treatment of Menopausal Insomnia: Sleep, Depression, Daytime Outcomes
- R01NR015029: Bone-Loading Exercises Versus Risedronate on Bone Health in Post-Menopausal Women
- R01NR013913: Efficacy of a M-Health Self-Management Intervention
- U01NR004061: Study of Women's Health Across the Nation (SWAN V): Michigan Site

Pregnancy, Childbirth, and Perinatal Health

Health issues during pregnancy and the perinatal period comprise a significant part of NINR's research portfolio in women's health. NINR investigators continue to make significant contributions to improving pregnancy outcomes and improving the health of mothers and their children.

Variation in Gene Modifications Associated with Preeclampsia in Caucasian and African-American Women. Endoglin is a cell membrane protein involved in a cellular signaling pathway that contributes to vascular integrity. As a result, endoglin can affect uterine tissue and implantation. Endoglin gene expression is elevated during pregnancy in women who develop preeclampsia. Endoglin gene variants were found in Caucasian women with preeclampsia, along with modifications in genes for other proteins in the endoglin signaling pathway. African-American women with preeclampsia had variations in many more genes in the endoglin signaling pathway, but not in the endoglin gene itself. These findings suggest that there are different biological mechanisms underlying preeclampsia in Caucasian and African-American women. (Bell et al. 2013)

Environmental Factors Associated with Prenatal Posttraumatic Stress Disorder in Native Hawaiian/Pacific Islander Women. Pregnant women have a higher rate of posttraumatic stress disorder (PTSD) than the general population. Interpersonal violence is a significant risk factor for prenatal PTSD, which has a more significant negative effect on low-income, minority women than other socioeconomic categories. The majority of a sample of low-income, pregnant Native Hawaiian/Pacific Islander women had experienced interpersonal violence, but not all developed PTSD. Factors associated with prenatal PTSD in this cohort included depression, lack of family support, stress in significant familial relationships, and violent experiences within the community. Identification of these factors can guide interventions for prenatal PTSD in low-income Native Hawaiian/Pacific Islander women. (Dodgson, Oneha, & Choi, 2014)

Nighttime Breastfeeding Contributes to Better Sleep for New Mothers. Sleep is a precious commodity for new mothers. A cohort of first-time mothers had equivalent sleep length in the last trimester of pregnancy, but those who breastfed exclusively slept an average 30 minutes longer at night than women who included formula in their feedings. Hence, an emphasis on breastfeeding shortly after birth may improve mothers' nighttime sleep quality. (Doan, Gay, Kennedy, Newman, & Lee, 2014)

New Mothers with Traumatic Histories Are at Risk for Postpartum Problems. Pregnant women and new mothers who experience PTSD or childhood maltreatment, including physical or sexual abuse, face increased risk of postpartum depression or problems in bonding with their newborn children. These situations, in turn, can lead to childhood and adult psychological trauma in the subsequent generation. Interventions can be targeted to pregnant women with these predisposing risk factors to interrupt the cycle of depression and abuse. (Seng et al., 2013)

Human Milk Can Improve Health and Cost Outcomes in Very Low Birth Weight Infants. Sepsis occurs in a significant (22 percent) number of very low birth weight infants in the United States. Neonatal intensive care unit (NICU) costs for these babies are very high, and survivors often suffer from other debilitating health conditions, including neurodevelopmental issues. A study found that feeding human milk, which contains high concentrations of protective factors, to very low birth weight infants in their first month decreases their chances of developing sepsis and, as a result, decreases NICU costs. These effects were dose-dependent, so the risk of sepsis and associated NICU costs decreased as the amount of human milk increased. (Patel et al., 2013)

In addition to these advances, NINR supported the following grants during 2013–2014:

- R01NR014851: A Novel Pregnancy Prevention Intervention for Latino Middle School Girls
- R01NR014784: Revealing the Role of the Cervico-Vaginal Microbiome in Spontaneous Preterm Birth
- R01NR014800: Biobehavioral Determinants of the Microbiome and Preterm Birth in Black Women
- R01NR013662: The Effectiveness of Non-Pharmacological Treatment for Perinatal Insomnia
- R01NR014826: Influence of Modifiable Factors on the Vaginal Microbiota and Preterm Birth
- R01NR013661: Maternal Stress, Obesity, and Influenza Virus Vaccine Immunogenicity in Pregnancy
- R01NR014540: RCT of a Tailored Walking Program to Reduce Stress Among Pregnant Women
- R01NR014792: A Multiomics Approach Towards Deciphering the Influence of the Microbiome on Preterm Birth
- R01NR014245: Informing Evidence-Based Maternal Weight Gain Guidelines for Twin Pregnancies
- R03NR013961: Localizing Maternal and Fetal Message in Translation of Preeclampsia Candidate Genes
- R21NR014413: Integrating HIV with Innovative Group Antenatal Care in Two African Countries
- R00NR013187: Sleep-Related Determinants of Gestational Diabetes
- F31NR014605: Pathways to Shortened Gestation Among Black Women
- F31NR015010: Determinants of Infant Feeding Practices Among HIV-Positive Mothers in Ethiopia
- F31NR014061: Comparative Effectiveness of Labor Management in Obese, Nulliparous Women
- F32NR014622: Mechanisms Modulating the Association Between the Eng Pathway and Preeclampsia
- F31NR014094: Risk Factors Associated with Unintended Pregnancies

Obesity, Physical Activity, and Disease Prevention

While obesity is a health problem for both genders, women suffer a disproportionate burden of disease due to overweight and obesity. The prevalence of female obesity in the United States is high, with around 64 percent of adult women being overweight or obese. Obesity is more prevalent in minority communities, with between 75 percent to 78 percent of African-American and Hispanic women either overweight or obese. Furthermore, the link between female obesity and diabetes is more pronounced than in men. Obesity is also a risk factor for a number of chronic conditions, including heart disease, stroke, high blood pressure, breathing problems, arthritis, depression and some cancers (including but not limited to endometrial cancer, cervical cancer, breast cancer, and ovarian cancer). Maternal obesity also has profound impacts on infants and children. Finally, obesity is often found along with other chronic conditions, which make physical activity difficult. Nurse scientists have been at the forefront of some of the public health efforts to address the obesity epidemic through community- and clinically based research,

especially within medically underserved and minority communities. Findings in this area from NINR-supported scientists in 2013–2014 included the following:

Teenage Girls Improve Their Eating Habits with Internet Obesity Prevention Programs. More and more adolescents in the United States are becoming overweight and obese, particularly in African-American and Latino populations. These excess pounds can lead to debilitating physical and psychological conditions, so adolescence is a critical time for nutritional and lifestyle education and intervention. Teenage girls who participated in Internet-based obesity prevention programs for adolescents showed significant improvement over 6 months in breakfast habits and reducing junk food consumption, as well as better exercise and other eating habits. These obesity prevention programs include goal setting, self-monitoring, health coaching, social networking, and lessons in nutrition, metabolism, portion control, and physical activity. The Internet format is low-cost, easily distributed, and appealing to young people. (Whittemore, Jeon, & Grey, 2013)

Excessive Weight Gain During Teen Pregnancy Remains Many Years Later. A high percentage of low-income African-American women who gave birth for the first time in adolescence gained excessive (more than 30 pounds) weight during their first pregnancy. More than half of the girls who were overweight or obese before conception gained excessive weight during their first pregnancy. They continued to be overweight or obese 12 and 18 years later, putting them at risk for multiple negative health outcomes while still in their 30s; however, excessive weight gain over time was not a significant characteristic among women who smoked heavily. Pregnant, low-income African-American adolescents are a key target population for interventions to prevent excessive gestational weight gain. (Groth, Holland, Kitzman, & Meng, 2013)

Improvements in Adult Latinas' Physical Activity with Tailored Interventions. Adult Latinas in the United States have lower rates of physical activity than their non-Latina Caucasian counterparts, which likely contributes to high rates of type 2 diabetes and obesity. Previously inactive Latinas who followed a tailored intervention increased their physical activity significantly over 6 months. Positive outcomes in behavioral and cognitive measures suggest that these women will be able to maintain their new levels of physical activity. The intervention included printed Spanish-language physical activity manuals and tip sheets that could be disseminated widely to reach populations with poor access to wellness programs. (Marcus et al., 2013)

Distance Learning Interventions Improve Blood Pressure, Diet, and Physical Condition in Rural Women. Heart disease is the leading killer of women, yet women are frequently unaware of their blood pressure, an important indicator of prehypertension. Rural women in the United States are at particular risk for hypertension due to high rates of abdominal obesity, diet, low rates of physical activity, and less access to health care and preventive health resources in comparison with urban women. An intervention was tested in rural, middle-aged women that included education about hypertension and prehypertension, goal-setting, and personalized (Web-based, or printed and mailed) instructions about healthy eating and activity and self-monitoring of activity, diet, and blood pressure. After 12 months, there were notable decreases in blood pressure in the cohorts receiving Web-based or printed instructions in comparison with the group receiving a single educational and goal-setting session. After 24 months, there were significant reductions in waist circumference and improvements in the women receiving the intervention. (Hageman, Pullen, Hertzog, & Boeckner, 2014)

NINR supported research grants in FY 2013–FY 2014 related to obesity, physical activity, and women's health, including the following:

- R01NR010589: Web-Based Weight Loss and Weight Maintenance for Older Rural Women
- R01NR011323: Kin Keeper: Reducing Disparities Through Cancer Literacy and Screening
- R03NR014329: Development and Evaluation of a Physical Activity Intervention for Latina Girls
- K23NR014661: Understanding Social Networks and Obesity-Risk Behaviors Among Black Women
- K01NR013195: Personalized Bio-Behavioral Weight Loss Intervention for African-American Women
- F31NR014960: Mother-Daughter Relationship Influences on Daughters' Dietary Practices

Inclusion: Sex/Gender Analysis at NINR

NINR has funded and continues to support a number of studies that are specifically designed to analyze gender differences in symptoms, responsiveness to treatment, or impact of chronic conditions on quality of life. These studies underscore the need to include women in clinical research and clinical trials, as women often respond to medications and other therapies differently than men; women have historically been excluded from clinical research studies and pharmaceutical development. Examples of research focused on sex/gender differences include the following:

Stress and Coping Can Affect Long-Term Outcomes of Heart Transplantation. Outcomes following heart transplantation are influenced by patients' stress factors and coping skills. In the first 5 years after transplant, female recipients are more likely than male recipients to experience more intense stress and to rely on negative coping strategies, such as denial, avoidance, fatalism, and emotions. Monitoring female transplant patients for these risk factors and providing support services may improve long-term outcomes. (Grady et al., 2013)

A Potential Biomarker for Patients at Risk for Sepsis. C-reactive protein (CRP) is a biomarker for several conditions, including cardiovascular disease and stroke and, potentially, sepsis. A sample of women at risk for sepsis had twice the levels of CRP in their blood than men in the same risk category, which could be used to target sepsis prevention strategies. (Wang et al., 2013)

Initiatives

In addition to supporting investigator-initiated research focused on women's health, NINR has sponsored or co-sponsored several funding opportunity announcements focused on this area of science. A few examples are described here:

- **Maternal Nutrition and Pre-Pregnancy Obesity: Effects on Mothers, Infants, and Children.** NINR cosponsors this initiative with the NIH Office of Dietary Supplements to fund interdisciplinary research on maternal nutrition and pre-pregnancy obesity in mothers and their children. Obesity in pregnancy has profound impacts on fetal development and post-birth health status and development in children, and also is a contributing factor in poor maternal outcomes such as gestational diabetes, pregnancy-induced hypertension, preeclampsia and eclampsia, and venous thromboembolism. Obesity can also lead to a higher rate of instrumental delivery and cesarean section, and longer postpartum hospital stays compared to non-obese women. [PA-15-100]
- **The Influence of the Microbiome on Preterm Labor and Delivery.** NINR sponsored this initiative, which leveraged the efforts of NIH's Human Microbiome Project, including research that found that a shift in bacterial species occurs in women during pregnancy. In some cases, these changes in resident bacteria could contribute to preterm labor and delivery. This initiative encouraged the use of genetic, epigenetic, and genomic analysis to understand the influence of the microbiome on preterm labor and delivery. [RFA-NR-13-002]
- **Administrative Supplements for Research on Sex/Gender Differences.** NINR participated in this supplement program to support the examination of sex/gender differences or similarities through the inclusion of additional subjects in a study to examine if sex/gender differences exist in the experience of a disease or condition, or in response to therapies. [PA-13-018]

Women's Health, Health Disparities, and Special Populations Research

The investigation and elimination of health disparities is a major area of research emphasis throughout NINR's research portfolio. Special populations addressed in NINR-supported research include rural women, racial and ethnic minority adolescents and women, and women in poverty. NINR's training portfolio also reflects a special emphasis on health disparities, supporting the education and development of the next generation of nurse scientists focused on health disparities. Examples of NINR-supported women's health research findings and current efforts focusing on health disparities and/or special populations are presented below.

Health Disparities

Type 2 diabetes is growing problem worldwide, and minority populations in the United States are affected by the condition disproportionately in terms of prevalence and complications. Self-management of the disease is complex and burdensome, especially for patients with socioeconomic disadvantages, so self-management is an important target in addressing health disparities in minority diabetes patients. Examples of research on this topic include the following:

- **The Role of Spirituality for African-Americans with Type 2 Diabetes.** Middle-aged African-Americans with severe complications from type 2 diabetes are faced with significant challenges in self-management of their conditions. Spirituality helps them to cope with the stress of their disease and the burden of self-care and is associated with better foot care and dietary control. A study found that among women in this patient group, social support from the religious community was associated with ability to adhere to a diabetes-specific diet. These findings indicate that patient spirituality and social support are important factors in self-management interventions for African-Americans with type 2 diabetes. (Watkins, Quinn, Ruggiero, Quinn, & Choi, 2013)
- **Addressing Health Disparities in Korean Immigrants with Diabetes.** Korean immigrants with type 2 diabetes experience health care disparities due to lack of insurance, language barriers, and cultural issues, such as the social stigma created by dietary restrictions. A study found that female Korean immigrants with diabetes may neglect self-management of their conditions by giving priority to household and caregiving duties. Increasing diabetes awareness in the community, including the entire family in discussions of diabetes self-management, and providing translation services in the health care setting are important topics in addressing health disparities in this patient population. (Nam, Song, Park, & Song, 2013)

NINR-supported grants in FY 2013 and FY 2014 exploring the health of minority women and adolescents included the following:

- R01NR011589: Injury in Latina Women After Sexual Assault: Moving Toward Health Care Equity
- F31NR011106: Skin Elasticity and Skin Color: Understanding Health Disparity in Sexual Assault
- F31NR013326: East African Immigrant Females: Adolescent Developmental Protective/Risk Factors

HIV/AIDS and Sexual Health

Globally, women account for 25 percent of all new cases of HIV, while the proportion of AIDS diagnoses reported among women have more than tripled since 1985. In the United States in 2009, 64 percent of women diagnosed with HIV were African-American. All told, African-American and Hispanic women constitute 26 percent of the female population in the United States, but they account for a disproportionate 82 percent of AIDS cases among women. NINR has supported a number of studies examining HIV/AIDS experiences and interventions to improve the quality of life of HIV-positive individuals, especially women. Findings in 2013 and 2014 include the following:

Addressing HIV and Other Health Risks Associated with Sexual Activity in Adolescent Girls. Adolescent girls (ages 15–19) are at greater risk for contracting HIV through sexual activity than adult heterosexual males, for biological (e.g., prior sexually transmitted infections [STIs], changes in genital physiology) and behavioral (e.g., immaturity) reasons. Girls in this age group with male partners older than them were more likely than girls with same-age partners to be sexually active at a young age, to have more incidents of STIs, and to engage in risky behavior, such as unprotected sex and binge drinking (Morrison-Beedy, Xia, & Passmore, 2013). Training girls in sexual risk reduction strategies that were tailored to gender, developmental, and cultural perspectives, rather than a general health promotion program, resulted in significantly greater use of sexual risk reduction methods in practice. (Morrison-Beedy, Crean, Passmore, & Carey, 2014)

A Youth Development Intervention for Adolescent Girls Influences Responsible Sexual Behavior. A youth development intervention for adolescent girls at high risk for pregnancy focused on healthy relationships, interpersonal and social-emotional skills, and responsible sexual behavior (e.g., contraception use), in both group and one-on-one counseling sessions. Girls in the intervention group were more likely to refuse unwanted sex and to use condoms, hormonal contraception, or both consistently in comparison with girls in the control group. Those receiving

the intervention were less likely to participate in sex for exchange of material items, and they reported greater family connectedness. (Sieving et al., 2013)

Interpersonal Communication and Mass Media Influence HIV Risk Perception in College Women. Unprotected sex is also a primary HIV and STI risk factor for the next age group of young women, up to age 24. College women's perception of HIV risk was greatly influenced by educational information available through mass media, such as the Internet, as well as by discussions with parents. However, these women—particularly Hispanic and African-American college women—have more communication with their partners than with their parents about sexual risk behavior, although these discussions may not be protective against HIV and STIs. Particular types of media exposure increase college women's communication with parents and partners about sexual risk behavior, such as popular television programs; magazine, Internet, and newspaper stories; and radio messages about condom use. (Chandler et al., 2013)

Young Women's Perceptions About Genital Herpes. A study exploring young women's knowledge of STIs recruited women (ages 18–24) from a university and from public health clinics. Study participants predicted that receiving a diagnosis of genital herpes would have significant psychosocial effects, such as shame, embarrassment, depression, and significant worry over informing current or future intimate partners; 15 percent of the women in the cohort believed that herpes infections were lethal. A large percentage held misconceptions about genital herpes that could put them at risk for contracting or transmitting the disease. These findings indicate a need for targeted health education for young women about the transmission, pathophysiology, and treatment of STIs that also addresses perceptions and beliefs surrounding these diseases. (Royer, Falk, & Heidrich, 2013)

NINR-supported research in the health of HIV-positive women and gynecological health in 2013 and 2014 included the following:

- R01NR013507: Technology-Enhanced Community Health Nursing to Reduce Recurrent STIs After PID
- R01NR012150: A Longitudinal Study of Substance Abuse and HIV Risk Among Adult Latina Mother-Daughter Dyads
- K23NR014107: Self- and Family-Management Intervention in HIV+ Chinese Women
- K01NR013435: Tailoring an HIV Prevention Intervention for College-Aged Black Women
- F31NR013585: Sexual Distress and Body Image Distress in Younger Breast Cancer Survivors
- F31NR013864: Social Patterns and Pathways of HIV Care Among HIV Positive Transgender Women
- F31NR014628: Social Determinants of Health for African-American HIV-Infected Mothers

Training in Health Disparities and Women's Health

NINR supports a number of institutional training grants (T32) that focus on health disparities research and include women's health and special populations of women, including minorities, rural women, and women of lower socioeconomic status, as a major research and training focus, including the following:

- Interdisciplinary Training in Health Disparities (Allen; T32NR007968)
- Reducing Health Disparities Through Informatics (Bakken; T32NR007969)
- Reducing Disparities in Underserved Populations (Dancy; T32NR007964)
- Vulnerable Populations/Health Disparities Research (Nyamathi; T32NR007077)
- Transdisciplinary Training in Health Disparities Science (Reifsnyder; T32NR12718)
- Health Promotion/Risk Reduction Interventions with Vulnerable Populations (Villarruel; T32NR007073)

Science, Technology, Engineering, and Mathematics Efforts: Career Development, Women, and Women's Health

NINR has historically placed a special emphasis on training the next generation of nurse scientists, designating on annual average of 8 percent of its appropriated funding to extramural grants that support training and career development awards. While nurses of both genders pursue

advanced degrees, as the nursing workforce is 95 percent female, much of this funding supports the research and education of women. NINR uses a variety of mechanisms in supporting these training and research experiences, including the Ruth L. Kirschstein National Research Service Award program (F31, F32, and T32) as well as mentored career development grants. These research training awards support individual and institutional pre- and postdoctoral trainees at institutions across the United States, supporting many female scientists during their advanced training. An expanded scientific workforce will significantly contribute to evidence-based improvements and reforms to the health care system in the coming years. Two of the NINR institutional training programs have focused directly on women's health, especially women from vulnerable populations (Research on Vulnerable Women, Children, and Families, Sommers; T3NR2007100; Health Promotion/Risk Reduction Interventions with Vulnerable Populations, Villarruel; T32NR007073). Collectively, NINR training activities address the national shortage of nurses by contributing to the development of the nursing faculty needed to teach and mentor individuals entering the field.

NIH Strategic Plan for Women's Health Research

NINR's research and training programs support the implementation of the NIH Strategic Plan for Women's Health Research. In particular, NINR's training program and portfolio on the science of symptom management meet goals and objectives of the NIH Strategic Plan for Women's Health Research.

Goal 6: "Employ Innovative Strategies to Build a Well-Trained, Diverse, and Vigorous Health Research Workforce"

As stated earlier, NINR is strongly invested in training the next generation of nurse scientists through individual and institutional training grants and mentored career development grants that facilitate career development. These training programs provide the next generation of scientists with the necessary interdisciplinary education and research skills that will enable them to improve clinical practice, enhance quality of life for those with chronic illness, and support preventive health. While not all of these trainees were pursuing women's health research, the grants largely went to women scientists; in a recent analysis of the NINR training program from 1992 to 2012, it was found that 93 percent of NINR-supported trainees were female.

In addition to supporting pre- and postdoctoral research fellowships and career development awards in the extramural community, NINR also leads and participates in a number of training programs through its intramural research program, the NINR Division of Intramural Research (NINR-DIR). NINR-DIR provides scientific leadership and intensive research training to enhance the biologic and physiologic research foundation of the nurse scientist workforce. For example, NINR-DIR supports a research fellows training program and several summer training initiatives. In particular, NINR-DIR's Summer Genetics Institute provides training in molecular genetics to build the research capacity of the nursing science community and to expand clinical practice in genetics among clinicians. The Symptom Research Methodologies Boot Camp, a 1-week research training course, provides a foundation in the latest research methodologies. The focus of the 2014 Boot Camp was on Big Data and featured lectures by distinguished guest speakers, classroom discussion, and hands-on training. Many graduates of NINR intramural training programs subsequently return to the extramural community as university faculty in nursing programs across the country. These scientists are increasing the research intensity and capacity of schools of nursing, serving as role models to future nurse scientists and as educators and mentors in laboratory and clinical research arenas.

Objectives met by this activity:

- Objective 6.1: "Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH."
- Objective 6.2: "Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage the evaluation of mentoring practices."

- Objective 6.3: "Address the organizational, institutional, and systemic factors that impede the recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical scientists."

Goal 3: "Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women"

Developing new and better ways to manage adverse symptoms is vital to improving quality of life for those with chronic illnesses. Today, more people are living with long-term chronic illnesses, as well as the adverse symptoms that result from them. New advances in genomics and other fields have allowed nurse scientists to better understand the symptoms of chronic illness. Symptom science focuses on developing personalized strategies to treat and prevent the adverse symptoms of illness across diverse populations and settings Often, these symptoms are associated with a chronic condition, such as insomnia experienced by those living with chronic heart failure, or they may be treatment-related, as in the case of cancer patients experiencing pain associated with chemotherapy. Throughout its history, NINR has supported research on new and better ways to manage the symptoms of illness. Symptom science research supported by NINR focuses on understanding the biological and behavioral aspects of symptoms such as pain and fatigue, with the goal of developing new knowledge and new strategies for improving patient health and quality of life. The Institute supports research at universities, hospitals, and other institutions across the Nation on a broad range of topics related to symptom science. In addition, NINR maintains a robust intramural research program on the NIH campus in Bethesda, MD, dedicated to improving the understanding of the underlying biological mechanisms of a range of symptoms, their effect on patients, and the biological and behavioral bases for how patients respond to interventions.

Although the symptom science research supported by NINR addresses symptoms experienced by both men and women, NINR supports research (both in its intramural and extramural programs) on conditions and symptoms that primarily affect women. For example, current NINR-DIR research focuses on fatigue associated with fibromyalgia, chronic fatigue syndrome, and depression, as well as symptoms related to gastrointestinal conditions including IBS, all of which overwhelmingly affect women.

In NINR's extramural research portfolio, symptom science research in women's health includes research on IBS and cancer, among other conditions. Grants supporting research on symptoms, symptom clusters, and symptom management in women's health in 2013 and 2014 included the following:

- F31NR014759: Neurophysiological and Psychological Correlates of Vulvodynia
- K23NR014885: Mechanisms of a Symptom Cluster: Dyspnea, Fatigue and Sleep Disturbance in Chronic Illness
- R01NR014195: Multimodal MRI Biomarker of Mild Cognitive Impairment in Breast Cancer
- R01NR013906: Can the Sunshine Vitamin Improve Mood and Self-Management in Women with Diabetes?
- R01NR015117: Unraveling the Link of Sleep to IBS: A Metabolomics Approach
- R01NR012667: Epigenetics and Psychoneurologic Symptoms in Women with Breast Cancer
- R01NR014479: Microbiome and Pain in IBS
- R01NR014182: HippoPCI Hippocampal Predictors of Cognitive Impairment in Breast Cancer Patients
- R01NR012479: Mechanisms of Cancer Treatment-Related Symptoms
- R01NR015079: Imaging Lymphatic Function in Patients with Breast Cancer-Related Lymphedema
- R21NR014331: Is TFF-3 a Biomarker for Functional Gastrointestinal Symptoms?

Objectives met by this research area:

Objective 3.8: "Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent women, self-management of symptoms, preservation of cognitive functions, and health-related quality of life."

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Fogarty International Center

Executive Summary

The mission of the Fogarty International Center (FIC) is to advance the mission of NIH by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the United States and abroad and training the next generation of scientists to address global health needs. ORWH is among the many NIH ICs that collaborate with FIC to support this mission. Although FIC does not have any programs that are designed to specifically address women's health issues, several of them support research and research training related to conditions that disproportionately or exclusively affect women or girls. FIC programs also enhance some areas of understanding of sex as a biological variable and gender differences. Scientific areas of focus include violence against women, cervical cancer research, HIV/AIDS research, pregnancy, and other reproductive health/contraception issues.

FIC accomplishments and activities particularly relevant to women's health and highlighted in this report include the following:

The Trauma and Injury Research Training Program supports research training in the diagnosis, prevention, and/or treatment related to injury and trauma in low- and middle-income countries (LMICs).

The International Research Scientist Development Award supports U.S. scientists in the formative stages of their careers to pursue careers in research on global health and prepare for independent research.

The Mobile Health: Technology and Outcomes in Low and Middle Income Countries (mHealth) program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology.

The Chronic, Non-Communicable Diseases and Disorders Across the Lifespan program is a collaborative research training program that supports training of scientists to conduct research on chronic, non-communicable disease and disorders.

The Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC research sites.

The International Tobacco and Health Research and Capacity Building Program provides opportunities for scientists to engage in locally relevant observational, intervention, and policy research and build research capacity related to tobacco consumption in LMICs.

The AIDS International Training and Research program began in 1988 as one of the first of a new generation of research training programs sponsored by Fogarty. Later, the program transitioned to become the Fogarty HIV Research Training Program, which provides training for LMIC scientists.

The Global Brain and Nervous System Disorders Research Across the Lifespan program supports collaborative research and capacity-building projects relevant to LMICs on brain and nervous system disorders throughout life.

In the NIH/President's Emergency Plan for AIDS Relief (PEPFAR) PMTCT Implementation Science Alliance, FIC collaborates with the Office of the U.S. Global AIDS Coordinator to bring together researchers, program implementers, and policymakers from the United States and sub-Saharan Africa who are pursuing interventions to prevent mother-to-child HIV transmission (PMTCT), as well as representatives from multilateral organizations, to translate effective PMTCT interventions into community- and population-level services, programs, and strategies at scale.

FIC is working with other NIH ICs, key Federal agencies, and the Global Alliance for Clean Cookstoves to promote and support the generation of scientific evidence that will inform efforts to reduce household air pollution and promote cleaner cookstoves.

Accomplishments and Activities

The FIC portfolio includes a variety of programs and projects related to research that disproportionately or exclusively affects women and/or girls. Several of these are in areas of expressed congressional interest, including neuroscience; cardiovascular disease and stroke; inclusion of women in clinical research; and sex differences in basic, applied, and clinical research. Finally, they fall under several of ORWH's strategic goals—primarily, Goal 4: "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research," and Goal 6: "Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce." Highlights of these programs and projects are detailed below.

Trauma and Injury Research Training Program

FIC's Trauma and Injury Research Training Program (TRAUMA) program supports research training in diagnosis, prevention, and/or treatment related to injury and trauma in LMICs. The research training areas of focus include treatment at the scene, emergency medical facilities and services, diagnosis imaging, post-acute care, and long-term care, including rehabilitation. Some of the gender-relevant research training under the TRAUMA program addresses violence against women with an emphasis on intimate partner violence in pregnancy, the impact of trauma on South African women in abusive HIV serodiscordant relationships, and sexual violence against Zimbabwean refugees in South Africa.

One key study within the TRAUMA program was published in Metabolic Brain Disease and demonstrated how interpersonal violence (IPV) during pregnancy contributes to low birth weight in South African infants. IPV was shown to have detrimental effects on health outcomes for the fetus and the child. Pregnant subjects presenting at two antenatal clinics in a low-income, semi-rural region outside of Cape Town participated in the study. Researchers administered the Childhood Trauma Questionnaire, a survey tool specifically tailored to study IPV in this context, in conjunction with the World Health Organization's IPV Questionnaire. After controlling for: study site, maternal height, ethnicity, socioeconomic status, substance use, and childhood trauma, the study confirmed that exposure to IPV resulted in the delivery of an infant with a low birth weight (Koen et al., 2014).

International Research Scientist Development Award

The International Research Scientist Development Award (IRSDA) supports U.S. postdoctoral biomedical, epidemiologic, clinical, social, and behavioral scientists in the formative stages of their careers to pursue careers

in research on global health and prepare for independent research by engaging in a mentored career development experience. Current IRSDA investigators are studying the use of midwives in Ghanaian maternity clinics, prevention of mother-to-child HIV transmission in Malawi, prevention of intimate partner violence in India, and mental and sexual health in pregnant Liberian women.

With support from this program, Dr. Jodi Rae Lori examined the impact of maternal waiting homes (MWH) and traditional midwives on labor and delivery outcomes in rural Liberia and found lower rates of maternal and perinatal death with her intervention (Lori et al., 2013). The objective of this study was threefold: to ascertain whether MWHs improve the use of skilled birth attendants at rural primary health clinics, to assess whether traditional midwives can work collaboratively with them, and to understand whether maternal and child mortality and morbidity was reduced in these circumstances. Using a traditional randomized control trial structure, five Liberian communities built a MWH, while another five communities did not. Focus groups were conducted to solicit views on how the traditional midwives were integrated as part of the labor and delivery team in these communities. Communities with MWHs experienced a significant increase in team births, more integration of traditional midwives, and lower rates of maternal and perinatal death than the communities without MWHs.

Mobile Health: Technology and Outcomes in Low and Middle Income Countries

The mHealth[1] program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology. The overall goal of the program is to contribute to the evidence base for the use of mobile technology to improve clinical outcomes and public health. mHealth researchers are developing and testing mobile phone interventions that could enhance conception safety for HIV serodiscordant couples in Kenya[2] and improve maternal and child health home visits by community health workers in Mali.[3]

Chronic, Non-Communicable Diseases and Disorders Across the Lifespan

This collaborative research training program pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their countries. This project includes work in areas of particular congressional interest, including cardiovascular disease and stroke.

A current award under this program with the University of Ibadan in Nigeria trains scientists to study the unique molecular and genetic profiles of breast cancer in Nigerian women and relate these risk factors to a patient's response to chemotherapy. The study of certain microbiomes in Nigerian breast cancer tissues using DNA extracted from breast tissues will also give insight into the involvement of microbes in breast cancer etiology among Nigerians.[4]

Global Health Fellows and Scholars

The Fogarty Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC sites. The most recent gender-based clinical research topics include maternal and child health, knowledge and attitude towards contraception methods, and progestin-only injectable contraceptives to determine increased risk of HIV infection.

One program participant was able to show differences in knowledge about contraceptives between HIV-positive and HIV-negative women in Malawi. Malawi has a high maternal death rate, a high fertility rate, and a high HIV prevalence. A few studies have reported negative drug interactions between antiretrovirals and hormonal contraception methods. However, there is a paucity of data on how much HIV-positive Malawian women know about long-acting reversible contraceptives. To better understand

[1] R21, PAR-14-028

[2] R21TW009908

[3] 1R21TW009885

[4] D43TW009112

the situation, authors of this study assessed family planning knowledge, attitudes, and practices among post-partum HIV-infected and HIV-uninfected women. HIV-infected women were more likely than HIV-uninfected women to report that their most recent pregnancy was unintended. HIV-positive women were also more prone to respond that they did not want to have more children. However, HIV-positive women were less likely to be aware that intrauterine devices (IUD) and implanted contraceptives are safe during breastfeeding (O'Shea et al., 2015).

Another Fogarty Fellow, Dr. Jennifer Tang, aims to help improve the health prospects of women in Malawi as a researcher as well as an obstetrician-gynecologist. Receiving a Fogarty fellowship enabled her to explore making research part of her career. For her fellowship project, she assessed family planning knowledge, attitudes, and practices among 634 postpartum women. Although more than 80 percent of the women were planning to use one of two long-term, reversible contraceptives to avoid another pregnancy, 3 months later, very few women had followed through. Only 14 percent used a hormonal implant, and one percent had an IUD. Dr. Tang also learned that correct knowledge about a contraceptive's safety was the largest single influencer of contraceptive use. Her work suggests that new educational interventions are both effective and needed (Kristiansen, 2014a).

International Tobacco and Health Research and Capacity Building Program (TOBAC)

With support from TOBAC, scientists engage in locally relevant observational, intervention, and policy research and build capacity in epidemiologic and behavioral research, prevention, treatment, communications, health services, and policy research related to tobacco consumption in LMICs. This program supports the expansion of a network for tobacco control among women in Parana, Brazil, to conduct community-based participatory research on gender-relevant tobacco control issues, such as light smoking.[5]

AIDS International Training and Research

The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by Fogarty. It was not renewed in 2011, and Fogarty's HIV Research Training Program has taken its place. AITRP provided training for scientists in LMICs through partnerships between high-income and LMIC research institutions. The primary goal of this program was to build multidisciplinary biomedical, behavioral, and social science research capacity for the prevention, care, and treatment of HIV/AIDS and HIV-related conditions for those adults and children affected by HIV/AIDS in the collaborating country. AITRP supported training in the United States, in other countries, and in the home countries.

Researchers supported by AITRP examined the risk factors for cervical pre-cancer and cancer among HIV-positive women screened for cervical cancer at two medical institutions in Abuja, Nigeria. They found that HIV-positive Nigerian women were at a marginally increased risk of cervical pre-cancer and cancer. The group found an overall 6 percent prevalence of cervical pre-cancer among the study subjects. Women who had five or more abortions or vaginal wall abnormalities were at a greater relative risk than other women for positive cervical cancer screens. There was also an inverse relationship between cervical cancer risk with age and high CD4 counts—females of advanced age with high CD4 counts had a lower risk of cervical cancer (Ononogbu et al., 2013).

Another group of researchers in the same group investigated the importance of adherence in microbicide trials. High and consistent adherence to using tenofovir gel before and after intercourse is needed to prevent HIV. The group found that adherence support activities with relatively high success rates will be critical to the success of future microbicide trials (Mansoor et al., 2014). Eight hundred and eighty-nine women were followed for an average of 18 months to track adherence. At the beginning of the study, individual counseling was utilized, but midway through, the strategy was changed to a structured theory-based adherence support program. By inspecting the number of applicators, the investigators estimated adherence to using the microbicide

[5] R01TW009272-01

over the course of the entire study to be at 72.2 percent, nearly 10 percent under the self-reported adherence rate. This suggests that any microbicide trial's success in investigating a new drug rests in large part on the participant's willingness and ability to use the product per the instructions (Mansoor et al., 2014).

Fogarty HIV Research Training Program

The Fogarty HIV Research Training Program[6] seeks to strengthen the human capacity to contribute to the ability of institutions in LMICs to conduct HIV-related research on the evolving HIV-related epidemics in their countries and to compete independently for research funding. Mentored research training projects conducted under this program include addressing AIDS-related cervical cancer (screening, exploring disease mechanisms, and treatment strategies)[7] and the prevention of mother-to-child HIV transmission.[8]

Global Brain and Nervous System Disorders Research Across the Lifespan (Brain) Program

The Brain program supports collaborative research and capacity-building projects that are relevant to LMICs on brain and nervous system disorders throughout life. Grantees have developed innovative, collaborative research programs that contribute to the long-term goal of building sustainable research capacity in nervous system function and nervous system impairment.

Neuroscience and stroke research are of particular interest to Congress in this reporting period. These are important in global health—because stroke is the major cause of vascular dementia and cognitive disorders worldwide—and in developing countries, there is a dearth of information regarding the public health magnitude of stroke. One group funded in the Brain program sought to assess the prevalence of vascular behavioral and cognitive disorders, ranging from mild vascular cognitive impairment (VCI) to vascular dementia (VaD), in a cohort of acute first-ever symptomatic stroke patients in Mexico. They recruited relatively young acute stroke patients. They found that VCI-VaD patients were more likely than cognitively intact post-stroke subjects to be female (Arauz et al., 2014).

Household Air Pollution

FIC has been working to support evidence-based practice surrounding household air pollution in collaboration with other NIH ICs and key Federal agencies and as a member of the Global Alliance for Clean Cookstoves (U.S. Department of State, 2014). Half of the world's population relies on elemental stoves for cooking or heating. Those using cookstoves usually burn dung, wood, soft coal, or rice husks, all of which produce toxic carbon emissions. The resulting indoor air pollution is estimated to take 1.9 million lives each year due to increased risks of acute pneumonia in children under age 5 and chronic obstructive pulmonary disease and lung cancer in women. Building on a workshop that FIC hosted in late 2012, a group of collaborating researchers published an article calling for evidence-based technology and delivery mechanisms and identified research priorities for global efforts to implement effective clean cooking solutions, with important implications for disease control programs, exposure measurement and biomarker validation, behavioral considerations for effective adoption, and program evaluation (Martin et al., 2013). In addition, FIC published a training materials for those working in the field in 2014 (Kristiansen, 2014b). Ulaanbaatar, the capitol city of Mongolia, has one of the highest levels of air pollution of all world capitals, and the pollution is largely caused by coal burning. One research group, funded by a FIC grant in partnership with National Institute of Environmental Health Sciences, was able to provide evidence that pollutants from coal-burning stoves are strongly associated with miscarriages in Mongolia (Kavanagh, 2014).

Preventing Mother-to-Child Transmission of HIV

FIC is collaborating with the Office of the U.S. Global AIDS Coordinator (OGAC) to host the NIH-PEPFAR PMTCT Implementation Science Alliance (the Alliance). This novel platform brings together PMTCT researchers, program

[6] D43, PAR-13-126; D71, PAR-13-214; G11, PAR-13-215

[7] D43TW009606-01

[8] D71TW009616-01

implementers, and policymakers from the United States and sub-Saharan Africa as well as representatives from multilateral organizations. The Alliance aims to improve communication among these stakeholders and catalyze collaboration to enhance the evidence base for translating effective PMTCT interventions into community- and population-level services, programs, and strategies at scale. Coordinators in this initiative published a key article in the *Journal of Acquired Immune Deficiency Syndrome* (*JAIDS*) that calls for increasing implementation science to inform understanding of key implementation barriers and successful adaptation of scientifically proven interventions to the local environment. They state that advancing implementation science will require deliberate and strategic efforts to facilitate collaboration, communication, and relationship-building among researchers, implementers, and policymakers (Sturke et al., 2014).

NIH Strategic Plan for Women's Health Research

FIC work maps closely to the ORWH/NIH Strategic Plan Goal 4: "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research," and Goal 6: "Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce."

As mentioned above in Accomplishments and Activities, FIC participation in the Global Alliance for Clean Cookstoves supports ORWH/NIH Goal 4—primarily, Objective 4.6: "Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries"; and, secondarily, Objective 4.4: "Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups." FIC's research training portfolio generally addresses Goal 6 by supporting scientists' career development. Many grants involve a significant mentorship component. In addition, FIC's Medical Education Partnership Initiative (MEPI) and Global Health Program for Scholars and Fellows both address Goal 6—primarily, Objective 6.1: "Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH"; and, secondarily, Objective 6.2: "Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs, and encourage evaluation of mentoring practices."

MEPI funds foreign institutions in sub-Saharan African countries that receive PEPFAR support and their partners to develop or expand and enhance models of medical education and clinical research training. MEPI supports African institutions in a dozen countries, forming a network including more than 30 regional partners, country health and education ministries, and more than 20 U.S. and foreign collaborators. The recent Limited Competition: Research Training for Career Development of Junior Faculty in MEPI Institutions[9] states, "Support for increased engagement of female junior faculty and mentors in research activities in any relevant health area is also highly desired." FIC also supports the careers of emerging young global health leaders through the Global Health Program for Scholars and Fellows. Following their year abroad, many female scholars and fellows successfully compete for a FIC IRSDA career development award (see Accomplishments and Activities) and acquire a faculty position at an academic institution.

In addition, as mentioned above, the Alliance is a collaboration of PMTCT researchers, program implementers, and policymakers in the United States and sub-Saharan Africa, as well as representatives from multilateral organizations, that aims to improve communication among these stakeholders. The group seeks ultimately to catalyze collaboration to enhance the evidence base for translating effective PMTCT interventions into community- and population-level services, programs, and strategies at scale. Coordinators in this initiative published a key article in *JAIDS* that calls for increasing implementation science to inform understanding of key implementation barriers and successful adaptation of scientifically proven interventions to the local environment.

[9] D43RFATW14003

Inclusion

FIC has incorporated the following language in its research training announcements, which encourages research training activities related to sex and gender differences: "Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies."

Moreover, FIC-funded research incorporates the inclusion of women and girls in research. For example, the TRAUMA program supported a study in Zimbabwe that identified gender differences in trauma and post-traumatic stress disorder (PTSD) among displaced people (Idemudia, William, Boehnke, & Wyatt, 2013). The study examined the disparity between trauma and PTSD experiences between male and female Zimbabwean refugees in South Africa. The pre- and post- migration stressors, demographics, and mental health of a convenience sample of displaced Zimbabwean refugees relocated to Limpopo were assessed using the General Health Questionnaire and the PTSD checklist. These questionnaires looked at pre- and post-migration stressors that correspond to three domains related to life and family, deprivational conditions where basic resources are scarce (e.g., hunger), and sexual/physical abuses. Men were unaffected by pre- and post-migration stress, and poor mental health did not result in PTSD. In women, however, a significant association was found between poor mental health and PTSD.

Science, Technology, Engineering, and Mathematics Efforts

The Fogarty Global Health Program for Fellows and Scholars is a 1-year mentored clinical research experience in 27 LMIC sites for postdoctorates, medical students, or graduate students in the health sciences. The most recent gender-based clinical research topics include maternal and child health, knowledge and attitude towards contraception methods, and progestin-only injectable contraceptives to determine increased risk of HIV infection. Over the last 2 years, there have been 122 fellows, 71 of whom were women. In the same time frame, 46 scholars were supported, 31 of whom were women.

Funding Initiatives, Workshops, and Conferences

Several funding initiatives are relevant to relevant to women's health or the influence of sex on disease in this reporting period. The mHealth program[10] (December 2013) funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology.[11]

The Chronic, Non-Communicable Diseases and Disorders Across the Lifespan program (April 2013) is a collaborative research training program pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their countries.[12]

The Fogarty Global Health Program for Fellows and Scholars (annual) supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC sites.

The Fogarty HIV Research Training Program (April 2013) seeks to strengthen the human capacity to contribute to the ability of institutions in LMICs to conduct HIV-related research on the evolving HIV-related epidemics in their countries and to compete independently for research funding.[13]

The Brain program (September 2014) supports collaborative research and capacity building projects that are relevant to LMICs on brain and nervous system disorders throughout life.[14]

[10] R21, PAR-14-028

[11] PAR-14-028

[12] PAR-10-257; PAR-10-277

[13] D43, PAR-13-126; D71, PAR-13-214; G11, PAR-13-215

[14] PAR-14-331; PAR-14-332

In addition to funding initiatives, there have been several FIC-sponsored workshops and conferences relevant to women's health or the influence of sex on disease. An estimated 3 billion people rely on basic cookstoves and/or open fires fueled by coal or solid biomass to cook and to heat their homes. Limited research has been conducted to isolate and define the household air pollution risks caused by basic cookstoves and open fires, understand the health impacts of an improved cookstove, and identify low-cost stoves and interventions. In response to this need, FIC held a 3-day training course for scientists from the United States and LMICs interested in developing research projects on the health effects of traditional and improved cookstoves. Faculty from diverse disciplines, backgrounds, and sectors used a mix of didactic and participatory methods to enable approximately 20 investigators to better define and understand the health risks associated with household air pollution; the epidemiological principles that can inform the development of robust and appropriate research study designs; the critical role of the social, behavioral, and cultural factors influencing stove adoption; and the complex and evolving technologies for improved stoves and fuels, exposure monitoring, and biomarker development.

FIC is collaborating with OGAC to host the PMTCT Implementation Science Alliance. This novel platform brings together PMTCT researchers, program implementers, and policymakers in the United States and sub-Saharan Africa as well as representatives from multilateral organizations. The Alliance aims to improve communication among these stakeholders and catalyze collaboration to enhance the evidence base for translating effective PMTCT interventions into community- and population-level services, programs, and strategies at scale. Coordinators in this initiative published a key article in *JAIDS* that calls for increasing implementation science to inform understanding of key implementation barriers and successful adaptation of scientifically proven interventions to the local environment. They state that advancing implementation science will require deliberate and strategic efforts to facilitate collaboration, communication, and relationship-building among researchers, implementers, and policymakers (Sturke et al., 2014). In the reporting period, the Alliance held two meetings, the first in March 2013 and a follow-up in September 2014.

Health Disparities

Health disparities work is embedded in a variety of FIC programs and projects. For example, the study mentioned within the TRAUMA program that demonstrated how IPV during pregnancy contributes to low birth weight in South African infants speaks to an exposure that disproportionately affects women, resulting in negative health outcomes for their children. In the study, exposure to IPV was shown to result in the delivery of an infant with a low birth weight (Koen et al., 2014).

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National Center for Complementary and Integrative Health

Executive Summary

The National Center for Complementary and Integrative Health (NCCIH) is the lead Federal agency for scientific research on the usefulness and safety of complementary and integrative health practices. Complementary and integrative health approaches include modalities and products with a history of use or origins outside of conventional medicine. Examples include mind-body interventions, such as massage, acupuncture, yoga, and meditation, and natural products, such as dietary supplements and probiotics. To address the need for objective evidence as to the safety and efficacy of many of these approaches, NCCIH supports rigorous scientific investigation to better understand how and for whom these interventions work and the optimal method of practice and delivery.

Many individuals seek complementary and integrative health approaches to improve their health and well-being or to manage symptoms associated with chronic diseases or conditions. Results from the 2012 National Health Interview Survey, conducted by the Centers for Disease Control and Prevention with support from NCCIH, indicates that over one-third of the U.S. population uses complementary and integrative health approaches (Clarke, Black, Stussman, Barnes, & Nahin, 2015). Natural products such as nonvitamin, nonmineral dietary supplements are the most commonly used complementary health approach, followed by deep breathing exercises and yoga.

NCCIH and the NIH Office of Dietary Supplements fund five dietary botanical supplement research centers (http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-001.html), two of which are focused on women's health. The University of Illinois at Chicago/NIH

Center for Botanical Dietary Supplements Research in Women's Health focuses on the safety of botanical dietary supplements and their impact on estrogenic hormones. The Botanical Research Center at the University of Illinois at Urbana-Champaign addresses the safety, efficacy, and mechanism of action of botanical estrogens consumed by women. Results of studies conducted at these research centers indicate that compounds isolated from soybeans and licorice may influence the development of ovaries and have estrogenic activity, respectively. Another study suggests that treatment with the probiotic *Lactobacillus reuteri* may prevent bone loss during menopause.

Accomplishments and Activities

Reproductive Health

Genistein, the primary isoflavone in soy, has been shown to adversely affect various endocrine-mediated endpoints in rodents and humans. For example, soy formula intake by human infants has been associated with early age at menarche and decreased female-typical behavior in girls. In addition, adipose (fat) deposition and expansion are also hormonally regulated, and genistein has been shown to alter these processes. However, little is known about the impact of early-life soy intake on metabolic homeostasis in adulthood. A recent study examined the impact of early-life genistein exposure on adult body composition and the molecular signals mediating adipose expansion. In this study, rat pups were fed genistein from days 1 through 22 post-gestation. They were given an amount that mimics the blood genistein levels in human infants fed soy formula. The female rats fed genistein, but not the male rats, had an increased fat to lean mass ratio, an increased fat mass, and decreased muscle fiber perimeter. These data suggest that in rats, genistein exposure early in life has gender-specific effects on adiposity that closely parallel the effects of a postweaning high-fat diet. These results underscore the importance of the timing of exposure and of gender when establishing safety recommendations for early-life dietary genistein intake. (Stakovsky et al., 2014)

Metabolic Syndrome

Insulin resistance is a condition in which a normal or elevated insulin level results in abnormal biologic responses, including glucose uptake. It often develops 5 to 10 years before the onset of diabetes and is therefore considered a prediabetic condition. There is a much higher prevalence of insulin resistance in women from racial and ethnic populations (57 percent and 26 percent in Blacks and Hispanics, respectively). Previous studies have shown that the botanical extract PMI 5011 from Russian tarragon (*Artemisia dracunculus L.*) increases the abundance of proteins involved in glucose metabolism and increases glucose uptake and metabolism. In addition, it enhances insulin sensitivity. To further understand how PMI 5011 exerts its effects, investigators explored whether and how it affects a type of protein modification called phosphorylation. Working with muscle cells from obese, insulin-resistant individuals, they found that PMI 5011 stimulates protein phosphorylation in a pattern and amount similar to that of insulin. (Kheterpal et al., 2014)

Menopause

The increased cancer risk associated with hormone therapies has encouraged many women to seek non-hormonal alternatives, including botanical supplements such as hops (*Humulus lupulus*) and licorice (*Glycyrrhiza* spec.), to manage menopausal symptoms. This study evaluated the potential estrogenic effects of three licorice species (*Glycyrrhiza glabra*, *G. uralensis*, and *G. inflata*) with different contents of liquiritigenin, a type of phytoestrogen, in comparison with hops. The estrogenic activity decreased in the order *H. lupulus*, *G. uralensis*, *G. inflata*, *G. glabra*. These data demonstrated that *Glycyrrhiza* species with different contents of liquiritigenin have various levels of estrogenic activities. This result illustrates the importance of precise labeling of botanical supplements. (Hajirahimkhan et al., 2013)

Osteoporosis occurs when the creation of new bone does not keep up with the removal of old bone, thus causing bones to become weak and brittle. Menopausal estrogen deficiency in women is a major contributor to bone loss. It is estimated that approximately 50 percent of women over the age of 50 will experience an osteoporosis-related bone fracture in their lifetime. In addition, a lack of awareness of the risk for osteoporosis and an increasing elderly population, along with lack of adherence to medications, likely contribute to decreased bone health. Novel and more effective approaches for increasing bone density and preventing osteoporosis are

needed. One intriguing approach involves altering intestinal microbiota. Recent evidence indicates the importance of bacteria in the intestinal tract (gut microbiota) for sustaining health. The potential role of probiotics (i.e., bacteria and yeasts) in adding to, maintaining, or restoring gut microbiota is an area of active investigation. However, the effects of microbiota on bone health, especially during menopause, are not known. To test the potential impact of probiotics on bone during menopause, researchers used an estrogen-deficient menopausal mouse model. In their study, some "menopausal" mice were given and had access to an established probiotic species, *L. reuteri* 6475, in their drinking water, while another group of mice were not given the probiotic. After 4 weeks, bone loss was assessed in all mice. The menopausal mice that did not receive *L. reuteri* 6475 showed a significant bone volume loss that was absent in mice receiving the probiotic. This study demonstrates that in mice, oral administration of the probiotic *L. reuteri* 6475 can prevent bone loss under estrogen-deficient, menopausal-like conditions. Since many existing therapies have adverse side effects, the possibility of being able to use a well-tolerated, natural product to treat menopause-induced osteoporosis is appealing. However, future clinical studies will be needed to determine the long-term efficacy of probiotics such as *L. reuteri* 6475 in treating menopause-induced bone loss. (Britton et al., 2014)

Memory complaints increase as women transition from premenopausal to postmenopausal stages. NCCIH-funded researchers explored whether self-reported memory complaints were associated with objective tests of memory, mood, and menopausal symptoms such as hot flashes. This study included 68 midlife women who had 35 or more hot flashes per week. Each woman completed questionnaires about memory function and mood, objective cognitive tests, and an inventory of menopausal symptoms. An analysis of the data indicates that the women's self-reported memory complaints correlated with objective measurement of memory. The analysis also indicates that there was a weaker correlation between the women's memory complaints and their mood and the frequency of their hot flashes. These findings indicate that menopausal women can detect small changes in memory performance during the transition. (Drogos et al., 2013)

NIH Strategic Plan for Women's Health Research Goals

Genistein from Soybean Promotes the Development of Obesity in Female, but Not Male Rats. [P50AT006268: W. Helferich]: Genistein exposure during the early postnatal period favors the development of obesity in female, but not male rats.

Goal 1, Objective 2: "Explore sex differences in the structure and function of male and female cells, tissues, organs, and physiological research."

Botanical Estrogens for Menopausal Symptoms. [P50AT00155: J. Bolton]: Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms.

Goal 3, Objective 9: "Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life."

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Office of Research Infrastructure Programs

Executive Summary

Established in December 2011, the Office of Research Infrastructure Programs (ORIP) is located within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the NIH Office of the Director. ORIP brings together the research activities managed by the Division of Comparative Medicine, the Division of Construction and Instruments, and the Science Education Partnership Awards (SEPA) Program that were formerly located in the National Center for Research Resources. ORIP is also the home of the Office of Science Education (OSE). The NIH SEPA Program was moved into the OSE in 2014. The overall mission of ORIP is to provide research infrastructure, research-related resource programs, and coordination of NIH's science education efforts. Some scientific programs within ORIP have been supported and fostered by NIH for 50 years. ORIP's infrastructure programs are trans-NIH in nature and align with DPCPSI's mission to ensure that NIH effectively and efficiently addresses and coordinates important areas of emerging scientific opportunities to improve human health.

ORIP stimulates innovation and leverages shared resources to do the following:

- Develop and provide access to critical animal models, including those relevant to women's health;
- Provide access to state-of-the art technologies and instruments that enable both basic biomedical research and clinical investigations of a multitude of health issues, including those of consequence to women and girls;
- Explore strategies for identification and consideration of sex differences of animals and cell lines that can be used in NIH-funded studies as a means of enhancing experimental design and increasing reproducibility in preclinical research in women's health, sex differences research, and other research areas and disciplines;
- Train veterinarian-scientists to become valuable partners in an integrated, multidisciplinary approach to biomedical and translational research;
- Provide funding to renovate existing animal research facilities to conduct critical studies on women's and men's health;
- Improve the public understanding of medical research and provide adults and children with information about healthy living and science career opportunities, including issues of importance to women and girls; and
- Plan, develop, and coordinate comprehensive science education programs across NIH to strengthen and enhance NIH's efforts to attract young people, especially girls and underrepresented minorities, to biomedical and behavioral science careers and to improve science literacy in both adults and children.

Research on women's health uses many of the animal models supported by ORIP, from invertebrates such as worms and fruit flies to vertebrates such as fish and mammals, including rodents, swine, and nonhuman primates. This report highlights one featured program from ORIP, the National Primate Research Centers, which supports the implementation of the first three goals of the NIH Strategic Plan for Women's Health Research. This report also provides an overview of ORIP's accomplishments

and programs within its broad-based research portfolio on women's health, including research on the effects of other diseases such as HIV and diabetes on women's health. These programs also include reproductive health research including endometriosis, fertility and contraception, physiology, polycystic ovary syndrome, pregnancy, prenatal and perinatal health, and sexually transmitted diseases. Research on aging and menopause, diet, behavior, stem cells, and regenerative medicine is also included within ORIP's research portfolio in women's health. This report also includes highlights of ORIP's initiatives to enhance education and diversity of the future biomedical workforce through training and mentoring programs that focus on veterinary students and veterinarians, as well as pre-college science, technology, engineering, and mathematics (STEM) educational programs targeting girls, underrepresented minorities, and underserved communities. ORIP's engagement with outreach and educational activities focus on improving the public's understanding of women's health and health disparity issues is also summarized. In addition, this report describes several ORIP-sponsored initiatives, including program announcements, conferences, and workshops, with a focus on women's health and related trans-NIH research and training programs.

NIH Strategic Plan for Women's Health Research

This section highlights one featured program from ORIP, which supports the implementation of the NIH Strategic Plan for Women's Health Research.

The National Primate Research Centers (NPRCs)

Monkeys provide critical models for understanding many issues related to the health of women and girls, including studies on both normal physiology and disease conditions. Of all widely available animal models, monkeys are closest to humans in physiology, behavior, and genetic relatedness. Furthermore, the environment and diet of monkeys can be controlled rigorously, thus eliminating variables that often confound preclinical research in humans.

NIH awarded support more than 50 years ago for the NPRCs to facilitate the use of nonhuman primates (NHPs) for basic and translational research related to human health. As it is not cost-effective or feasible to duplicate these specialized facilities at every institution, the NPRCs were established. Collectively, the seven NPRCs facilitate more than 1,000 individual projects involving more than 2,000 researchers per year. Each individual NPRC is a national resource and can accommodate the needs of a researcher located anywhere in the United States. The NPRCs support research projects funded by all NIH Institutes and Centers, as well as scientific foundations and other research entities. The NPRC Research and Capabilities Web site (http://nprcresearch.org), launched in 2014, provides comprehensive information for researchers and the public regarding the range of available programs and resources, as well as achievements of the NPRCs.

The ORIP Division of Comparative Medicine manages the NPRCs' activities aligned with three of the ORWH and NIH Strategic Plan Goals and Objectives, described below.

Goal 1: "Increase Sex Differences Research in Basic Sciences Studies." Studies using systems biology–based approaches, such as DNA and RNA sequencing and proteomic analysis, are performed at the NPRCs to facilitate a better understanding of sex differences at the genetic and molecular levels (Objectives 1.1, 1.3, and 1.8). For example, monkeys exhibit many of the same behaviors as humans, including those related specifically to the well-being of women and girls. Individual female monkeys living in large groups experience varying levels of social stress, depending on the dominance status of the particular female. The effects of stress on the physiology of the female are studied at the NPRCs, including differences in the expression of specific genes in females experiencing varying levels of stress. The NPRCs also are studying how the diet and caloric intake of monkeys can be controlled stringently. This permits analysis of the differential effects of maternal nutrition on female versus male fetuses, which can also lead to differences in the health of newborns and neonates. Sophisticated molecular analysis is being used to understand the particular genes and physiological processes in the fetus and placenta that are affected by maternal nutrition.

Goal 2: "Incorporate Findings of Sex/Gender Differences in the Design and Application of New Technologies, Medical Devices, and Therapeutic Drugs." Female monkeys can serve as an animal model of many diseases and conditions that women experience, including diabetes, endometriosis, polycystic ovary syndrome,

and HIV/AIDS. For example, a major priority in HIV/AIDS prevention is the development of new devices or therapies that give women personal control (Objective 2.7). The NPRCs have pioneered many studies using the monkey model of human AIDS, which involves analysis of animals infected with simian immunodeficiency virus (SIV), the monkey analog of HIV. In addition to testing strategies for AIDS vaccines, the NPRCs have helped lead the development and testing of potential microbicides, which are compounds that a woman can use as a topical preparation to decrease acquisition of HIV.

Goal 3: "Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women." Most aspects of the reproductive life cycle are the same in monkeys and humans, including fertility, conception, pregnancy, and menopause. The NPRCs conduct studies on all aspects of the female reproductive cycle. NPRC investigators are developing novel, nonhormonal contraceptives that may have fewer adverse effects than current types of birth control pills. These strategies are based on a detailed analysis of the molecular events underlying release of primate eggs from the ovary prior to fertilization (Objective 3.1). Investigators at the NPRCs are studying the effects of various hormones on the menopausal transition, with the aim of describing and ultimately finding new treatments for weight gain, loss of libido, metabolic syndrome, and cardiovascular disease that some women experience as a consequence of menopause (Objective 3.1).

The projects described above are just a few examples of the many studies related to women's health that are performed at the NPRCs.

Accomplishments and Activities

This section provides an overview of ORIP's accomplishments and activities within its broad-based research portfolio on women's health research.

Disease

Diabetes and Obesity: The Role of Body Fat in Regulating Metabolism Differs in Men and Women. It is increasingly recognized that there are important sex differences in biology that require the study of both sexes in medical research and in clinical trials for new drugs and treatments for human disease. Studies performed at the Oregon NPRC using rhesus monkeys, whose physiology is very close to that of humans, focus on the role of fat tissue in controlling the body's metabolism of lipids and glucose. Defects in these processes underlie serious medical conditions, such as obesity and diabetes, and their complications, such as heart disease. These investigators have found that fat tissue responds to the need to dispose of glucose and lipids derived from food differently in males and females and that, in females, this can also vary depending on the stage in the menstrual cycle (Varlamov, Bethea, & Roberts, 2014; Varlamov et al., 2013, 2014). These findings argue for a careful consideration of sex differences when evaluating treatments for obesity and diabetes. Funded by ORIP, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute on Aging (NIA).

Focal Dermal Hypoplasia (FDH): Molecular Mechanisms of Disease. FDH is an uncommon genetic disorder characterized by distinctive skin abnormalities and a wide variety of defects that affect the eyes; teeth; and skeletal, urinary, gastrointestinal, cardiovascular, and central nervous systems. About 90 percent of affected individuals are female. This syndrome was recently mapped to the PORCN gene at the University of Utah (Bankhead et al., 2015). These researchers have generated a conditional knockout allele of mouse Porcn and demonstrated that it provides an animal model of FDH, including ectopic fat deposition and incomplete body wall closure, to which the mouse model provides unique access. This project provides the first evidence that Wnt ligands regulate adult adipocyte differentiation in an intact animal. These studies also support the hypothesis that ectoderm-derived Wnt signaling is a critical mediator of body wall development and raises the possibility that these signals are central to a genetic cascade that unifies the diverse genes already implicated in mouse abdominal wall defects (AWDs) and yet to be discovered in human AWDs. Funded by ORIP.

HIV/AIDS: Identification of Genetic Loci that May Contribute to the Ability to Control Human Acquired Immunodeficiency Virus Replication. A small percentage of HIV-infected people and SIV-infected monkeys can control virus replication without antiretroviral treatment.

While the major determinant of this "elite control" is expression of certain major histocompatibility complex (MHC) alleles, other genetic loci have been thought to modify this protective effect. Investigators at the Wisconsin NPRC performed whole genome sequencing of SIV-infected monkeys and identified additional candidate genetic loci that may contribute to the protective effect. Control of virus replication appears to be sexually differentiated, where females with identical MHC genotypes show higher levels of virus replication (Ericsen et al., 2014). These findings suggest that sex differences must be taken into account in the rational design of a vaccine that prevents AIDS. Funded by ORIP and the National Institute of Allergy and Infectious Diseases (NIAID).

HIV/AIDS: Risk of Neonatal Vaccination for HIV/SIV-Exposed Infants. Vaccinations are the most successful and cost-effective interventions in modern medicine. While an HIV vaccine could save millions of lives and would be the centerpiece of HIV prevention efforts, there are numerous challenges that remain in developing a vaccine that shows substantial efficacy in humans. Infants are one group likely to benefit from vaccine protection by preventing the nearly 400,000 new mother-to-child transmissions of HIV worldwide each year. In South Africa and many other developing countries, the two vaccines given at birth are Bacillus Calmette–Guerín (BCG) and Oral Polio Vaccine (OPV). These vaccines have clear protective benefits, but the immune activation that elicits these beneficial responses may simultaneously increase an infant's susceptibility to HIV. Investigators at the Washington NPRC are testing the hypothesis that early administration (within days of birth) of BCG or OPV increases the risk of oral SIV acquisition in infant monkeys. These studies may provide insight into the role of BCG and OPV neonatal vaccinations on oral mother to child HIV transmission. Funded by ORIP and National Institute of Dental and Craniofacial Research.

HIV/AIDS: Preventing and Determining the Earliest Events in Vaginal HIV Transmission. The majority of new HIV infections occur in women. While it is impossible to determine the earliest events involved in vaginal HIV transmission in humans, NHP (monkey) models are necessary to determine the initial cellular and molecular mechanisms involved in vaginal HIV infection. If the major early target cells or tissues can be identified, investigators can design more effective vaccines or microbicides to stop HIV at the portal of entry, before viral acquisition and dissemination can occur. Scientists at the Tulane NPRC are using new technologies to define how HIV-1 interacts with different tissues of the female reproductive tract (FRT), using the rhesus monkey vaginal transmission model. They have shown that HIV-1 can penetrate both intact columnar and squamous epithelial barriers of the vagina to depths where the virus can encounter and infect highly susceptible CD4+ T cells in the underlying lamina propria. These investigators have also demonstrated the presence of infected cells within 48 hours of SIV inoculation throughout the entire FRT. HIV consistently infects CD4+ T cells resident throughout the FRT, which are the primary target in the initial stages of infection. Systemically administered anti-HIV neutralizing antibodies are secreted at high levels in the FRT sufficient to prevent vaginal acquisition of SIV or HIV. These findings establish a new perspective that the entire FRT is susceptible and the virus can reach as far as the ovary and local draining lymph nodes. They also have demonstrated that protection of the FRT can be achieved if sufficient levels of antibodies are present in the FRT at the time of vaginal HIV exposure (Carias et al., 2013; Klein et al., 2013; Stieh et al., 2014). Funded by ORIP and NIAID.

HIV/AIDS: Prevention of Vaginal HIV Transmission Using Topical Molecular Fusion Inhibitors as Microbicides. Although the use of oral prophylactic drugs such as tenofovir has been licensed for HIV prevention, there are significant safety concerns associated with systemic administration of antiretroviral drugs to uninfected persons. Most antiretrovirals, including tenofovir, act at late stages of the viral replication cycle and permit cellular infection to occur in vaginal tissues, which can result in inflammatory signals being released that make the vagina more susceptible to subsequent HIV exposures. Investigators at the Tulane NPRC are studying a different type of anti-HIV drug, termed a topically applied Fusion Inhibitor, which can safely prevent attachment and entry of HIV in the vagina. They are formulating and testing these compounds in sustained release vaginal gels or rings that can provide sustained protection yet are not absorbed systemically, which may be a safer approach to HIV prevention. To date, they have shown that compounds that block CCR5 expression on CD4+ T cells in the vaginal vault can prevent vaginal acquisition and transmission. These studies demonstrate that topically applied agents

that specifically target specific molecules involved in viral attachment and entry can help women protect themselves again HIV infection (Fetherston et al., 2013; Malcolm et al., 2013a, 2013b). Funded by ORIP and NIAID.

HIV/AIDS: Differences in HIV Susceptibility During Menstrual Cycle Phase, Using the SIV-Monkey Model. Monkey models have demonstrated an increased susceptibility to vaginal viral infection during the luteal phase of the menstrual cycle. The biological reasons for the decreased resistance to viral infection are not known. In this study, investigators at the Yerkes NPRC used high-throughput genetic technology to examine changes in thousands of genes between the luteal (increased infection) and follicular phase (higher resistance to infection) of pig-tailed macaque monkeys. These researchers identified 76 genes that regulate immune responses that were missing in the luteal phase. These results have significant public health implications as it has been shown that high-dose, long-lasting, injectable progestin-based contraception can mimic the luteal phase and may predispose women on birth control to HIV-1 acquisition. Funded by ORIP and the U.S. Centers for Disease Control and Prevention.

HIV/AIDS: Sex Differences in HIV Pathogenesis. Men and women show a clear difference in their response to many viral infections, including HIV. Women infected with HIV exhibit greater control of viremia during early stages of infection, but present with elevated immune activation during later, chronic stages. Studies at the Yerkes NPRC have demonstrated that a portion of the female-male disparity may be explained by the quality of the viruses transmitted to women or to men (Carlson et al., 2014). On average, women that acquire HIV-1 harbor viruses with more mutations associated with immune pressure than men who harbor viruses with more conserved residues. However, by approximately 2 years post-infection, both women and men have viruses with similar numbers of immune pressure mediated mutations on average. This may explain the early but transient clinical advantage in women that is not seen in men. Elucidating the host barriers that mediate this restriction may pinpoint weaknesses in the virus that can be exploited for rational vaccine design. Funded by ORIP and NIAID.

HIV/AIDS: Multipurpose Microbicides for the Protection of Women from HIV and Herpes Simplex Virus (HSV) Vaginal Transmission. New HIV transmission disproportionately affects young women in developing countries and in the US. While condoms represent an effective barrier to transmission, their use is often difficult to negotiate for women. Hence, the development of a female controlled and inconspicuous mode of protection from HIV and other sexually transmitted pathogens, such as HSV, is essential. Scientists at the Tulane NPRC and their collaborators have shown that a gel-based microbicide can inhibit infection by both an analog of HIV and HSV in monkeys (Kizima et al., 2014). Scientists at the Yerkes NPRC are testing broadly neutralizing HIV and HSV human monoclonal antibodies produced in Nicotiana plants as a strategy for vaginal protection, using the monkey model. Funded by ORIP, NIAID, and the National Cancer Institute.

Reproductive Health

Endometriosis: Development of a Model of Early-Stage Disease. Endometriosis is a disorder defined by the presence of endometrium-like tissues at "ectopic" sites outside the uterus. Endometriosis affects approximately 10 percent of reproductive-age women, and infertility is a common outcome in 30 percent to 50 percent of these patients. The underlying cause of endometriosis-associated infertility remains controversial due to multiple disease-related factors. Spontaneous endometriosis occurs only in women and menstruating Old World monkeys. Investigators at the Oregon NPRC have demonstrated that endometriosis can be induced in naturally cycling rhesus monkeys. This provides a functional model of early stage disease relevant to preclinical study (Franasiak et al., 2014; Slayden, 2013). As the animals develop endometriotic cysts similar to those in women, this animal model can be used for studies of novel therapies and treatments for the disease. Funded by ORIP and NICHD.

Fertility and Contraception: Estrogens Produced in the Primate Brain Regulate Female Reproductive Hormone Secretions. In all female mammals, fertility is dependent upon the production of gonadotropin-releasing hormone (GnRH), a brain neuropeptide that regulates pituitary hormone release and controls ovarian functions. The ovaries produce estradiol and other hormones that exert feedback effects in the brain to maintain a desired level of activity in the hormone axis. Investigators at the Wisconsin NPRC have determined that ovarian estrogens are not alone in

regulating GnRH release. They have shown that the primate brain produces estradiol in amounts that clearly regulate GnRH release directly (Kenealy et al., 2013). Further studies will provide an understanding of the role these estrogen actions may play under normal conditions and in female infertility associated with stress, altered metabolic function, and disease. Funded by ORIP and NICHD.

Fertility and Contraception: Effects of Long-Term Binge Drinking Episodes Before Ovulation on Later Pregnancies. Binge drinking is an increasing public health concern, especially among young adult women. The California NPRC has used rhesus monkeys to study the effects of binge alcohol consumption on fertility. These investigators have provided the first evidence that binge ethanol drinking has the potential to affect oocyte quality and subsequent embryo development, even if alcohol is stopped before the final maturation and fertilization of oocytes (VandeVoort, Grimsrud, Midic, Mtango, & Latham, 2014). The study also revealed an increased rate of spontaneous abortion during very early gestation in ethanol-treated female monkeys after natural mating, a previously unrecognized effect of binge ethanol drinking. Funded by ORIP and the National Institute on Alcohol Abuse and Alcoholism.

Fertility and Contraception: Nonsurgical Permanent Contraception for Women. A number of agents have been evaluated for their potential to occlude the fallopian tubes after transcervical administration directly into the uterine cavity. One of the challenges has been the ability to achieve high rates of bilateral occlusion following a single application. Investigators at the Oregon and Southwest NPRCs investigated transcervical administration of polidocanol foam (PF), a U.S. Food and Drug Administration–approved treatment for uncomplicated "spider" and "reticular" varicose veins. These studies, performed in monkeys and baboons, demonstrated that transcervical administration of 5 percent PF blocks the intramural portion of the fallopian tube without affecting menstrual cyclicity. Development of a safe, low-cost nonsurgical method of permanent contraception would address a vast unmet need for family health planning, particularly in low-resource settings where surgery is risky (Jensen et al., 2014). Funded by ORIP, NICHD, and the Bill and Melinda Gates Foundation.

Fertility and Contraception: Mitochondrial Replacement Therapy. Mutations in mitochondrial DNA (mtDNA) occur in oocytes and their transmission to children results in serious disorders. Declining mitochondrial function in oocytes has been considered a major factor responsible for female infertility due to advanced maternal age (over 35 years of age). Mitochondrial replacement therapy (MRT) in unfertilized oocytes was pioneered at the Oregon NPRC using the rhesus monkey. It was designed to prevent second-generation transmission of mtDNA defects. MRT efficacy and safety was demonstrated by live births of rhesus monkey offspring with complete mtDNA replacement and normal growth curves to adulthood. MRT also offers replacement of deficient cytoplasm in oocytes from older patients, with the expectation of high pregnancy rates following in vitro fertilization (Tachibana et al., 2013). Funded by ORIP and NICHD.

Fertility and Contraception: Design and Validation of Ovary-Based Contraceptives. Recent advances in contraception for women have generally focused on modifications of steroid hormone levels ("the pill") approaches. While these approaches have been shown to be effective, concerns remain regarding side-effects on many tissues besides those involved in reproduction. Investigators at the Oregon NPRC are investigating nonhormonal approaches to female contraception in NHPs. Since prostaglandin E2 (PGE2) is required for follicle rupture and oocyte release in primates, these investigators have tested whether chronic administration of an antagonist to one subtype of PGE2 receptor 2 was contraceptive in adult female monkeys. Their studies have shown that chronic treatment significantly reduced fertility compared to controls without altering cyclic ovarian steroid hormone patterns or menstrual cyclicity (Peluffo et al., 2014). Additionally, they showed that fertility was recovered as early as one month after ending treatment. This approach provides a prototype for further studies to develop ovary-based non-hormonal contraceptives that do not alter menstrual cycles and permit restoration of fertility after use. Funded by ORIP and NICHD.

Fertility and Contraception: Development of a Novel, Nonhormonal Contraceptive. Investigators at the Washington NPRC are testing in an animal model a novel method of contraception based on a cell surface target called

Sperm Acrosomal SLLP1 Binding (SAS1B, encoded by the ASTL gene). Due to its unique biological characteristics, SAS1B is a cell surface target for both a female contraceptive and a cancer therapeutic (Pires et al., 2013). SAS1B presents an opportunity for a nonhormonal and fully reversible mechanism of contraceptive drug action in a new class of contraceptives known as oolysins. Several biological drugs are currently being developed to selectively target tumor cell surface SAS1B. A monkey model for SAS1B allows these drugs to be tested for safety and efficacy in NHPs. Funded by ORIP.

Fertility and Contraception: Improving Cryopreservation to Preserve Egg Viability. The ability to preserve spermatozoa and eggs for a long period of time is critical for retaining fertility and increasing the reproductive life span of individuals. Although spermatozoa survive freezing, oocyte preservation is more complex because of the cell's large size and complex structure. Current methods to preserve the oocyte are far from optimal. Using domestic cats as a model, investigators at the Smithsonian Institution collected and stored the egg nucleus (called the germinal vesicle) from donor cats. These germinal vesicles can be transferred to an egg from a different animal, from which the resident nucleus has been removed. This procedure reconstitutes a viable egg containing the genetic material of the egg donor. When applied to humans, these techniques may provide women with more viable options to preserve the genetic integrity of their eggs, for example when preparing for cancer treatment (Comizzoli & Wildt, 2013; Graves-Herring, Wildt, & Comizzoli, 2013). Funded by ORIP.

Physiology: Rat Models for Sex Steroid Action. Estrogens and progestins are key hormones affecting the physiology of the entire organism. Estradiol binds and signals through estrogen receptor alpha and estrogen receptor beta, while progesterone signals through the progesterone receptor. Researchers at the University of Kansas Medical Center are generating and characterizing rat models for sex steroid hormone action by independently targeting Esr1, Esr2, and Pgr2. They are focusing on the effects on the female reproductive tract (Karim Rumi et al., 2014). Rats possessing disruptions in estrogen and progesterone signaling will provide new tools for biomedical scientists in a range of disciplines. Funded by ORIP.

Polycystic Ovary Syndrome: Effects of Prenatal Androgen Exposure. Polycystic ovary syndrome (PCOS) is prevalent in reproductive-aged women and confounded by metabolic morbidities, including insulin resistance and type 2 diabetes. Although the etiology of PCOS is undefined, the contribution of androgen (male sex hormone) exposure prenatally has been proposed in a rhesus monkey model. Prenatal androgen exposed female infants exhibit higher levels of insulin circulating in the blood than expected relative to the level of glucose, suggesting future metabolic disease. Collaborative studies conducted at the California and Wisconsin NPRCs have assessed the consequences of prenatal androgen exposure on pancreatic islets (the anatomical structures that produce insulin) to identify evidence of early programming on islet development (Nicol, O'Brien, Dumesic, Tarantal, & Abbott, 2014). These studies suggest that in utero androgen excess combined with mild maternal glucose intolerance can alter infant and adult islet structure, implying that development of these cells is altered. Funded by ORIP, the National Center for Advancing Translational Sciences, NICHD, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Polycystic Ovary Syndrome: Effects of Diet. Investigators at the Oregon NPRC have examined if the modest elevation in androgen (testosterone) observed in adolescent girls at risk for PCOS, alone or in combination with a "western-style" (high-fat, high-calorie, and high-fructose) diet (WSD), causes symptoms comparable to PCOS. Using female rhesus monkeys, testosterone exposure beginning prior to puberty and into young adulthood caused some features reminiscent of PCOS plus others (e.g., insulin insensitivity, numerous small antra follicles or "cysts" in the ovaries) when combined with the WSD (McGee et al., 2014). Based on these positive results, these investigators are performing an extensive trial over 5 years to evaluate, in the monkey model, the effects of androgen, WSD, alone and combined, on neuroendocrine, reproductive, and metabolic parameters. The findings may increase the understanding of the causes of phenotypic changes (symptoms) in early PCOS and the possible value of preventing androgen or diet effects to restore fertility. Funded by ORIP and NICHD.

Pregnancy: Impact of Maternal Obesity on Placental Function. The dramatic rise in obesity rates around the

world is partially due to the availability and consumption of calorie-rich, high-fat foods, the so-called WSD. In the United States, more than 20 percent of women are now obese (with a body mass index of more than 30 kg/m2) at the start of pregnancy, which has associated risks for the health of the developing baby (Armitage, Taylor, & Poston, 2005). Because the placenta mediates nutrient exchange from mother to baby, investigators at the Oregon NPRC have focused on examining the effects of diet-induced maternal obesity on placental function, using a monkey model. They have demonstrated that consumption of a WSD during pregnancy reduces maternal blood flow to the placenta and increases placental inflammation. Using magnetic resonance imaging techniques to examine blood flow, these investigators have developing methods to identify pregnancies that are at-risk for placental dysfunction. These studies allow testing for the safety of dietary interventions before implementing their use in humans (Frias et al., 2014; Roberts et al., 2014.) Funded by ORIP, NICHD, and NIDDK.

Pregnancy: Experimental Model for Studying Chorioamnionitis and Preterm Labor. Preterm birth remains a significant economic and public health burden and the incidence is rising around the world. Predominant risk factors for preterm birth and neonatal morbidity are invasive bacterial infections that mainly begin in the uterus. The mechanisms that enable bacterial invasion of the amniotic fluid and fetus are unknown. The inability to repeatedly sample multiple compartments during human pregnancy (e.g., mother, fetus, amniotic fluid) and the lack of animal models that simulate in utero host-pathogen interactions occurring in humans has contributed to this knowledge gap. Investigators at the Washington NPRC have recently overcome these limitations by developing a monkey model of pregnancy that closely emulates human pregnancy and allows investigations on the mechanisms by which bacteria invade the uterus and the amniotic sac. Funded by ORIP.

Pregnancy: Uterine Vascular Remodeling. An estimated 25 percent to 60 percent of conceptions result in pregnancy failure depending on the mammalian species. In humans, recurrent pregnancy loss occurs in about 1 percent of pregnancies and is among the most common complications of pregnancy. Disruption of the renin-angiotensin system, specifically components that regulate vasodilation, is thought to be causally linked to the development of preeclampsia in human pregnancy. Using genetically modified mice, investigators at Washington State University are examining the function of a novel G-protein coupled receptor called MRGPRG, which, in uterine stroma, functions as a mediator for angiotensin-(1-7)-induced vasodilation at the maternal-embryo interface. This receptor is likely functionally required for normal pregnancy. Flaws in placental blood flow can lead to major complications of pregnancy and an understanding of the processes that lead to this will represent a significant advance for the field. Funded by ORIP.

Prenatal and Perinatal Health: Prenatal Exposure to Bisphenol A (BPA) Disrupts Fetal Development. BPA is used in the manufacturing of various plastics and food packaging. Additional information is needed on how early exposure to ubiquitous chemicals like BPA affects pulmonary health, in part through their effect on the fetus. Pregnant rhesus monkeys were given oral or subdermal BPA on gestation days 50 to 100 or from day 100 to term. The results suggest that environmentally relevant BPA exposure levels during pregnancy cause detectable developmental aberrations in multiple organ systems in the developing primate fetus. To place these findings in the context of human exposures, investigators compared levels of bioactive BPA attained in maternal and fetal serum by comparison with those observed in a relevant human biomonitoring study of midgestation pregnancies. This comparison suggests that the results obtained from this small group of extensively studied rhesus monkeys has direct relevance to humans (Calhoun et al., 2014; Chapalamadugu, Vandevoort, Settles, Robison, & Murdoch, 2014; Vom Saal et al., 2014). Funded by ORIP and the National Institute of Environmental Health Sciences.

Prenatal and Perinatal Health: Preventing Preterm Birth and Associated Health Risks of Prematurity. Preterm birth remains a persistent problem in obstetric medicine and represents a significant public health burden around the world (Blencowe et al., 2013). Preterm birth is most often precipitated by intra-amniotic infection with *Ureaplasma* species. Investigators at the Oregon NPRC have shown the effectiveness of macrolide antibiotic therapy in eradicating *U. parvum* from the amniotic cavity, delaying preterm labor and reducing the severity of fetal lung injury in monkeys (Acosta et al., 2013; Frias et al., 2014). Funded by ORIP and NICHD.

Prenatal and Perinatal Health: Fetal Development and Maternal Nutrient Reduction. Maternal undernutrition increases the risk of perinatal complications and predisposes offspring to metabolic and cardiovascular disease later in life. Emerging evidence suggests that changes in placental function due to maternal under-nutrition plays a role in early onset of adult disease. Investigators at the Southwest NPRC are using baboons to study these issues. Pregnant baboons were divided into two groups: a control group that ate ad lib and a nutrient reduced group that ate 30 percent less than controls. The caloric reduction was similar to that of women dieting during pregnancy. These investigators identified genes and genetic networks in controls and nutrient-reduced groups for female and male placentas and found female placentas exhibited a highly coordinated genetic response to nutrient reduction, suggesting adaptation to the nutritional environment. Male placentas did not exhibit these coordinated responses. These findings suggest that female placentas initiate complex adaptive responses to an adverse intrauterine environment that may contribute to increased survival and better pregnancy outcomes in girls than in boys. These studies reinforce the concept that even moderate lack of nutrients impacts the health of the children of those pregnancies (Cox et al., 2013). Funded by ORIP and NICHD.

Prenatal and Perinatal Health: Adult and Transgenerational Toxicity Due to Developmental 2,3,7,8 Tetrachlorodibenzo-p-Dioxin (TCDD) Exposure. This project examines in the zebrafish model the effects of prenatal or perinatal exposure to the environmental toxin TCDD on disease later in adult life. Researchers at the University of Wisconsin–Madison have shown that a single low-level exposure to TCDD in juvenile zebrafish can cause skeletal malformations similar to scoliosis in humans, as well as reproductive, nervous system, and behavioral toxicity as these fish grow to become adults. Similar abnormalities were observed in the next two generations of progeny in the absence of exposure to the toxin (Baker, King-Heiden, Peterson, & Heideman, 2014). These studies will facilitate the further analysis of the effects of exposure to this toxin using the zebrafish model, which should be directly applicable to studies in humans. Funded by ORIP.

Sexually Transmitted Diseases (STDs): Evaluation of Topical Microbicides in NHPs. One strategy for decreasing the prevalence of STDs is to develop topical microbicides that can be applied to the vagina or to the rectum to block infectious agents. Investigators at the Washington NPRC are conducting research to determine the safety and effectiveness of a microbicide compound for preventing transmission of several different STDs, including *Trichomonas vaginalis,* chlamydia, and HIV in pigtail macaque monkeys (Gupta et al., 2013). Funded by ORIP and NIAID.

STDs: Examining the Influences of Hormones on the Vaginal Epithelium. Recent studies in women suggest that injectable hormone contraceptives containing progestins may make women more susceptible to vaginal HIV transmission. However, such studies are difficult to interpret due to the low incidence rate of HIV transmission to women. Studies of contraceptive use in women are also confounded by numerous variables including decreased condom use. Other reports do not support an increased risk for HIV transmission in women on contraceptives. Several years ago, investigators at the Tulane NPRC demonstrated that progestin-based compounds, such as those used in injectable hormonal contraceptives, result in thinning of the vaginal epithelium and markedly increased susceptibility of rhesus monkeys to vaginal SIV infection. Monkeys are clearly the best model for understanding the differences in susceptibility of the vagina to human STDs. These investigators have compared differences in the vagina of monkeys, correlating changes in the architecture and barrier function of the vaginal epithelium with hormone levels at different stages of the menstrual cycle with those of women. Consistent differences in vaginal epithelial thickness were detected at specific stages of the menstrual cycle in monkeys. The vaginal epithelium was significantly thicker in the follicular compared to the luteal phase of the cycle. These findings also suggest that women may be more susceptible to certain STDs during the luteal stage of the menstrual cycle (Hadzic et al., 2014; Veazey, 2013). These researchers are testing strategies that maintain or thicken the vaginal epithelium throughout the menstrual cycle that may help prevent STDs in women. Funded by ORIP and NIAID.

Aging and Menopause

Aging: Monkey Model of Alzheimer's Disease. The amyloid burden in the brains of young adult and older female vervet monkeys was evaluated by scientists at the Wake Forest School of Medicine. There was a significant increase in the amount of amyloid beta proteins Aβ40 and Aβ42 as well as glial fibrillary acidic protein (a marker of astrocytes) with age. The study suggests that the vervet monkey will be a useful model for exploration of mechanisms underlying development of Alzheimer's disease in humans (Kalinin et al., 2013). Funded by ORIP; the National Heart, Lung, and Blood Institute; NIA; and the U.S. Department of Veterans Affairs.

Menopause: Hormonal Effects on the Menopausal Transition. Until recently, the primary focus in understanding sex differences in aging has been on the ovary, with the assumption that an age-related decrease in ovarian function and accompanying loss of sex steroids were the primary causes of symptoms and adverse health trajectories in middle-aged women. Studies at the California NPRC have shown that the adrenal cortex of the female monkey expresses receptors for luteinizing hormone (LH). When activated, these receptors respond to the rise in circulating LH and increase steroid production. Furthermore, treatment of ovariectomized females with a combined hormone replacement therapy containing both an estrogen and a progestin further increases the capacity of the adrenal cortex to produce sex steroids, mainly androgens. Intervening with estrogen alone does not have this same effect (Baxter et al., 2013; Conley et al., 2013; Lasley, Crawford, & McConnell, 2013; Moran, Chen, Gee, Lohstroh, & Lasley, 2013; Young et al., 2013). These findings provide a new concept to potentially explain the increase in weight gain, metabolic syndrome, and cardiovascular disease that occurs in some women during the menopausal transition and before a significant decline in circulating estrogen can be detected. Funded by ORIP and NIA.

Diet

Factors that Initiate and Sustain Emotional Feeding in Females. Overconsumptions of caloric dense diets are thought to be a primary cause of the obesity epidemic in the United States. However, vulnerability to excessive consumption of these diets is quite variable. Emotional feeding resulting from chronic exposure to psychosocial stressors is likely a key factor for excess food intake. This may be particularly important for women, who consistently report more stress-induced eating and have higher rates of obesity than men. Using adult female rhesus monkeys at the Yerkes NPRC, investigators have examined how chronic exposure to social stressors, mediated by social subordinate in group-housed animals, interacts with the dietary environment to initiate and sustain excessive food consumption leading to obesity. Social subornation in adult female rhesus monkeys produces a number of stress-related characteristics, similar to those observed in women. A prominent feature of socially subordinate females is a compromised dopamine reward circuitry, as seen on neuroimaging scans. The data suggest that excessive consumption of high-fat, high-sugar diets is a form of self-medication in view of the unrelenting stressor of being subordinate. Studies show that stress hormone signals are important in maintaining excessive consumption of these diets, as short-term administration of a stress hormone antagonist attenuates emotional feeding in subordinate females (Johnson et al., 2013; Moore, Johnson, Michopoulos, Toufexis, & Wilson, 2015; Moore et al., 2013; Moore, Michopoulos, Johnson, Toufexis, & Wilson, 2013; Wilson, Moore, Ethun, & Johnson, 2014). These researchers are investigating whether a behavioral intervention, to alleviate chronic stress, improves dopamine function and diminishes emotional feeding. These studies will increase our understanding of factors that sustain emotional feeding, even in a healthy dietary environment and will highlight the notion that chronic social stress is a precipitating factor for the emergence of obesity in people. Funded by ORIP, NIDDK, and the National Institute of Mental Health (NIMH).

Behavior

Chronic Stress Negatively Affecting Genome-Wide Expression and Immune Function. The social environment has a clear and profound impact on human health and well-being. Chronic social stress and reduced access to social support are predictive of a number of adverse health outcomes including cardiovascular disease and diabetes. Evidence suggests that social stress is linked to life expectancy itself. Poor social integration, for example, has been estimated as a risk factor for mortality on the scale of familiar health risks like smoking and obesity.

Despite keen interest in social stress as a human health concern, the mechanistic relationships linking social stress to its impact on the body are still poorly understood, particularly on the level of the genome. Investigators at the Yerkes NPRC are investigating how dominance rank in female rhesus monkeys influences genome regulation. Dominance status in monkeys is an excellent model for human social stress: The natural hierarchical organization of monkey social groups is characterized by increased rates of harassment and threats directed towards lower ranking group members, which are reflected in a number of rank-related stress characteristics. Additionally, dominance rank assignments can be experimentally imposed in this species by altering group membership. An individual's exposure to social stress can also be manipulated, yielding an experimental system for investigating the effects of social stress on the genome that is directly translatable to humans, but that is practically and ethically impossible in humans themselves (Michopoulos, Higgins, Toufexis, & Wilson, 2012). Small social groups of adult female rhesus monkeys were successfully formed following removal from their natal groups. Studies show that subordinate females have a chronic up-regulation of proinflammatory genes and down regulation in anti-inflammatory genes in the face of glucocorticoid resistance. Ongoing analyses will determine whether immune function is compromised in subordinates by challenging cells in vitro with a number of pathogens. To determine whether immune system regulation is improved by stress alleviation, the social groups have been successfully rearranged so that some formerly subordinate females are now dominant while some formally dominant females are now subordinate. These efforts will illustrate how social stress changes gene expression in an important animal model for human social stress, including how stress mitigation might offset the physiological costs of prior stress and how increased stress may alter individual vulnerability to disease. Funded by ORIP and the National Institute of General Medical Sciences.

Stressor Exposure Altering the Behavioral Effects of Hormones in Females. Female ovarian hormones, most notably estradiol, are thought to have a major neuroprotective effect on the brain. However, women have disproportionately higher rates of stress-induce behavioral problems compared with men, suggesting that stress may alter these protective effects on brain function. Using female rhesus monkeys at the Yerkes NPRC, investigators determined how social stressor exposure, mediated by social subordination in group-housed animals, altered the efficacy of estradiol action on behavior. Social subordination in adult female rhesus monkeys produces a number of stress-related characteristics, similar to those observed in women. In particular, the stress hormone axis becomes disrupted such that subordinate females are not capable of responding appropriately to stressors. Data from these studies show that social subordination reduces the efficacy of estradiol to increase affiliation with group members, including adult males. These differences in the hormonal regulation of behavior are associated with changes in brain chemistry, assessed by positron emission tomography imaging, and an alteration in how the region of the brain involved in top down control of behavior (the prefrontal cortex) in magnetic resonance imaging (Asher, Michopoulos, Reding, Wilson, & Toufexis, 2013; Michopoulos et al., 2013, 2014). These data indicate that stressor exposure in females disrupts estradiol action on the brain and affects behavior, suggesting that these alterations may explain how stress may impair behavioral health in women. Funded by ORIP and NIMH.

Increased Vulnerability to Adverse Consequences of Stress During Adolescence in Females. Adolescence is a time for increased vulnerability to social stressors and increased risk to develop emotional problems. Furthermore, girls show a higher frequency of stress-induced emotional reactivity more often than boys. In order to determine developmental changes in brain circuitry that regulate behavior during adolescence in girls, socially housed, juvenile female rhesus monkeys at the Yerkes NPRC were studied longitudinally from pre-puberty through post-puberty. Female offspring assume the relative dominance rank of their mothers, and socially subordinate females within these groups show a number of stress-related characteristics. The study was able to examine how this social stressor affected neurobehavioral development. Since the ovarian hormone is thought to organize brain development as females progress through puberty, half of the dominant and subordinate females were treated with a hormone that arrests reproductive maturation (depot Lupron). Using a number of neuroimaging techniques coupled with behavioral testing, the studies show that social subordination changes brain structure and connectivity. Subordinate juveniles have significantly larger amygdala, and this is associated with increased emotional reactivity.

Furthermore, connections within the prefrontal cortex that project to other limbic regions are also altered. The data further suggest that estradiol may differentially affect neurobehavioral development, as females with no developmental increase in estradiol (i.e., those treated with Lupron) were less emotionally reactive and had a different trajectory of brain maturation (Embree et al., 2013; Howell et al., 2014; Wilson et al., 2013). These data indicate that developmental increases in estradiol coupled with exposure to social stressors changes brain structure and function in females and increases incidence of emotional reactivity. The data highlight the importance of providing girls with appropriate coping strategies to mitigate the adverse consequences of stress during adolescence. Funded by ORIP and NIMH.

Stress and Obesity Effects on Neurobehavioral Development in Females. Studies of animals and children show that postnatal stress may have lasting effects on brain structure and function, resulting in behavioral and cognitive impairments, particularly for females. It is also unclear how social stress experienced by the mother during gestation synergizes with postnatal stress experienced by her offspring to further increase these developmental differences. Other environmental factors that may interact with stressor exposure to affect brain development during childhood are frequently overlooked, most notably the consumption of calorically dense diets and resulting obesity. There is likely a synergy, as chronic social stress is a cumulative risk factor for childhood obesity. Not only may obesity accelerate the tempo of puberty, but limited data in children suggest that the developing brain is vulnerable to these metabolic insults, as increased body fat is associated with altered brain structure and deficits in cognition and emotional processing. As prospective studies of this nature are not possible in girls, investigators at the Yerkes NPRC are studying female rhesus monkeys from in utero through puberty. Since female offspring assume the relative dominance rank of their mothers and socially subordinate females within these groups show a number of stress related characteristics, females are exposed to varying levels of adverse social experience. Half of the subjects are maintained on a typical low-fat, high-fiber primate diet, while the other half are fed a choice between this prudent diet and a diet high in fat and sugar, comparable to what American children consume. In order to disentangle the effects of pre- versus postnatal factors on neurobehavioral development, females are studied longitudinally with a variety of behavioral and cognitive tests coupled with extensive structural and functional magnetic resonance imaging. Key biological signals could be stress-induced elevations in cortisol and proinflammatory cytokines that are exacerbated by increased fat mass. Understanding the impact of stress and obesity on neurodevelopment is critically relevant, given alarming rates of obesity in children, likely due to the consumption of high-fat, high-sugar diets. Funded by ORIP and NICHD.

Stem Cells and Regenerative Medicine

Endocrine Disruption of Myometrial Stem Cell Activities. The adult uterus undergoes repeated cycles of "injury and repair" in response to hormonal signals during the estrous cycle in mice as well as the menstrual cycle in primates. This occurs numerous times in a normal reproductive life span, as well as during pregnancy, when the uterus grows tenfold to accommodate the fetus. Although this process of remodeling is essential for reproduction, the molecular mechanisms involved are largely unknown, particularly in primates where the top layer of the endometrium is shed and regenerated every month. Investigators at Michigan State University have examined whether disruption of Wnt/β-catenin signaling in uterine myometrial smooth muscle stem cells leads to uterine pathologies such as leiomyoma and fibroids. They have identified the regenerative myometrial smooth muscle stem cells in mice and in humans and are investigating whether environmental estrogens (1) impact the differentiation and pluripotency of myometrial stem cells during cycling, pregnancy, and leiomyoma development; (2) dysregulate the molecular mechanisms of Wnt/β-catenin signaling; and (3) alter the differentiation and pluripotency of myometrial stem cells during the perinatal window of myometrial development (Park et al., 2014; Patterson, Zhang, Arango, Teixeira, & Pru, 2013). The results of these investigations will help determine whether environmental estrogens have a significant impact on the differentiation and function of myometrial stem cells. Funded by ORIP.

Career Development Activities and Programs

The Division of Comparative Medicine (DCM) at ORIP participates in many NIH Career Development Programs. The Mentored Research Scientist Development Award (Parent K01) assists graduate veterinarians to become independent investigators in research related to comparative medicine. The T32 and T35 Training Grants also provide opportunities for career development, providing long- and short-term support for training highly qualified veterinarians and veterinary students for research careers in biomedical areas related to comparative medicine, comparative pathology, or research related to applications that improve and extend healthy lives and prevent illness. Women are well-represented as mentors and trainees in all these programs. In the K01 program, just over 70 percent of the DCM awards are made to women. Women represent just over 75 percent of the trainees in the T32 and T35 mentoring and training programs. The DCM also solicits Research Education Grant (R25) applications to provide research education for veterinarians interested in pursuing a career in Laboratory Animal Medicine focusing on biomedical investigations, with an emphasis on performing collaborative research, development and maintenance of animal models for translational research activities, and professional direction for animal resource/research programs. Women represent approximately 75 percent of participants within these R25 research education programs.

STEM Efforts

Science Education Partnership Award

The SEPA program (http://www.nihsepa.org), established in 1991, supports diversity in the workforce by providing opportunities for female and male students from underrepresented minorities and underserved communities, including American Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, low-income populations, and rural populations, to consider careers in the fields of basic or clinical research. SEPA encourages partnerships with the Institutional Development Awards (IDeA), Research Centers in Minority Institutions, Clinical and Translational Science Awards programs as well as with other Federal agencies. Examples of SEPA-funded projects that target health disparity in underrepresented minorities and underserved communities as well as between the sexes include SEPA Community-Based Participatory Research projects on disease prevention, including prevention of obesity, diabetes, and cardiovascular disease. SEPA-funded informal science education (ISE) projects include science center and traveling health exhibits, public service announcements on radio and TV, and documentaries and other films. Outreach activities, such as Science Cafes and Community Health Fairs, educate students, teachers, and the community on the correlation between lifestyle and health, including issues of importance to women and girls. Just over 60 percent of the principal investigators of SEPA projects are women.

Teaching to Learn: West Virginia Health Sciences Technology Academy (HSTA) Students Take Community-Based Participatory Research to Their Community. Rural and minority populations have less access to health care and experience poorer health outcomes than affluent socioeconomic groups. In rural Appalachia, the disparity of access to health is paralleled by the high prevalence of chronic diseases related to obesity. Over the last decade, the West Virginia SEPA project HSTA (http://www.wv-hsta.org) at the West Virginia University Health Sciences Center has created a novel design to improve health literacy and biomedical career opportunities for underserved Appalachian populations (McKendall, Kasten, Hanks, & Chester, 2014). HSTA targets 9th- to 12th-grade students from medically underserved communities in West Virginia by using a student and teacher-driven community-based participatory research mode to educate the students and their communities on the health benefits of behavioral changes that address nutrition, physical activity, and lifestyle. A quantitative evaluation study was conducted to determine if student participation in the HSTA program led to significant differences in the math and reading/language arts scores on the West Virginia Educational Standards Test 2. Outcome data comparing HSTA students with a matched control group demonstrated that there is a statistically significant difference in math and reading/language arts of the cohort of 168 students (70 percent female) from African-American, White, Hispanic, and Asian communities who participated in the program. To date, HSTA has graduated

2,049 students with a college matriculation rate of 99 percent, versus 59 percent for all West Virginia students. Ninety percent of HSTA students, versus 66 percent for West Virginia, graduate with a 4-year degree. Fifty-one percent of HSTA college graduates are engaged in a health or STEM-related careers. Funded by ORIP.

Health Disparities

Get in the GROOVE! This SEPA project (http://www.miamisci.org/groove) addresses the health disparities affecting underserved female youth, as well as the national need to cultivate diversity in preparing the next generation of female health professionals. Get in the GROOVE!, targeting middle school girls from underrepresented communities, is designed (https://clinicaltrials.gov/ct2/show/NCT02187939) to stimulate interest in science careers while promoting healthy behavior in young girls by addressing the two key factors contributing to health disparities in youth: education and behavior. Given the alarming rate of obesity among high school minority youth, the project focuses on middle school with the primary aim of reaching middle school girls before unhealthy habits become firmly ingrained. The project brings together the research and ISE community in an innovative effort to contribute to the knowledge base with regard to the impact of informal learning environments as a delivery system for communicating key health messages to diverse populations and to explore the use of virtual world technology as a vehicle for motivating interest in learning how a healthy diet and physical activity can affect an individual's well-being throughout life. Get in the GROOVE!'s goals are to (1) increase female middle school students' awareness of and interest in nutrition and physiology related STEM career pathways; (2) develop science-rich health education resources for female middle school students that motivate interest in adopting a healthy lifestyle; (3) increase parental awareness, within a culturally appropriate context, of the importance of good nutrition and physical activity for children's health; (4) rigorously evaluate, in a multicenter randomized controlled trial, conducted at the Miami Science Museum and the New York Hall of Science, the extent to which a 3-D Virtual World environment explored in an informal museum setting produces gains in middle school girls' self-efficacy, health knowledge, and readiness for positive behavior change; and (5) broadly disseminate the evaluated project results and research findings to the global community of health, ISE, and K-12 research communities. Funded by ORIP.

Funding Initiatives, Workshops, and Conferences

Program Announcements

ORIP led several funding opportunities in FYs 2013 and 2014. Those that included a focus on women and related trans-NIH topics are listed below.

Pilot Centers for Precision Disease Modeling (U54) (PAR-14-280). ORIP solicited applications for collaborative research projects that link personalized medicine efforts in human subjects with advances in animal genomics and technologies for genetic manipulation and creation of interspecies somatic hybrids. Functionally linking these research areas will produce programs to enhance the predictive value of preclinical studies based on use of precision animal models. Centers will establish demonstration pipelines for preclinical scientific discovery, disease modeling, and development of interventions based on innovative animal models. These preclinical pipelines eventually will be an integral part of diagnostics, care and therapeutic treatment of patients of both sexes (http://grants.nih.gov/grants/guide/pa-files/PAR-14-280.html).

PAR: NIH ORIP SEPA (R25) (PAR-14-228). The goal of the SEPA program is to invest in educational activities that enhance the training of a workforce to meet the nation's biomedical, behavioral and clinical research needs. This funding opportunity announcement encourages the development of innovative educational activities for pre-kindergarten to grade 12, teachers and students from underserved communities with a focus on courses for skills development, research experiences, mentoring activities, curriculum or methods development, ISE exhibits, and outreach activities (http://grants.nih.gov/grants/guide/pa-files/PAR-14-228.html).

PAR: NIH SEPA Serious STEM Games for Pre-College and Informal Science Education Audiences (SBIR) (R43/R44) (PAR-14-325) and PAR: NIH SEPA Serious STEM Games for Pre-College and Informal Science Education Audiences (STTR) (R41/R42) (PAR-14-326).

The goal of these Funding Opportunity Announcements (FOAs) is to encourage eligible small business concerns to submit SBIR/STTR grant applications to develop educational STEM games with a focus on biology that addresses health and medicine questions for (1) pre-kindergarten to grade 12 students and pre- and in-service teachers or (2) ISE audiences. It is anticipated that these SBIR/STTR FOAs will facilitate translation of new or existing health and medicine-based, pre-kindergarten to grade 12 STEM curricula and museum exhibits into educational games providing hands-on, inquiry-based and learning-by-doing experience for students, teachers and the community (http://grants.nih.gov/grants/guide/pa-files/PAR-14-325.html, http://grants.nih.gov/grants/guide/pa-files/PAR-14-326.html).

Conferences and Workshops (in chronological order)

Annual SEPA U13 PI/NIH SciEd Conference, May 13–16, 2013; May 4–6, 2014. The overriding goal of the annual SEPA SciEd Conference is to establish collaborations, identify best practices for each type of project, and document rigorous and appropriate evaluation tools. The major focus of the 2013 and 2014 conferences was information exchange between NIH-funded projects and the lead Federal agencies engaged in STEM education—the U.S. Department of Education, the National Aeronautics and Space Administration, the National Oceanographic and Atmospheric Administration, and the National Science Foundation. The 76 NIH R25 STEM projects represented at the conference were funded by SEPA, the National Institute on Drug Abuse, NIAID, the National Institute on Minority Health and Health Disparities, the IDeA Networks of Biomedical Research Excellence, and the NIH K-12 Blueprint for Neuroscience. Agency program staff conducted plenary sessions about each agency's STEM initiatives. Breakout sessions covered synergies of multiagency funding, the approaches in which NIH P-12 STEM projects and programs or projects at each agency can interact synergistically, and different types of projects (e.g., authentic research experiences, curriculum development, early STEM, ISE, rural education, teacher professional development).

Annual Mobil Laboratory Coalition (MLC) Conference (SEPA R13), June 23–26, 2103; June 24–27, 2014. The MLC Conference is the premiere conference and networking event specifically for STEM educators, professionals, suppliers, and partners. The only conference of its kind, the MLC Conference allows attendees to learn about advances in ISE, share ideas, and collaborate with industry thought leaders. The conference is targeted at both new and established ISE programs with sessions appropriate for staff in a variety of roles. The conference includes plenary sessions, poster presentations, and workshops that address key topics such as collecting meaningful evaluation data, engaging diverse learners, preparing the students for an evolving job market, incorporating next-generation science standards, interfacing with the audience, incorporating technology into teaching, marketing the program, and identifying funding sources.

Animal Models and Personalized Medicine, October 28–29, 2013. The goals of the workshop were (1) to discuss the status of human personalized genomics and the use of comparative functional genomics in other organisms to interpret patient information for clinical use, (2) to review the current status of the development and use of the personalized animal models based on a variety of animal species, (3) to evaluate the potential use of personalized animal models for translational medicine applications, and (4) to develop the consensus and provide recommendations to NIH regarding the potential strategic initiatives that would make a valuable contribution to the field. Discussions included the creation and use of predictive animal models for individualized medicine of heterogeneous patients of both sexes.

From Tank to Bedside: Zebrafish and Translational Research, October 29–30, 2013. The objectives of the workshop were (1) to provide input to NIH on the current status of projects and technologies that directly inform studies related to human health using the zebrafish as an animal model and (2) to provide advice to NIH on initiatives that can enhance the use of zebrafish in translational research involving both sexes.

Animal Models Impacting Human Disease: Tenth Comparative Medicine Resource Directors Meeting, August 12–13, 2014. The objective of this biennial meeting supported by ORIP was to provide a forum to (1) exchange new information, advances, and ideas among grantees and

NIH staff members from several Institutes and Centers (ICs); (2) increase collaborations and sharing among DCM-funded Resources and between these Resources and various NIH ICs; (3) inform Resources and NIH staff about accomplishments and challenges; and (4) identify

Resource-related scientific advances on evolving animal-human correlations, emerging technologies, and reproducibility in animal models of human disease. The issue of sex differences in animal disease models was one of the topics discussed during a scientific session on the impact of the reproducibility of animal studies on animal model resources. The development or enhancement of technologies and protocols for sex determination of embryonic, larval, juvenile, and adult life stages of zebrafish and other aquatic species was identified as a critical need for ensuring reproducibility of research with these types of animal models.

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Office of Strategic Coordination (NIH Common Fund)

Executive Summary

The NIH Common Fund was first launched as the Roadmap for Medical Research in 2004 and renamed the Common Fund in the NIH Reform Act of 2006. Managed by the Office of Strategic Coordination (OSC) within the Division of Program Coordination, Planning, and Strategic Initiatives, the Common Fund supports research in areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps that deserve special emphasis; that would benefit from strategic coordination and planning across the NIH ICs; and that are designed to address specific, high-impact goals and milestones within a 5- to 10-year time frame. Common Fund programs transform the way science is conducted through the establishment of new scientific fields or paradigms, the development of technologies or methods that change the way scientists approach their work, or the generation of comprehensive data sets or other resources that catalyze investigator-initiated research and enable discovery. Collectively, Common Fund programs represent strategic investments aimed at solving problems or building resources to catalyze research throughout the entire biomedical research enterprise.

In FY 2014, the OSC recognized an opportunity to provide substantial insights into sex differences through enhancements to a number of programs. The Common Fund supported supplements to existing Common Fund grants to bolster analysis of the effects of sex in preclinical and clinical studies. The total amount of these supplements is approximately $4 million. Additionally, Common Fund-supported investigators are being encouraged to consider sex as an important biological variable that should be considered in the course of doing research, as appropriate.

Accomplishments and Activities

In FY 2014, the Common Fund supported supplements for sex differences research within several Common Fund programs.

Genotype-Tissue Expression (GTEx)

The Common Fund's GTEx program provides data on how human DNA variation correlates with variation in gene expression levels, uncovering valuable insights into the mechanisms of gene regulation and how perturbations in gene expression may be related to various diseases. Although data were being collected from male and female donors, dedicated analysis of sex differences had not been planned.

GTEx Supplements

Dr. Christopher Brown and Dr. Barbara Englehardt (supplement to R01-MH-101822). This supplement aims to understand the impact of sex specificity on gene expression. The investigators will identify gene transcripts and splice sites that are differentially expressed in males and females and will look for sex-based differences in gene expression levels that correlate with genetic variation.

Dr. Nancy Cox and Dr. Emmanouil Dermitzakis (supplement to R01-MH-101820 and R01-MH-101814). This supplement is developing and using novel methods to characterize the role of sex in gene transcription, including transcriptional variation, sex-specific gene expression, and the relationship of sex-biased transcriptome biology to disease.

Dr. Andrew Feinberg (supplement to U01-MH-104393). This supplement investigates sex differences in gene expression within the brain that may be controlled by modification to DNA or DNA-associated proteins, called epigenetic modifications.

Dr. Michael Snyder (supplement to U01-HG-007611). This supplement aims to identify sex-specific differences in protein expression and sexually dimorphic biological pathways.

Dr. Barbara Stranger (supplement to U01-HG-007598). This supplement is evaluating proteins across multiple tissues in many individuals, focusing on sex-biased gene expression levels, hormone signaling pathways, sex-chromosome encoded genes, and proteins implicated in complex diseases with sex-biased characteristics.

Human Health and Heredity in Africa (H3Africa)

H3Africa, part of the Common Fund's Global Health program, aims to enhance the capabilities and capacities of African scientists to enable a contemporary research approach to the study of the genomics and environmental determinants of disease and to use this information to improve the health of Africans and populations around the world.

H3Africa Supplements

Dr. Guida Landoure (supplement to U01-HG-007044). This supplement is examining sex differences in psychosocial burden related to hereditary neurological disorders. Early results show that women disproportionately experience negative psychosocial consequences of such disorders, and this research aims to elucidate the factors contributing to this phenomenon and identify preventive solutions.

Dr. Michele Ramsay (supplement to U54-HG-006938). This supplement is enhancing sample collection and analysis for two robust African cohorts, providing a rich resource to explore sex differences in adiposity and cardiometabolic diseases.

High Risk, High Reward

The Common Fund's High Risk, High Reward program consists of the Pioneer, New Innovator, Transformative Research, and Early Independence awards, each of which is designed to support exceptionally creative scientists undertaking bold and innovative research projects. These awards support paradigm-changing research in all areas within the NIH mission.

High Risk, High Reward Supplements

Dr. Nicole Basta (Early Independence Award, supplement to DP5-OD-009162). This supplement aims to investigate sex-specific differences in nutritional status and markers of inflammation and their role in driving heterogeneity in immune response to vaccines that protect against meningococcal disease, tetanus, and pneumococcal disease. This research will address observed sex-specific differences in immunity, provide insight into the mechanisms by which variation in immunity is sustained in the population, and provide evidence for future policy-based decisions regarding targeted vaccination strategies.

Dr. Lauren Weiss (New Innovator Award, supplement to DP2-OD-07449). This supplement aims to better understand sex differences in autism traits using data sets from both inherited and idiopathic cases of autism spectrum

disorders. This project has potential for understanding how sex interacts with genetic variants to mediate autism risk and may provide insight into new therapeutic approaches.

Library of Integrated Network-Based Cellular Signatures (LINCS)

The LINCS program aims to develop a "library" of molecular signatures that describes how different types of cells respond to a variety of perturbing agents.

LINCS Supplement

Dr. Srinivas Iyengar (supplement to U54-HG-008098). This supplement is investigating differences in cellular signatures between male and female cardiac myocytes in response to drugs that have been shown to have sex-specific cardiotoxic effects.

Metabolomics

The Metabolomics program aims to increase the national research capacity in metabolomics, the study of low molecular weight molecules found in cells and biological systems. Metabolomics provides a measure of the output of biological pathways and is therefore a useful representation of the functional state of cells and biological systems.

Dr. James Crapo (supplement to R01-HL-089897). This supplement is identifying sex-specific changes associated with chronic obstructive pulmonary disease (COPD) and emphysema, looking at combined effects of sex/age and sex/smoking, and investigating changes associated with menopause. This study may identify sex-specific markers for susceptibility to developing advanced COPD and emphysema.

Dr. Charles Czeisler (supplement to P01-AG-009975). This supplement aims to investigate sex differences in how chronic sleep loss and circadian disruption independently affect metabolic health, analyzing both metabolic and lipidomic samples.

Dr. Vicki Ellingrod (supplement to R01-MH-082784). This supplement is investigating the influence of sex on risk for developing metabolic syndrome in males and females with schizophrenia, where women are known to be at higher risk. This research will examine metabolic signatures associated with the development of this condition and whether sex differences in these signatures are evident.

Dr. Irva Hertz-Picciotto (supplement to R01-ES-015359). This supplement will investigate serum metabolic signatures in children with autism spectrum disorders, which demonstrate a clear sex difference in diagnosis rates. This research could provide insights into the pathology of autism spectrum disorders, reveal clues about the disproportionate sex distribution, and contribute to the identification of modifiable risk factors that could serve as targets for intervention.

Dr. Samia Mora (supplement to R01-HL-117861). This supplement aims to advance our understanding of lipid species that differ in men and women, including specific lipids related to high-density lipoprotein (HDL) function and statin therapy. These studies will also examine how the menopause transition affects HDL structure and function.

Dr. Eugenia Trushina (supplement to R01-ES-020715). This supplement is investigating sex-dependent metabolic differences in human fibroblasts derived from patients with Alzheimer's disease. This research may uncover dynamic changes in cell metabolism associated with Alzheimer's disease and may reveal sex differences in these metabolic pathways.

Dr. Kenneth Wright (supplement to R01-HL-109706). This supplement is examining sex differences in the human metabolome in response to sleep deprivation, which may underlie observed sex differences in energy expenditure, food intake, hormone levels, and weight gain in response to insufficient sleep. This study will also examine whether the benefits of weekend recovery sleep are the same or different in males and females.