HIGHLIGHTS OF NIH WOMEN'S HEALTH AND SEX DIFFERENCES RESEARCH 1990–2010

OFFICE OF RESEARCH ON WOMEN'S HEALTH
IN COLLABORATION WITH THE NIH COORDINATING
COMMITTEE ON RESEARCH ON WOMEN'S HEALTH

OFFICE OF RESEARCH ON WOMEN'S HEALTH
NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Highlights of NIH Women's Health and Sex Differences Research

1990 - 2010

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Office of the Director

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Introduction

As the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) prepared for the events celebrating its 20th Anniversary in 2010, at which time a revised research agenda would be unveiled with goals and strategies for the future, it seemed equally important to highlight some of the progress and achievements in women's health research during the years of ORWH's existence. Looking back over so much that had been accomplished during these decades, as recorded in the voluminous biennial reports (see Appendix) that describe the totality of ORWH programs and selected highlights from the NIH Institutes and Centers (ICs), the information was remarkable in its scope. It was decided that as the strategic plan for future research was introduced, it was important to have a distillation of landmark studies and seminal research or programs that represent some of the multiple aspects of past progress in women's health and sex differences research.

What started as a collection of two or three brief examples from each IC was eventually expanded into this extensive and exciting document. This occurred because of the overwhelming and enthusiastic response of the ICs through the NIH internal advisory Coordinating Committee on Research on Women's Health (CCRWH), composed of IC directors or their designees. The ORWH proudly presents this report, entitled Highlights of NIH Women's Health and Sex Differences Research, 1990-2010, in which the ICs themselves have identified their best examples of women's health and sex differences research. It is even more encouraging to note that these highlights by no means are intended as a comprehensive list, but represent "snapshots" of examples from the 20 years of ORWH's existence. It should also be noted that woven across the report are such overarching themes as genetic and molecular research, clinical trials and translational studies, prevention research, global health concerns, and minority health and health disparities.

Without the immediate and generous contributions and efforts of the CCRWH and their IC colleagues, and the extraordinary efforts of several CCRWH members, including Kate Nagy, M.A. (NIA), Karen Parker, Ph.D. (NCI), Mona Rowe, M.C.P. (NICHD), and Cora Lee Wetherington, Ph.D. (NIDA), this impressive collection of briefing highlights would not have been possible. The ORWH and the women's health research community thank our partners from the NIH ICs; the research scientists who designed, conducted, and coordinated this research; and the women and men who participated in these research studies. Their contributions have and will move forward our knowledge about girls' and women's health and sex/gender factors that may affect the health of women and men.

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Abbreviations

Department of Health and Human Services	HHS
National Institutes of Health	NIH
NIH Office of the Director	OD
Division of Program Coordination, Planning, and Strategic Initiatives	DPCPSI
NIH Coordinating Committee on Research on Women's Health	CCRWH
NIH Advisory Committee on Research on Women's Health	ACRWH

NIH INSTITUTES AND CENTERS

National Cancer Institute	NCI
National Eye Institute	NEI
National Heart, Lung, and Blood Institute	NHLBI
National Human Genome Research Institute	NHGRI
National Institute on Aging	NIA
National Institute on Alcohol Abuse and Alcoholism	NIAAA
National Institute of Allergy and Infectious Diseases	NIAID
National Institute of Arthritis and Musculoskeletal and Skin Diseases	NIAMS
National Institute of Biomedical Imaging and Bioengineering	NIBIB
Eunice Kennedy Shriver National Institute of Child Health and Human Development	NICHD
National Institute on Deafness and Other Communication Disorders	NICDCD
National Institute of Dental and Craniofacial Research	NIDCR
National Institute of Diabetes and Digestive and Kidney Diseases	NIDDK
National Institute on Drug Abuse	NIDA
National Institute of Environmental Health Sciences	NIEHS
National Institute of General Medical Sciences	NIGMS
National Institute of Mental Health	NIMH
National Institute of Neurological Disorders and Stroke	NINDS
National Institute of Nursing Research	NINR
National Library of Medicine	NLM
Center for Information Technology	CIT
Center for Scientific Review	CSR
John E. Fogarty International Center	FIC
National Center for Complementary and Alternative Medicine	NCCAM
National Center on Minority Health and Health Disparities	NCMHD
National Center for Research Resources	NCRR
NIH Clinical Center	CCRWH

NIH OD PROGRAMMATIC OFFICES

Division of Program Coordination, Planning, and Strategic Initiatives	DPCPSI
Office of AIDS Research	OAR
Office of Behavioral and Social Sciences Research	OBSSR
Office of Disease Prevention	ODP
Office of Dietary Supplements	ODS
Office of Medical Applications of Research	OMAR
Office of Rare Diseases Research	ORDR
Office of Strategic Coordination	OSC
Office of Research on Women's Health	ORWH

OTHER FEDERAL AGENCIES

Department of Health and Human Services	HHS
HHS Office of the Secretary	OS
Administration for Children and Families	ACF
Administration on Aging	AoA
Agency for Healthcare Research and Quality	AHRQ
Agency for Toxic Substances and Disease Registry	ATSDR
Centers for Disease Control and Prevention	CDC
Centers for Medicare and Medicaid Services	CMS
Food and Drug Administration	FDA
Health Resources and Services Administration	HRSA
Indian Health Service	IHA
Substance Abuse and Mental Health Services Administration	SAMHSA
Department of Defense	DoD
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Research Highlights

Women's Health Resources Web Portal

The NLM Division of Specialized Information Services, Outreach and Special Populations Branch, has partnered with ORWH to create the Women's Health Resources Web Portal (*http://www.womenshealthresources.nlm.nih.gov*). This portal gives researchers and consumers access to the latest information in a centralized location about significant topics in women's health from scientific journals, peer-reviewed sources, NIH Institutes and Centers, and health news sources.

The portal focuses on health topics and the NIH Priorities for Women's Health to identify research initiatives and overarching themes. The Health Topics section is organized by disease or condition categories, and an A to Z index is available to provide consumers with an easy way to locate specific health topics. The NIH Priorities for Women's Health section is created from the annual recommendations put forth by the CCRWH and ACRWH. The topics for this section include life span, sex/gender determinants, health disparities/differences and diversity, and interdisciplinary research.

Within each section, one will find topics with links to resources which were selected based upon their relevance and authority for the specific topic. NLM has created specific user friendly strategies for these topics to ease searching within ClinicalTrials.gov and PubMed. Other Web resources created and maintained by NLM include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIHSeniorHealth. The portal is also using social media to connect with the public for health awareness campaigns. (NLM)

Infancy through Adolescence, Reproductive Years Including Pregnancy, the Menopausal Transition, and Old Age

INFANCY THROUGH ADOLESCENCE

Newborn Screening for CMV

A study funded by NIDCD has found that the traditional "heel stick" test is not an effective screening tool for congenital cytomegalovirus (CMV) infection, a leading cause of hearing loss in children. Researchers compared the effectiveness of a common molecular diagnostic technology using dried blood samples to the standard method for detecting CMV in newborns, which is labor-intensive and not conducive to a widespread screening program. The researchers are now assessing whether analysis of saliva samples using the same diagnostic technology can do a better job than dried blood spots when compared with the standard method. (NIDCD)

Reference:

Boppana SB, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. 2010 Apr 14;303(14):1375-82.

Adolescent Health

Investigators using The National Longitudinal Study of Adolescent Health (Add Health) data have examined gender differences in a wide variety of areas related to health, including deviance, depression, violence, victimization, relationship values, educational attainment, and obesity, and the factors—including genetic factors—that contribute to these domains. These publications have appeared in diverse journals representing the social sciences, public health, and criminal justice. To illustrate, a number of studies have examined linkages between obesity, mental health, and educational attainment. They have demonstrated clear gender disparities in the impact of obesity. Compared with males, female adolescents are more likely to overestimate their weight, are more likely to diet, and at higher body mass, are less likely to be nominated by their peers as a friend. Overweight and obese females are less likely to complete high school and as young adults have lower status attainment and more depressive symptoms. In contrast, obesity is unrelated to psychosocial outcomes such as mental health and social status among males.

References:

Crosnoe R, Frank KA, Mueller AS. Gender, body size, and social relations in American high schools. *Soc Forces*. 2008;86(3):1189-1216.

Martin MA, Frisco ML, May AL. Gender and race/ethnic differences in inaccurate weight perceptions among U.S. adolescents. *Women's Health Issues*. 2009;19(5):292-9.

Merten MJ, Wickrama KAS, Williams AL. Adolescent obesity and young adult psychosocial outcomes: gender and racial differences. *J Youth Adolesc*. 2008;37(9):1111-22.

Okunade AA, Hussey AJ, Karakus MC. Overweight adolescents and on-time high school graduation: racial and gender disparities. *Atl Econ J*. 2009;37(3):225.

Vaughan CA, Halpern CT. Gender differences in depressive symptoms during adolescence: the contributions of weight-related concerns and behaviors. *J Res Adolesc*. 2009;20(2):389-419.

REPRODUCTIVE HEALTH OF GIRLS AND WOMEN

Disruption of the Female Reproductive System by the Phytoestrogen Genistein

NIEHS research indicates the ability of genistein to disrupt female reproductive development and function at environmentally relevant doses. Genistein is one of several known isoflavones which are found in coffee and a number of plants including fava beans, soybeans, and psoralea. Some of these effects may not be apparent until later in life. These alterations in reproduction and abnormal ovarian differentiation in experimental animal models, combined with prior studies describing an increased incidence of uterine neoplasia following developmental exposure to genistein, suggest that additional studies with the human population exposed to high levels of phytoestrogens during development is warranted. (NIEHS)

Reference:

Newbold RR, Banks EP, Bullock B, Jefferson WN. Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res*. 2001 Jun 1;61(11):4325-8.

Tubal Sterilization

NICHD, in collaboration with CDC, conducted a study investigating the risk of menstrual anomalies following tubal sterilization. Previously, there was a lack of consensus among the medical community about whether tubal sterilization increased a woman's chances of menstrual problems such as an irregular cycle, bleeding or spotting between periods, and menstrual pain. This study—the largest, most comprehensive of its kind at that time—demonstrated that women who underwent tubal sterilization were at no greater risk of menstrual problems than the general population up to five years after undergoing the procedure. (NICHD)

Reference:

Westhoff C. Tubal sterilization—safe and effective. *N Engl J Med*. 2000 Dec 7;343(23):1724-6.

Insight into the Genomics of Endometriosis

Endometriosis is one of the most common gynecological diseases. At least 5.5 million women in North America alone have endometriosis, causing very painful cramps or periods, and affecting the quality of a woman's life. In addition, about 30 percent to 40 percent of women with endometriosis are infertile, making it one of the top three causes for female infertility. Investigators at the NCRR-supported South Dakota Biomedical Research Infrastructure Network in the University of South Dakota, Vermilion, are studying the genomics of endometriosis to understand the pathology of the disease and gene expression in eutopic (internal, or inside the uterus) and ectopic (external, or outside the uterus) endometrium. They believe that the differential expression data thus obtained open new avenues for exploration of the pathology of endometriosis (e.g., a specific subset of inflammatory genes is upregulated). (NCRR)

Finding Suggests Strategies for New Treatments for Fibroid Tumors

NICHD researchers have shown that fibroid tumors are composed largely of abnormal collagen, a protein that doesn't respond to reproductive hormones. This research finding suggests that the conventional hormone therapies used to treat fibroid tumors are unlikely to produce much improvement and, at best, will only temporarily relieve symptoms. The researchers found that fibroids are composed of collagen fibrils that are arranged in large tangles, and loosely packed together. The tangled collagen masses constitute most of the fibroid tumors and contain little other uterine tissue. Fibroid tumors also appear to secrete substances that promote the formation of abnormal collagen mats outside the tumors, and these abnormal collagen fibrils are not affected by reproductive hormones. For this reason, attempting to influence fibroids by halting the production of reproductive hormones may shrink fibroids slightly, but will have little other effect. CDC estimates that from 25 to 40 percent of all US women experience symptoms from fibroids. These include painful menstrual periods, pain during sexual intercourse, infertility, urinary and fecal incontinence, and bowel obstruction. Women with fibroids are also more likely to go into labor prematurely and to experience a miscarriage. Fibroids also disproportionately affect African-Americans, with one study estimating that 80 percent of African-American women are affected by the growths by age 60. Understanding the composition of fibroids has laid the foundation for new studies of drug treatments that could prevent fibroids from forming or dissolve them after they have formed. (NICHD)

Reference:

Leppert P, Baginski T, Prupas C, Catherino WH, Pletcher S, Segars JH. Comparative ultrastructure of collagen fibrils in uterine leiomyomas and normal myometrium. *Fertil Steril*. 2004 Oct;82(Suppl. 3):1182-7.

Treatment Advancements for Uterine Fibroids—High-Intensity Focused Ultrasound

Uterine fibroids, or uterine leiomyoma, are the most common benign tumors found in females, occurring in about 40 percent of women by the age of 40. While the tumors are noncancerous, they can still cause considerable pain with only a few treatment options. Current treatment options involve medication and various forms of surgery, including myomectomy, uterine artery embolization, and hysterectomy depending on the severity of the case. Hysterectomies are the only sure way to cure fibroids. Most of these treatment methods have high risks, including loss of fertility, heavy bleeding, ovarian failure, and radiation exposure. In fact, 20 years ago uterine fibroids were the most common diagnosis associated with approximately 600,000 hysterectomies performed annually. In recent years, researchers have been working to develop treatments for uterine fibroids that do not require invasive surgeries. Investigators at Brigham and Women's Hospital have developed a magnetic resonance imaging (MRI)-guided, high-intensity focused ultrasound method that produces a color-coded temperature map of the targeted tissue that distinguishes ablated tissue from surrounding normal tissue. The MRI guidance technique uses a high-intensity ultrasound beam to focus on the targeted tissue and gradually destroy it without the need for invasive surgery. This method represents a major revolution in the treatment of uterine fibroids, providing a low risk, noninvasive

outpatient procedure with as little as one to two days of recovery time as compared with a hospital stay of three to five days and four to eight weeks of recovery time for a hysterectomy and myomectomy. The treatment was approved by the FDA for clinical use in 2004. (NIBIB)

References:

McDannold N, Tempany CM, Jolesz FA, Hynynen K. Evaluation of referenceless thermometry in MRI-guided focused ultrasound surgery of uterine fibroids. *J Magn Reson Imaging*. 2008;28(4):1026-32.

Centers for Disease Control and Prevention. Special focus: surveillance for reproductive health (CDC Surveillance Summaries, August 8, 1997). *MMWR*. 1997;46(No. SS-4).

Nonsurgical Treatments for Uterine Leiomyomas

The NCRR-supported Center for Women's Health Research at Meharry Medical College has investigated nonsurgical treatments for uterine leiomyomas (fibroid tumors) and demonstrated that an extract of green tea, epigallocatechin gallate (EGCG), has antiproliferative activity against human uterine leiomyoma cells and results in shrinkage of fibroid tumors in a mouse model. The implications of this finding are great in that they offer a novel nonsurgical option for the treatment of fibroids that could preserve fertility in women and provide major cost savings for the health care system. (NCRR)

Bone Density Appears to Recover After Discontinuing Use of Injected Contraceptive

NICHD-supported researchers found that lower bone density appears to recover in adolescent females once they stop using the injected contraceptive depot medroxyprogesterone acetate (DMPA). Previous studies had shown that women who use DMPA, marketed as Depo-Provera, experience a loss of bone mineral density during the time they are using the contraceptive. Because women develop a large amount of their bone mass from ages 15 to 19, researchers were concerned that DMPA use might place adolescents at higher risk for bone fracture or osteoporosis later in life. The data showed, however, that after adolescents stop using DMPA, their bone density can increase to levels comparable to those of other women in their age group. About 10 percent of US female adolescents from 15 to 19 who are using birth control use DMPA, as compared with 3 percent of US women overall. The younger women in this study both lost bone density and increased bone density more rapidly than did the older women in a previous study. Although the potential loss of bone density is one of many considerations that go into a woman's choice of contraceptive method, these studies provide reassurance that bone loss is regained, even in younger users. (NICHD)

Reference:

Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. *Arch Pediatr Adolesc Med*. 2005;159(2):139-44.

FERTILITY AND INFERTILITY

FOXL2: A Gene That Is Critical to Sex Determination and Maintenance of Fertility

Up to one percent of women experience menopause before age 40, a condition known as premature ovarian failure (POF). POF can occur as a result of acquired damage to the ovaries (for example, from radiation therapy, chemotherapy, or an autoimmune disorder), but appears to be inherited in approximately one-third of cases. In 2001, NIA and European investigators identified a gene called *FOXL2* that is mutated in blepharophimosis ptosis epicanthus inversus syndrome, a rare condition that causes eyelid defects in newborns and is associated with POF in affected women. *FOXL2* is the only gene identified to date that is uniquely expressed in the ovaries, and subsequent work has demonstrated that it is required both for ovarian follicle formation and for the determination and maintenance of female sex in the developing embryo. Its role in ovarian development and function suggests *FOXL2* as a possible target for treatment of some forms of infertility. (NIA)

References:

Crisponi L, Deiana M, Loi A, Chiappe F, Uda M, Amati P, Bisceglia L, Zelante L, Nagaraja R, Porcu S, Ristaldi MS, Marzella R, Rocchi M, Nicolino M, Lienhardt-Roussie A, Nivelon A, Verloes A, Schlessinger D, Gasparini P, Bonneau D, Cao A, Pilia G. The putative forkhead transcription factor *FOXL2* is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome. *Nat Genet*. 2001;27(2):159-66.

Ottolenghi C, Pelosi E, Tran J, Colombino M, Douglass E, Nedorezov T, Cao A, Forabosco A, Schlessinger D. Loss of *Wnt4* and *Foxl2* leads to female-to-male sex reversal extending to germ cells. *Hum Mol Genet*. 2007;16(23):2795-2804.

Uda M, Ottolenghi C, Crisponi L, Garcia JE, Deiana M, Kimber W, Forabosco A, Cao A, Schlessinger D, Pilia G. *Foxl2* disruption causes mouse ovarian failure by pervasive blockage of follicle development. *Hum Mol Genet*. 2004;13(11):1171-81.

Adult Mice Continue to Produce Eggs

One of the basic underpinnings of reproductive biology has been the tenet that the number of oocytes (eggs) in the ovaries of most mammals—including humans—is fixed at birth and declines throughout life, coinciding with a woman's diminishing fertility as she approaches menopause. However, in 2004, NIH-supported researchers uncovered surprising evidence that egg production in mice may continue on a small scale throughout life. While additional research is needed, the results of this study have called into question decades of scientific thought. The finding that new eggs are produced into adulthood in mice may, if extended to humans, lead to interventions to regulate the rate at which oocytes are formed. This could, in turn, have important implications for the treatment of premature ovarian failure, the extension of fertility, or even the timing of menopause. (NIA)

Reference:

Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature*. 2004(6979);428:145-50.

Primary Ovarian Insufficiency

Primary ovarian insufficiency (POI) is a condition in which the ovaries in women, generally younger than 40, stop functioning normally, leading to infertility and a range of symptoms associated with early menopause. This condition affects 1 in 100 women under the age of 40. A study conducted by NICHD found that the ovaries of women with POI contain immature eggs, adding to previous research showing that ovulation may occur in these patients. This important finding provides hope for developing new ways to treat the infertility that is generally associated with POI. (NICHD)

Reference:

Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM. Bone mineral density in estrogen-deficient young women. *J Clin Endocrinol Metab*. 2009;94(7):2277-83.

Addison's Disease

Researchers at NICHD demonstrated that the incidence of a life-threatening adrenal condition known as primary autoimmune adrenal insufficiency, or Addison's disease, is more than 300 times higher among women with primary ovarian insufficiency (POI) than among members of the general population. The risk of this adrenal condition among women with POI was 3.2 percent, compared with an incidence of 1 in 10,000 in the general population. The study suggested that an adrenal antibody test would be an effective screening tool for detecting adrenal insufficiency in women with POI. (NICHD)

Reference:

Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. *Hum Reprod*. 2002;17(8):2096-100.

Prevention of Postprandial Hypoglycemia Using n-3/n-6 PUFA in PCOS

Polycystic ovary syndrome (PCOS) affects 1 in 16 women; individuals with this condition commonly experience infertility, facial hair growth, and an increased risk for obesity, diabetes, and heart disease. Treatment of insulin resistance and obesity improves ovarian function and reduces infertility. NIH-supported investigators have demonstrated that PCOS patients frequently develop postprandial hypoglycemia (a drop in blood sugar two to four hours after eating), which causes sugar craving and overeating, and increases secretion of the hormones that lead to obesity and diabetes. Avoiding hypoglycemia may protect these patients from gaining additional weight and becoming diabetic. These investigators are now working to determine whether the essential and/or the long-chain omega (n)-3 polyunsaturated fatty acids (PUFAs), such as can be found in supplements including fish oil and flax seed oil, can prevent postprandial hypoglycemia and its unfavorable endocrine consequences in women with PCOS. (ODS)

Women's Fertility Is Better Understood

Basic aspects of human fertility were not known until fairly recently. Landmark papers by NIEHS researchers established the window of women's fertility in the menstrual cycle. Researchers showed that women are able to conceive only during six days of the menstrual cycle: the day of ovulation and the five days that precede it. Timing of sexual intercourse in relation to ovulation affects the probability of conception, survival of the pregnancy, and sex of the baby. If it were possible to accurately predict these six days, women could perfectly control their fertility through timing of intercourse alone. Unfortunately, the natural variability of the menstrual cycle makes these six fertile days difficult to predict.

Furthermore, home pregnancy tests are not as trustworthy as the package inserts may suggest. NIEHS researchers showed that the natural variability in ovulation can produce a negative reading at the missed period even in a cycle where the woman has conceived. (NIEHS)

References:

Wilcox AJ, Baird DD, Dunson D, McChesney R, Weinberg CR. Natural limits of pregnancy testing in relation to the expected menstrual period. *JAMA*. 2001;286(14):1759-61.

Wilcox AJ, Dunson D, Baird DD. The timing of the fertile window in the menstrual cycle: day-specific estimates from a prospective study. *BMJ*. 2000;321(7271):1259-62.

Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation: effects on the probability of conception, survival of the pregnancy and sex of the baby. *New Engl J Med*. 1995;333(23):1517-21.

Acupuncture May Facilitate Pregnancy Achievement in Women Undergoing IVF

Research findings based on a review of seven clinical trials of acupuncture given with embryo transfer in women undergoing *in vitro* fertilization (IVF) indicate that acupuncture may improve rates of pregnancy. The reviewers found that acupuncture given as a complement to IVF increased the odds of achieving pregnancy. According to the researchers, the results indicate that 10 women undergoing IVF would need to be treated with acupuncture to bring about one additional pregnancy. The study results, which are considered preliminary, point to a potential complementary treatment that may improve the success of IVF and lay the groundwork for additional clinical trials to confirm these findings. (NCCAM)

Reference:

Manheimer E, Zhang G, Udoff L, Haramati A, Langenberg P, Berman BM, Bouter LM. Effect of acupuncture on rates of pregnancy and live birth among women undergoing *In Vitro* fertilization: systematic review and meta-analysis. *BMJ.* 2008;336(7643):545-9

Improving Methods for Recovering Eggs at Earlier Stages

For the first time, NICHD-supported researchers activated mouse egg cells at the earliest stage of their development and brought them to maturity. Researchers also replicated the finding by bringing human eggs to maturity in the laboratory. Current infertility treatment techniques

stimulate immature eggs so they develop to the stage at which the eggs can be fertilized, but these techniques work only on eggs at a comparatively late stage of development. These later-stage eggs are few in number and much more difficult to recover than the early-stage eggs used by the researchers in this study. Using the new technique, the researchers brought dormant mouse eggs to full maturity within the laboratory. The eggs then were fertilized and transferred into female mice, which carried them to term. The human eggs were not fertilized. The technique is still in its early stages, has not been sufficiently studied for human use, and will require several more years of study. According to the researchers, this technique could one day be used to treat female infertility, particularly forms of infertility in which the supply of available eggs is diminished or limited. Similarly, the technique could be combined with efforts to bank the ovarian tissue of women in need of cancer therapy that might cause infertility. (NICHD)

Development of the Hamilton Thorne ZILOS-tk Laser to Assist Reproduction Technologies

The NCRR-supported Laser Microbeam and Medical Program (LAMMP) at the University of California at Irvine provided essential laser methods and technologies for development of the Hamilton Thorne ZILOS-tk Laser. This is a commercial product for laser-assisted hatching of human embryos in *in vitro* fertilization procedures, which uses a precisely focused laser beam as a rather gentle approach to assisted hatching. The development of laser microbeams and their application to gamete manipulation in assisted reproduction technologies was pioneered in the LAMMP facility. A description of the instrument is available at *http://www.hamilton-thorne.com/products/lasers/zilostk/index.htm*. (NCRR)

PREGNANCY AND THE PERINATAL PERIOD

An Experimental Vaccine to Protect the Fetus from a Common Virus

The herpes virus cytomegalovirus (CMV) is quite common in the United States and, with important exceptions, does not cause symptoms in infected individuals. CMV infection in a pregnant woman, however, can infect the fetus, causing stillbirth, or in surviving infants, long-term consequences including cerebral palsy, intellectual and developmental disabilities, and/or hearing loss. Although CMV is treatable, there is no way to prevent it and its typically asymptomatic presentation means that it may not be detected in time during a pregnancy to prevent fetal infection. In a 2000 report, the Institute of Medicine identified creation of a CMV vaccine as a top priority and an NICHD-supported investigator has taken an important step toward achieving that goal. A vaccine created by the investigator significantly reduced CMV-related stillbirths in experimental rodents, an advance that could ultimately lead to a safe and effective CMV vaccine for humans. (NICHD)

Reference:

Schleiss MR, Lacayo JC. Preconceptual administration of an alphavirus replicon UL83 (pp65 homolog) vaccine induces humoral and cellular immunity and improves pregnancy outcome in the guinea pig model of congenital cytomegalovirus infection. *J Infect Dis*. 2007 Mar 15;195(6):789-98.

Preventing Preterm Labor: Using 17-Hydroxyprogesterone

Premature birth, which is defined as birth prior to 37 weeks of gestation, is a leading cause of infant morbidity and mortality. In the United States, approximately 12 percent of all births are premature, accounting for approximately 500,000 infants born annually. Prematurity also accounts for approximately 70 percent of all neonatal deaths and nearly 50 percent of long-term neurological problems in infants. Researchers have long sought the most effective ways to prevent preterm labor and premature births. The first such advance came with the discovery that 17 alpha-hyrdroxyprogesterone caproate (17P), when given to women who had had a previous preterm labor and were carrying a single baby, could reduce the risk of preterm birth by one-third. Given that the rate of twin pregnancies is increasing in the United States, due partly to the increase in assisted reproductive technologies, physicians started prescribing 17P for women carrying twins, who are also at increased likelihood of preterm birth. After a carefully controlled, randomized trial, researchers found that healthy women carrying twins who received 17P were just as likely to deliver preterm and experience a fetal death before 35 weeks and serious adverse fetal or neonatal events as similar women who received a placebo. (NICHD)

Reference:

Rouse DJ, et al. A trial of 17 Alpha-Hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med*. 2007;357(5):454-61.

Other Promising Therapies for Delaying an Early Preterm Delivery

Delaying a very preterm birth even by days or weeks can have profound effects on reducing neonatal mortality and morbidity. A significant percentage of preterm births that occur at less than 32 weeks are associated with infection. Unfortunately, medicines to slow labor or proactive antibiotic treatments for such conditions as bacterial vaginosis have been shown in previous research to be ineffective in preventing or significantly delaying delivery. Now, as a proof of principle using a nonhuman primate model, researchers have shown that treating the animal mother with both antibiotics (ampicillin) and anti-inflammatory agents (dexamethasone and indomethacin) significantly suppresses the level of inflammatory compounds in the amniotic fluid compared with animals who were given just an antibiotic alone or placebo. In addition, the combination therapy also significantly increased the interval between the time contractions began and the time of delivery. The findings show promise that combination therapy for the mother may help to prevent infection-induced preterm labor. (NICHD)

Reference:

Gravett MG, Adams KM, Sadowsky DW, Grosvenor AR, Witkin SS, Axthelm MK, Novy MJ. Immunomodulators plus antibiotics delay preterm delivery after experimental intraamniotic infection in a nonhuman primate model. *Am J Obstet Gynecol*. 2007;197(5):518.e1-8.

New Generation of Technology Helps to Predict Preterm Labors

About half of preterm births occur spontaneously following the premature onset of labor; however, two-thirds of pregnant women also experience false preterm labor—early contractions that do not result in a preterm delivery. Consequently, researchers have sought more effective ways to screen women in spontaneous preterm labor to allow clinicians to start needed treatment for those having true preterm labor and avoid unneeded treatment and hospitalizations for those who are simply having preterm contractions. NICHD-supported researchers developed a way to use uterine electromyography, or EMG, coupled with an artificial intelligence neural network computer program to analyze the resulting data and classify women as those simply experiencing preterm contractions versus those entering preterm labor. Using these new methods, 90 percent of the preterm labor women were correctly classified. Although such computing and new artificial intelligence technologies are just evolving, they mark the beginning of noninvasive advances that hold significant promise for predicting and distinguishing true from false preterm labor. Such advances can save unnecessary treatments for the mother and help reduce unneeded hospital expenditures. (NICHD)

Reference:

Maner WL, Garfield RE. Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. *Ann Biomed Eng*. 2007;35(3):465-73.

Artificial Placenta May Help Test Drugs During Pregnancy

Scientists have figured out a way to grow an artificial placenta, which may help researchers learn which drugs can be given safely during pregnancy. With NIGMS funding, a team of researchers including physicians, biologists, and engineers was able to get "trophoblast" cells from a real placenta to grow in a lab chamber called a bioreactor. To create the placenta, the researchers first designed a nonwoven, polyethylene (Dacron™) fabric on which the placental cells could survive and get the proper mix of nutrients from the circulating culture fluid. The artificial placenta is expected to help scientists sort out which drugs are safe in pregnancy, since there currently is no good way to test medicines for safety and effectiveness in pregnant women. (NIGMS)

References:

Ma T, Yang ST, Kniss DA. Oxygen tension influences proliferation and differentiation in a tissue-engineered model of placental trophoblast-like cells. *Tissue Eng*. 2001 Oct;7(5):495-506.

Xie Y, Sproule T, Li Y, Powell H, Lannutti JJ, Kniss DA. Nanoscale modifications of PET polymer surfaces via oxygen-plasma discharge yield minimal changes in attachment and growth of mammalian epithelial and mesenchymal cells in vitro. *J Biomed Mater Res*. 2002 Aug;61(2):234-45.

Maternal Health

Does Iron Deficiency Protect Pregnant Women From Malaria?

Low iron intake is an important factor in the development of anemia—a major cause of morbidity and mortality in pregnant women worldwide. Consequently, iron supplementation has been a core component of the recommended package of prenatal health interventions for pregnant women. However, studies in regions with high malaria prevalence have shown that iron supplementation may increase the risk of malaria-related illness and deaths. NIH-supported researchers examined the relationship between iron status and risk of malaria in pregnant women in a high-prevalence region of northeastern Tanzania. They found that malaria parasitemia was less frequent in women with iron deficiency than among those with normal iron status. The results from this study revealed for the first time that iron deficiency in pregnant women may provide protection from malaria. These findings warrant examination of current antenatal iron supplementation guidelines in malaria-endemic regions and further studies to guide the optimal use of iron supplementation in these regions. (FIC)

Reference:

Kabyemela ER, Fried M, Kurtis JD, Mutabingwa TK, Duffy PE. Decreased susceptibility to *Plasmodium falciparum* infection in pregnant women with iron deficiency. *J Infect Dis*. 2008 Jul 15;198(2):163-6.

Decreased Immune Response during Pregnancy

Studies showed that the hormone, estrogen, which is at higher serum levels during pregnancy, inhibits the response of innate immune cells to viral infection and reduces immune response during pregnancy. Investigators also found that levels of serum cytokines were changed in pregnant women, which may reduce the activity of certain immune cells. (NIAID)

References:

Escribese MM, Kraus T, Rhee E, Fernandez-Sesma A, López CB, Moran TM. Estrogen inhibits dendritic cell maturation to RNA viruses. *Blood*. 2008;112(12):4574-84.

Kraus TA, Sperling RS, Engel SM, Ge L, Garrido JL, Rodriguez-Garcia M, Moran TM. Peripheral blood cytokine profiling during pregnancy and post-partum periods. *Am J Reproduct Immunol*. 2010 Aug 15 [Epub ahead of print].

Point-of-Care Ultrasound for Maternal Health

Motherhood is often a positive and fulfilling experience but for too many women it is associated with suffering, ill-health, and even death. Every day, 1,500 women die from pregnancy or childbirth-related complications. Most of these deaths occur in developing countries and most are avoidable. In addition to the differences between countries, there are also large disparities within countries between people with high and low income and between rural and urban populations. One way to improve maternal health in these high-risk populations is to ensure skilled care before, during, and after pregnancy and childbirth.

Quality care often benefits from widely used technologies such as ultrasound to diagnose pregnancies, determine fetal age, detect abnormalities, evaluate placenta position, and determine multiple pregnancies. In order to bridge this gap, investigators from General Electric Global Research are developing a portable, low-cost imaging system with diagnostic capability to serve pregnant women in areas with limited access to health care services. The Digital Micro-Printing (DMP) method was developed as a new technology for producing low-cost transducers, which are the probes that will be used in new, low-cost ultrasound imaging systems. In addition, the investigators developed management algorithms that will be integrated into the imaging system to facilitate rapid identification of critical situations. The development of portable diagnostic and monitoring devices for near-patient testing, when combined with suitable telehealth technologies, will empower clinicians or other providers to make decisions at the point of care and improve outcomes. (NIBIB)

References:

http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM095487.pdf

http://www.ob-ultrasound.net/history2.html

http://www.who.int/topics/maternal_health/en/

Listeria Hides from the Immune System in the Placenta

NIAID-supported researchers discovered that the placenta is a protected niche for *Listeria* replication, from which the bacteria seed the maternal organs. Thus, subsequent preterm delivery (spontaneous abortion) represents a defense mechanism for maternal survival. Results from this study challenge the theory that the increased incidence of listeriosis in pregnant women is due to maternal immunosuppression. Rather, the investigators propose a new model wherein attributes specific to the placenta are responsible for the pathogenesis of listeriosis in pregnancy. (NIAID)

Reference:

Bakardjiev AI, Theriot JA, Portnoy DA. *Listeria monocytogenes* traffics from maternal organs to the placenta and back. *PLoS Pathog.* 2006;2(6):e66.

Preeclampsia Is Associated With Proteins Produced by the Placenta

Preeclampsia, which is often marked by a sudden increase in high blood pressure during pregnancy, affects 3 to 5 percent of all pregnancies. Not only can it impair the functioning of a mother's liver, kidneys, or brain, but if left untreated, it can be life threatening for the mother. The only cure is to deliver the baby. If the birth is premature, complications such as blindness, learning disabilities, or death of the infant may result. A research study funded by NICHD, NIDDK, and NHLBI provided strong evidence that high levels of two proteins produced by the placenta interfere with the growth and function of blood vessels, leading to preeclampsia. Identification of key molecules that can lead to preeclampsia suggests potential targets to either treat or prevent the condition altogether. (NICHD)

Reference:

Lindheimer MD, Umans JG. Explaining and predicting preeclampsia. *N Engl J Med*. 2006 Sep 7;355(10):1056-8.

High Doses of Vitamins and Minerals Do Not Prevent Preeclampsia

NICHD investigators have helped to settle a controversy over the effectiveness of high doses of calcium taken during pregnancy to prevent preeclampsia. The investigators combined and reanalyzed the data from many studies that, individually, had either reported inconclusive or inconsistent results. This reanalysis, the most comprehensive of its kind at the time, concluded that calcium supplementation during pregnancy does not confer any benefits to women who are at low risk of developing preeclampsia.

Meanwhile, additional studies have confirmed that other potential "magic bullets" to reduce the risk of preeclampsia and other hypertensive disorders in pregnancy are also ineffective. Most recently, a study showed that taking significantly higher doses of vitamins C and E—about 10 times the amount normally found in typical prenatal vitamins—does not prevent preeclampsia. These results are very useful for clinicians. In this case, results show that what appeared to be a promising treatment does not offer any clinical benefit to the mother. (NICHD)

References:

DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA*. 1999 Aug 18;282(7):664-70.

Roberts JN, et al. Vitamins C and E to prevent complications of pregnancy-associated hypertension. *N Engl J Med*. 2010 Apr 8;362(14):1282-91.

Treatment with Misoprostol after Miscarriage Is Beneficial

At least 15 percent of pregnancies result in miscarriage or pregnancy loss from natural causes before 20 weeks gestation. In some cases, a fetus dies in the womb; in other cases, a fetus may no longer be present but the woman continues to carry a placenta and amniotic sac. Occasionally, the uterus may fail to expel the remaining tissue naturally, leaving women at risk for infection. A randomized controlled trial conducted by researchers at NICHD and other institutions demonstrated that the drug misoprostol is an effective alternative to surgical treatment after miscarriage. Misoprostol induces labor by stimulating uterine contractions. Prior to this study, there was no conclusive evidence showing that misoprostol was effective and safe for routine use. The study gives women a less-costly alternative to surgery. In a subsequent study, NICHD–supported researchers found that giving the same drug provided a safe and inexpensive way to prevent postpartum hemorrhage, or excessive bleeding, a major killer of women in developing countries. (NICHD)

References:

Zhang J, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med*. 2005 Aug 25;353(8):761-9.

Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, Patted SS, Patel A, Edlavitch SA, Hartwell T, Chakraborty H, Moss N. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006;368(9543):1248-53.

"Late Preterm" Cesarean Delivery Puts Newborns at Significant Risk for Health Complications

Women who have experienced a Cesarean delivery are typically offered the option of delivering their next child by the same method. The American College of Obstetricians and Gynecologists (ACOG) recommends that elective Cesarean deliveries be performed at or after the 39th week of pregnancy. Many elective Cesarean deliveries are performed as early as at 37 weeks, however, even though shortening a pregnancy by even a little time is known to pose health risks to the infant. NICHD-supported researchers sought to better understand the types and severity of risks of such "late preterm" deliveries. They found that infants delivered by a repeat, elective Cesarean at or after 37 weeks but before 39 weeks experience problems in breathing, blood infection, and low blood sugar, and are significantly more likely than term infants to require neonatal intensive care. Infants born at 37 weeks are twice as likely to experience these problems, and even infants born in the last three days of the 38th week of pregnancy are 1.5 times more likely to experience adverse health effects. These findings provide strong support for the ACOG recommendation for elective Cesarean delivery only at the 39th week of pregnancy. (NICHD)

Reference:

Tita ATN, Landon MB, Spong CY, et al. Timing of elective repeat Cesarean delivery at term and neonatal outcomes. *N Engl J Med*. 2009;360(2):111-20.

Cesarean Delivery Elevates Risk of Placenta Previa, a Serious Birth Complication

Cesarean deliveries occur in over one million women each year in the United States, accounting for nearly 30 percent of all births. Among the known risks of Cesarean delivery is placenta previa. This dangerous condition occurs when the placenta, which transfers oxygen and nutrients to the fetus, detaches from the lower part of the uterine wall and blocks the cervix. The condition prevents vaginal birth and carries a high risk to both mother and infant from hemorrhage. Given evidence of rising rates of Cesarean delivery, women and clinicians need to better understand the association between Cesarean delivery and risk for placenta previa. With NICHD support, investigators analyzed data in a registry of more than 70,000 Cesarean deliveries over a four-year period. They found that maternal morbidity was higher in women with placenta previa and that adverse maternal outcomes occurred progressively more commonly as the number of prior Cesarean deliveries increased. These data are important for the counseling of women with a history of Cesarean delivery with placenta previa and for better informing clinical decision-making with regard to their delivery. (NICHD)

Vaginal Delivery after Caesarian Section Carries Less Risk Than Previously Believed

A study conducted by NICHD found that a vaginal delivery after a prior Cesarean section carries a very low risk of complications such as uterine rupture or infection, oxygen deprivation to the infant brain, or infant death. The risk of such complications was found to be slightly higher than for a repeat Cesarean delivery, though repeat Cesarean delivery carried its own risks, such as infection and other complications of surgery and complications in future pregnancies, such as having the placenta grow into the uterine wall, potentially leading to heavy bleeding and surgical removal of the uterus. This research presents additional evidence for women to consider when deciding between a vaginal delivery and a Cesarean delivery after a previous Cesarean. (NICHD)

Reference:

Landon MB, et al. Maternal and perinatal outcomes associated with a trial of labor after prior Cesarean delivery. *N Engl J Med*. 2004 Dec 16;351(25):2581-9.

Epidural Analgesia Does Not Increase Risk of Caesarian Section

Further information for women to consider when planning their delivery was provided by the results of a review of labor records conducted by researchers at NICHD and the Tripler Army Medical Center. This study found that epidural analgesia administered to reduce pain during labor does not increase a woman's chances of having a Cesarean delivery. This finding is in contrast to those previously reported. The results also indicate, however, that epidural analgesia prolongs labor by an average of 25 minutes. (NICHD)

Reference:

Zhang J. Does epidural analgesia prolong labor and increase risk of Cesarean delivery? A natural experiment. *Am J Obstet Gynecol*. 2001 Jul;185(1):128-34.

Does EPA or DHA Prevent Depressive Symptoms in Pregnancy and Postpartum?

Major depressive disorder is a significant cause of maternal morbidity during and subsequent to pregnancy. NIH-supported investigators are comparing the efficacy of fish oil rich in two different omega-3 fatty acids (EPA and DHA) in reducing the incidence and severity of depressive symptoms during pregnancy and postpartum. This proposal is designed to generate important data and hypotheses for the design and execution of future studies on the effects of fatty acids on mood disorders in pregnancy and postpartum and on infant and child development. (ODS)

Research Advances in Postpartum Depression

Research demonstrates that postpartum depression is a serious and debilitating disorder that affects up to 15 percent of new mothers. Women with depression who stop antidepressant treatment during pregnancy are at higher risk for relapse, and their risk of postpartum depression is significantly elevated as well. Several forms of treatment, including cognitive behavioral

therapy (CBT), interpersonal psychotherapy (IPT), and medication treatment are effective in treating this disorder. Research continues into prevention efforts and improved service delivery of treatments based on individual needs. (NIMH)

References:

Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry*. 1993 July;163(1):27-31.

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006 Feb 1;295(5):499-507. Erratum in: *JAMA*. 2006 Jul 12;296(2):170.

Dimidjian S, Goodman S. Nonpharmacologic intervention and prevention strategies for depression during pregnancy and the postpartum. *Clin Obstet Gynecol*. 2009 Sep;52(3):498-515.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, Brody S, Miller WC. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evidence report/technology assessment no. 119. Prepared by the RTI-University of North Carolina Evidence-based Practice Center, under contract no. 290-02-0016. AHRQ Publication No. 05-E006-2. Rockville (MD): Agency for Healthcare Research and Quality; 2005 Feb.

O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry*. 2000;57(11):1039-45.

Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, Perel JM, Jones-Ivy S, Bodnar LM, Singer LT. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry*. 2009 May;166(5):557-66.

Post-Pregnancy and the Immune System

A study found that women between four and six weeks postpartum had a significantly upregulated innate immune system compared with controls, as shown by higher levels of inflammatory cytokines and C-reactive protein, and fewer symptoms of common infectious illnesses. The results suggest that a new mother's immune system may be uniquely primed to counteract microbial infections following pregnancy. Further work showed that postpartum depression may be associated with reduced immunity and that suppressed levels of natural killer cell activity, which are present during pregnancy possibly to prevent rejection of the fetus, continue into the postpartum period. (NINR)

References:

Groer MW, Davis MW, Smith K, Casey K, Kramer V, Bukovsky E. Immunity, inflammation and infection in post-partum breast and formula feeders. *Am J Reprod Immunol*. 2005;54(4):222-31.

Groer MW, Morgan K. Immune, health and endocrine characteristics of depressed postpartum mothers. *Psychoneuroendocrinology*. 2007;32(2):133-9.

Groer M, El-Badri N, Djeu J, Harrington M, Van Eepoel J. Suppression of natural killer cell cytotoxicity in postpartum women. *Am J Reprod Immunol*. 2010;63(3):209-13

NIH State-of-the-Science Conference: Cesarean Delivery on Maternal Request, March 27–29, 2006

NICHD and OMAR convened an independent panel in 2006 to assess the available scientific evidence on the growing trend of elective Cesarean delivery. The panel found that there was insufficient evidence to fully evaluate the benefits and risks of Cesarean delivery on maternal request as compared with planned vaginal delivery and more research was needed. The panel further concluded that:

- Until quality evidence becomes available, any decision to perform a Cesarean delivery on maternal request should be carefully individualized and consistent with ethical principles.
- Given that the risks of placenta previa and placenta accreta rise with each Cesarean delivery, Cesarean delivery on maternal request is not recommended for women desiring several children.
- Cesarean delivery on maternal request should not be performed prior to 39 weeks of gestation or without verification of lung maturity, because of the significant danger of neonatal respiratory complications.
- Maternal request for Cesarean delivery should not be motivated by unavailability of effective pain management. Efforts must be made to ensure availability of pain management services for all women. (OMAR)

NIH Consensus Development Conference on Vaginal Birth after Cesarean: New Insights, March 8–10, 2010

OMAR worked with NICHD to convene the NIH Consensus Development Conference on Vaginal Birth after Cesarean (VBAC): New Insights in March 2010. A major finding of the Conference's independent panel was that given the available evidence, trial of labor is a reasonable option for many pregnant women with one prior Cesarean delivery by low transverse uterine incision. The panel further recommended that the American College of Obstetricians and Gynecologists and the American Society of Anesthesiologists reassess their requirement for "immediately available" surgical and anesthesia personnel in then-current guidelines, to address barriers that women with a prior Cesarean delivery face in gaining access to clinicians and facilities that are able and willing to offer trial of labor. In July 2010, the American College of Obstetricians and Gynecologists issued new guidance on the issue that emphasizes the importance of thorough counseling on risks and benefits of planned repeat Cesarean delivery compared with VBAC, including discussion of measures that can be taken if a woman who is otherwise a good candidate for VBAC is to deliver at a facility that may not meet the "immediately available" standard. (OMAR)

Maternal Influence on Infant and Child Health

DHA Supplementation and Pregnancy Outcome

Docosahexaenoic acid (DHA) is a member of the omega-3 fatty acid family; it is found in all cell membranes, and is accumulated in especially large quantities in the retina and brain. Over the past decades, evidence has accumulated in support of the hypothesis that DHA may have an important role in pregnancy health and outcome, as well as in the postnatal development of perceptual and cognitive function in infancy. However, prior work on this topic has focused on postnatal supplementation and the amelioration of risk in premature infants; this is in contrast to evidence indicating that DHA is accumulated in the fetal brain during gestation, probably through maternal dietary intake. NIH-supported investigators are now studying whether prenatal supplementation with DHA may lead to positive pregnancy and postnatal outcomes. In an earlier clinical trial conducted by this research team, a relatively low level of DHA supplementation (approximately 100 mg/day) during the last trimester of pregnancy was associated with a longer gestation period and improved infant cognitive outcomes. The current trial will elucidate the effects of a larger dose of supplement and longer duration of supplementation, and will provide important information regarding the use of this popular supplement in mid- to late pregnancy. (ODS)

Study Shows Adverse Effects of Air Pollution on Births

A study conducted by researchers at the University of California, Los Angeles, showed that women who lived in regions with higher levels of air pollution—caused mainly by vehicle traffic—were approximately 10 to 25 percent more likely to have a preterm baby than women who lived in less-polluted areas. This was especially true for women who breathed polluted air during the first trimester or during the last months and weeks of pregnancy. Air pollution remains a major public health problem that affects everyone, particularly pregnant women. (NIEHS)

Reference:

Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol*. 2007 Nov 1;166(9):1045-52.

Periodontal Disease May Not Be a Risk Factor for Preterm Birth

Earlier studies identified a significant association between maternal periodontal disease and preterm delivery (gestational age (GA) <37 weeks) and decreased fetal weight (birth weight (BW) <2500g). The Obstetrics and Periodontal Therapy Trial and the Maternal Oral Therapy to Reduce Obstetric Risk Trial found treatment of periodontal disease during pregnancy did not reduce the incidence of preterm birth or low birth weight. However, both studies found that dental treatment through the second trimester of pregnancy was safe. (NIDCR)

References:

Michalowicz BS. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med*. 2006 Nov 2;355(18):1885-94.

Offenbacher S, et al. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstet Gynecol*. 2009 Sep;114(3):551-9.

Genetic Risk Factors for Preterm Birth: Danish National Birth Cohort Study

Preterm labor resulting in the delivery of a premature infant is a complex problem with an enormous impact on individuals, families, and society. About 500,000 children will be born prematurely in the United States this year, and worldwide 5 million will die of prematurity and its complications. It is the single largest contributor to disability adjusted life years (DALYs), a measure of the lifetime impact of a disease. Despite the importance of the problem and its disproportionate occurrence in poor and minority populations, insufficient resources have been targeted to discover its underlying etiology. The largest single cause of prematurity is spontaneous preterm labor, and suspected triggers for this include infection, stress, poor nutrition, and genetic factors. Numerous family and twin studies provide strong evidence that genetic factors underlie about 40 percent of the risk for prematurity. The single best predictor for preterm delivery is a previous preterm birth. A major challenge in studying genetic factors in prematurity is that the risk could reside either in the mother and her uterus or in the infant/placenta. Thus, any approach to studying preterm birth should account for both infant and maternal risk, environmental covariates, and interactions.

The Danish National Birth Cohort Study is a well-established, prospective cohort study that has the advantage of enrolling women early in pregnancy, when the outcome is still unknown, so that bias in data collection and sampling is minimized. The Danish study has followed over 96,000 women beginning in the first trimester of pregnancy and has extensive biologic and epidemiologic data on the outcomes of both mother and child. In this research study, the team is performing a genome-wide case/control analysis using 1,000 very-well-characterized cases of spontaneous preterm birth, with biological samples on the mother and infant, drawn from the Danish National Birth Cohort Study. These are then matched to 1,000 mother/infant controls, born at 39 or 40 weeks gestation. Extensive epidemiologic variables are used as covariates in the analysis. To replicate positive findings, researchers can access the deep resource of additional controls from the same Danish National Birth Cohort Study as well as more than 1,000 mother/father/preterm infant triads available from a large sample collection in the United States, and a further 1,000 U.S. case/controls enriched for African-Americans, a population known to have high rates of preterm labor. Positive results involving environmental factors can be further investigated, as the Danish cohort has maternal serum samples from early and mid pregnancy, as well as additional epidemiologic and outcome data. The study should enable a better understanding of the biology of parturition, identify common genetic factors that play a role in prematurity, and suggest environmental modifications that can prolong gestation, with the goal of improving both neonatal and adult outcomes. (NHGRI)

Low Maternal Cholesterol Levels May Increase Risk of Preterm Delivery and Low Birth Weight

A study published in October 2007, led by NHGRI intramural researchers, showed that pregnant women who have very low cholesterol levels might face a greater risk of delivering their babies prematurely. The study found that low maternal cholesterol levels, which may be related to a woman's genetic makeup, diet, or other health factors, might also lead to low birth weight. Researchers noted a differing impact of low cholesterol levels on the rates of

premature delivery in white and African-American mothers, which is of particular interest since premature delivery is a leading cause of health disparities.

While most health advice warns against too much cholesterol, this study suggests dangerous implications from having too little cholesterol and emphasizes the importance of a moderate cholesterol intake during pregnancy. These findings give researchers renewed impetus to refine the understanding of cholesterol levels in pregnant women and to explore the genetic, nutritional, and other factors that influence maternal cholesterol. They will also lead to a better understanding of the biology of birth defects, thus suggesting more effective strategies for preventing them. (NHGRI)

Genetic Variation in the Fetus: Relation to Fetal Size at Birth and Maternal Metabolism

Low and high birth weights are a major cause of neonatal morbidity and mortality, and epidemiological data have established an association between birth weight and later risk of adult metabolic disease. Fetal growth is determined by complex interactions between fetal genes and the maternal uterine environment. Subtle or overt variation in maternal glucose tolerance which is in part genetically determined, is related to fetal size at birth. New emerging data suggest that genetic variation in the fetus can impact maternal metabolism.

Given the above, an NHGRI-funded research team hypothesized that during pregnancy, gene-environment interactions in the context of the maternal-fetal unit impact fetal size at birth and maternal metabolism. To address this hypothesis, the team is proposing to perform genome-wide association (GWA) mapping on a subset of ~37,000 DNA samples that were collected from mothers and their offspring as part of the NIH-funded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. HAPO is a multicenter, international study in which high-quality phenotypic data related to fetal growth and maternal glucose metabolism have been collected from 25,000 pregnant women of varied racial and sociodemographic backgrounds using standardized protocols that are uniform across centers. The team plans to genotype 1,500 infants and their mothers of European descent to examine the interaction between maternal genes, the intrauterine environment, and fetal genes to identify interactions that modulate genetic regulation of size at birth and fetal genetic variation that impacts maternal glucose tolerance. A replication study will be performed in additional infants and mothers of European descent with follow-up studies also planned in Afro-Caribbeans, Hispanics of Mexican descent, and Thais. (NHGRI)

Common Treatment (Magnesium Sulfate) to Delay Labor Also Decreases Risk for Cerebral Palsy in Preterm Infants

In the 1990s, findings from several studies seemed to suggest that magnesium sulfate, when given to pregnant women delivering prematurely, might help protect preterm infants from cerebral palsy, a condition that leaves individuals with serious lifelong disabilities. Researchers theorized that magnesium sulfate could protect against cerebral palsy by stabilizing blood vessels, preventing damage from oxygen depletion, and avoiding injury from swelling and inflammation. In recent controlled, randomized trials, researchers showed that babies born to women who were from 24 to 31 weeks pregnant and at risk for preterm delivery and who

received intravenous magnesium sulfate, were less likely to be born with cerebral palsy than were preterm infants whose mothers did not receive the treatment. The magnesium sulfate, however, did not reduce the proportion of deaths occurring in the preterm infants. These findings have significant public health implications given that almost one-third of children with cerebral palsy are born preterm. (NICHD and NINDS)

Reference:

Rouse DJ, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med*. 2008 Aug 28;359(9):895-905.

Folic Acid Supplements Reduce Babies' Risk of Facial Clefts

A new study finds that women who take folic acid supplements early in their pregnancies can substantially reduce their babies' chances of being born with facial clefts. Researchers found that 0.4 mg a day of folic acid reduced by one-third the baby's risk of isolated cleft lip (with or without cleft palate). Folic acid is a B vitamin found in leafy vegetables, citrus fruits, beans, and whole grains. It can also be taken as a vitamin supplement and is added to flour and other fortified foods. (NIEHS)

Reference:

Wilcox AJ, Lie RT, Solvoll K, Taylor J, McConnaughey DR, Abyholm F, Vindenes H, Vollset SE, Drevon CA. Folic acid supplements and risk of facial clefts: national population-based case-control study. *BMJ*. 2007 Mar 3;334(7591):464

Anti-Seizure Drugs and Birth Defects

A finding supported by NINDS showed that anti-seizure drugs taken by pregnant mothers, rather than epilepsy seizures themselves, were the cause of higher-than-normal rates of birth defects in their babies. It has long been recognized that anti-seizure drugs contribute to the higher birth defect rate among epileptic mothers; however, seizure activity was believed to be a major contributor. The new study found that when pregnant women stopped taking anti-seizure drugs, they were no more likely than other women to have children with birth defects. This finding emphasizes that additional research is needed to find more and safer drug choices for pregnant epileptic women. (NINDS)

Reference:

Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM. The teratogenicity of anticonvulsant drugs. *New Engl J Med*. 2001 Apr 12;344(15):1132-8.

The Antiepileptic Drug Valproate Increases Risk of Birth Defects

An NINDS-funded study examined the occurrence of birth defects and fetal death with four common epilepsy drugs: valproate, phenytoin, carbamazepine, and lamotrigine. Valproate posed the highest risk to the fetus, with over 20 percent of the pregnancies exposed to valproate resulting in death or birth defects such as skull and limb deformities and brain, heart, and lung problems. The study's findings are consistent with those of several other recent studies and suggest that women with epilepsy should avoid using valproate during pregnancy. (NINDS)

Reference:

Meador KJ, et al. *In utero* antiepileptic drug exposure: fetal death and malformations. *Neurology*. 2006;67(3):407-12.

New Research Suggests Link between Maternal Diet and Childhood Leukemia Risk

A new study suggests that eating more vegetables, fruits, and protein before pregnancy may lower the risk of having a child who develops leukemia, the most common childhood cancer in the United States. Additionally, the study found that some protein sources, such as beef and beans, also proved beneficial in reducing risk of childhood leukemia. The researchers looked further and found that glutathione was the nutrient in the protein group with a strong link to lower cancer risk. (NIEHS)

References:

Jensen CD, Block G, Buffler P, Ma X, Selvin S, Month S. Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control*. 2004 Aug;15(6):559-70.

http://www.niehs.nih.gov/news/releases/news-archive/2004/matdiet.cfm

Improving Maternal-Child Outcomes through the Nurse-Family Partnership

Thirty years of research on nurse home visitation for prenatal and postpartum women, as a means of enhancing the health and well-being of socially disadvantaged women and their first-born children, has shown that supporting mothers is an effective strategy for improving parent and child outcomes. One study examined whether the Nurse Family Partnership (NFP) reduced mothers' vulnerability to the effects of stressful life events several years after the program was completed. Data from a randomized trial of the NFP were examined for 324 mothers who were generally low-income, young, and unmarried at the time of the birth of their first child. Structured interviews done 15 years after the program began showed that experiencing uncontrollable stressful life events, such as the death of a loved one, led to fewer negative outcomes (fewer mental health problems, less binge drinking, and better parenting practices) among nurse-visited mothers than among mothers receiving no visitation. Furthermore, the program's effect on reducing vulnerability to the negative impact of life events was particularly evident among parents who were younger or had a lower sense of personal control at intake. These findings suggest that in addition to preventing the occurrence of the negative outcomes that were direct targets of the intervention, the NFP more generally enhanced mothers' ability to cope with future stressful life events. Funding for this study was provided by NINR, NIMH, and other sources. (OBBSR)

Reference:

Izzo CV, Eckenrode JJ, Smith EG, Henderson CR, Cole R, Kitzman H, Olds DL. Reducing the impact of uncontrollable stressful life events through a program of nurse home visitation for new parents. *Prev Sci.* 2005 Dec;6(4):269-74.

Improving Child Outcomes with Cash Incentives to Mother

Mexico's conditional cash transfer program, *Oportunidades*, was started to improve the lives of low-income children by providing mothers cash incentives for meeting health, nutrition, and educational targets in the children. From April 1998 to October 1999, low-income communities were randomly assigned to be enrolled in *Oportunidades* immediately (early treatment, n=320) or 18 months later (late treatment, n=186). When children were ages 8-10 years, they were assessed for outcomes including physical growth, cognitive and language development, and socioemotional development to investigate outcomes associated with participating an additional 18 months in the program. Early enrollment reduced behavioral problems for children in the early versus late treatment group. For all other outcomes, the two groups showed comparable benefit, except for those children whose mothers lacked formal education. Overall, children in the *Oportunidades* program improved significantly more on height, weight, language, and behavior than the children not enrolled in the program. These findings show that an additional 18 months in the *Oportunidades* program have independent beneficial effects other than just providing additional money to low-income families, especially for children of women with no formal education. Funding for this study was provided by NICHD, FIC, the Mexican Ministry of Social Development, and others. (OBSSR)

Reference:

Fernald LC, Gertler PJ, Neufeld LM. 10-year effect of Oportunidades, Mexico's conditional cash transfer programme, on child growth, cognition, language, and behaviour: a longitudinal follow-up study. *Lancet*. 2009 Dec 12;374(9706):1952-3.

Breastfeeding Saves Lives

NIEHS-funded research suggests that breastfeeding can reduce the risk of death for infants in their first year of life. Looking at infants between 28 days and 1 year of age, researchers concluded that promoting breastfeeding can potentially prevent nearly 1,000 postneonatal deaths in the United States each year. Children who were breastfed had 20 percent lower risk of dying between 28 days and 1 year of age than children who were not breastfed. Longer breastfeeding was associated with lower risk. The effect was the same in both black and white children. (NIEHS)

References:

Chen A, Rogan WJ. Breastfeeding and the risk of postneonatal death in the United States. *Pediatrics*. 2004 May;113(5):e435-9.

http://www.niehs.nih.gov/news/releases/news-archive/2004/infmort.cfm

THE MENOPAUSAL TRANSITION

Defining the Stages and Symptoms of the Menopausal Transition—the Seattle Midlife Women's Health Study

This longitudinal study produced a number of important findings regarding the changes that midlife women encounter as they progress through the menopausal transition, including changes in symptoms, hormone levels, stress, and use of health services. Findings included the identification of three predictable stages in reproductive aging; in particular, an early, middle, and late stage of the menopausal transition. In addition, the study defined clusters of symptoms that occur during the transition. The symptoms, including hot flashes, sleep disruptions, and depressed mood, appear to be interrelated, which suggests that clinicians should use caution in designing treatment approaches to avoid exacerbating one symptom when treating another. (NINR)

References:

Mitchell ES, Woods NF, Mariella A. Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: toward a more precise definition. *Menopause*. 2000;7(5):334-49.

Cray L, Woods NF, Mitchell ES. Symptom clusters during the late menopausal transition stage: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2010 Jul 9 [Epub ahead of print].

Tai Chi May Help Postmenopausal Women Maintain Bone Mineral Density

NCCAM-funded researchers completed a systematic literature review that suggested Tai Chi may be a safe, effective, and practical alternative to conventional exercise for maintaining bone mineral density in postmenopausal women. Moreover, Tai Chi may improve balance, reduce the frequency of falls, and increase musculoskeletal strength. (NCCAM)

Reference:

Wayne PM, Kiel DP, Krebs DE, Davis RB, Savetsky-German J, Connelly M, Buring JE. The effects of Tai Chi on bone mineral density in postmenopausal women: a systematic review. *Arch Phys Med Rehabil.* 2007 May;88(5):673-80.

Black Cohosh and Hot Flashes: The HALT Study

The Herbal Alternatives (HALT) for Menopause Study found that the herbal supplement black cohosh, whether used alone or with other botanicals, did not relieve hot flashes in women. HALT, cofunded by NCCAM and NIA, did find that women using menopausal hormone therapy received significant relief from their hot flashes and night sweats. (NCCAM)

Reference:

Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med*. 2006 Dec 19;145(12):869-79.

Botanical Dietary Supplements for Women's Health

The University of Illinois at Chicago/NIH Center for Botanical Dietary Supplements Research was established in 1999 to address issues of standardization, quality, safety, and efficacy of botanical dietary supplements. Using a multidisciplinary strategy, the Center studies botanicals with potential benefits for women's health, focusing on plants that are reported to alleviate the symptoms of menopause and premenstrual syndrome. Botanical extracts are subjected to rigorous chemical evaluation, followed by both *in vitro* and *in vivo* biological testing. Standardized botanical extracts that appear efficacious and demonstrate adequate safety profiles in *in vitro* and animal models then become candidates for clinical Phase I trials. Research conducted by Center investigators is greatly enhancing our understanding of the mechanism of action of botanicals and whether they are safe and efficacious for women's health. (ODS)

NIH State-of-the-Science Conference on Management of Menopause-Related Symptoms, March 21-23, 2005

The NIH State-of-the-Science Conference on Management of Menopause-Related Symptoms, held in early 2005, was convened to assess the available scientific evidence to help women make informed decisions about use of hormonal therapy and other strategies to manage troubling symptoms during the menopausal transition, especially in light of findings regarding important risks discovered through the Women's Health Initiative. The Conference's independent panel found that there are many potential alternatives to estrogen, but their effectiveness and long-term safety need to be studied in rigorous clinical trials in diverse populations of women. The panel further concluded that menopause is "medicalized" in contemporary U.S. society, and highlighted a great need to develop and disseminate information that emphasizes menopause as a normal, healthy phase of women's lives. The panel advocated that medical care and future clinical trials be focused on women with the most severe and prolonged symptoms and that any barriers to professional care for these women should be removed. (OMAR)

Study of Women's Health Across the Nation (SWAN): Focus on the Menopausal Transition

Menopause—the cessation of menstruation, signaling the end of a woman's reproductive capability—is a universal aspect of aging among women. However, as recently as 20 years ago, scientists knew remarkably little about how women navigated the menopausal transition. At the time, our knowledge of menopause and the menopausal transition was largely derived from women—a majority of whom were of Northern European ancestry—who visited their doctors for relief of particularly bothersome symptoms. Were these women's menopausal symptoms typical? Did women of different racial and ethnic backgrounds experience the menopausal transition differently? What constituted a "normal" menopausal transition? The answers to these questions were unknown.

In 1994, the Study of Women's Health Across the Nation set out to answer some of those questions. SWAN is the first major longitudinal study of the biological, behavioral, and psychosocial changes that occur in women as they transition from pre- to postmenopause. Approximately 3,300 women have participated in SWAN since its inception. An important aspect of the study is the multiethnic composition of the study population; SWAN includes white, African-American, Hispanic, Chinese, and Japanese women, so for the first time scientists have been able to identify and explore differences among women of different racial and ethnic backgrounds.

SWAN's Goals

The specific aims of SWAN are to gain a more comprehensive understanding of menopause in a cohort of socially and culturally diverse women, and to:

- Describe the symptoms, hormonal changes, and bleeding patterns of the menopausal transition
- Relate personality and behaviors, including lifestyle behaviors and use of menopausal hormone therapy, to age at onset, duration, symptoms, and physical changes of the menopause transition
- Differentiate menopause-related changes from age-related changes at midlife
- Elucidate the role of menopause in the development of the chronic diseases of aging (osteoporosis, type II diabetes, cardiovascular disease, osteoarthritis, etc.)
- Understand cultural and ethnic differences among women with respect to midlife aging and the menopausal transition.

What We Have Learned

Over its 16-year history, SWAN investigators have published over 200 scientific papers describing important—and sometimes surprising—discoveries. The investigators have identified specific racial and ethnic differences with regard to several aspects of the menopausal transition. Among other differences, Japanese women as a group go through menopause somewhat later than Caucasian or African-American women, and levels of several key hormones may differ by race. SWAN investigators have also found that body mass index has a profound effect on hormone levels and perimenopausal symptoms. For example, although conventional wisdom once held that women with higher body fat had fewer vasomotor symptoms (e.g., hot flashes), SWAN investigators have found that heavier women are actually more likely to report these symptoms. And SWAN investigators have confirmed that women going through perimenopause are more likely than premenopausal or postmenopausal women to experience depressive symptoms and certain forms of cognitive change, but that these symptoms often resolve after menopause.

Additional examples of findings from SWAN include:

- ***Age at menopause.*** The median age at natural menopause among women in the study was 51.4 years, although a number of factors, including smoking, marital status, education, past pregnancies, and race/ethnicity influence age at menopause.
- ***Changing hormone levels.*** Hormone profiles differ among ethnic groups, but these differences are highly influenced by body size. In fact, some ethnic differences in reproductive hormone concentrations may be explained by relative body size—a finding with enormous implications, given the global epidemic of obesity.
- ***Perimenopausal symptoms.*** Caucasian women are more likely to report symptoms such as hot flashes and night sweats than their Asian counterparts, but are less likely than African-American women to report these symptoms.
- ***Urinary incontinence.*** About half of all midlife women report some level of urinary incontinence. SWAN investigators have elucidated a number of risk factors for midlife incontinence, including worsening anxiety, high body mass index, weight gain, and new-onset diabetes.
- ***Sleep.*** Sleep disturbances are common among midlife women, and SWAN investigators have found that they are associated with hot flashes and changes in the levels of certain hormones.
- ***Weight gain.*** Weight gain has long been observed to occur in conjunction with the menopausal transition, but studies prior to SWAN have concluded that weight gain is driven primarily by age. SWAN has been able to identify specific aspects of the transition that contribute to weight gain over and above age, including higher levels of androgens, lower levels of sex hormone-binding globulin (SHBG), surgical menopause (i.e., menopause brought on by surgical removal of the uterus and/or ovaries), and early menopausal hormone therapy use—all key factors associated with the development of obesity and/or severe obesity.

- ***Cardiovascular risk factors.*** A longstanding hypothesis is that the menopausal transition sets the stage for later increased risk for heart disease. SWAN is providing fresh insights into exactly how the menopausal transition affects women's risk. It appears that a sharp rise in LDL and total cholesterol in the year before and after the final menstrual period, compared with comparable periods of time earlier or later, may be associated with increased risk of cardiovascular disease.
- ***Cognitive function.*** During perimenopause, SWAN participants were not able to learn as well as they had during premenopause. However, learning abilities rebounded to premenopausal levels when women became postmenopausal. The investigators also found that depressive symptoms and/or anxiety, sleep disturbance, and vasomotor symptoms did not account for this decline in cognitive performance. The investigators are continuing to pursue explanations for this phenomenon.
- ***Bone loss and osteoporosis.*** Age-related bone loss appears to be minimal in most pre- and early perimenopausal women but accelerates dramatically in late perimenopausal women. Rates of bone loss were considerably slower in women in the highest third of body weight. Although racial differences in rates of bone loss were evident in preliminary analyses, these differences disappeared when the data were adjusted for differences in body weight.
- ***Genetic factors.*** SWAN investigators have identified genetic variations related to daily sex hormone levels across the menstrual cycle as well as measures of bone mineral density, glucose levels and diabetes, cognition, lipids, circulating sex hormone levels, and hormone metabolites. Racial and ethnic differences that are correlated with these variations have also been identified.
- ***Functional limitations.*** About 10 percent of women reported substantial functional limitations (difficulties in climbing a flight of stairs, walking a block, or bathing/dressing themselves) by midlife, while another 10 percent of midlife women reported at least some degree of functional limitation. Surgical menopause and use of menopausal hormone therapy were more common in the women who reported physical limitations than in those who did not.

Future Directions

As the original group of women who have participated in SWAN passes through the transition into their postmenopausal years, the study will continue to generate a wealth of information about how women age in America. Now in its fourth wave of funding, SWAN will move from being a study of menopause to a study of aging in women. The study has begun to identify longitudinal patterns of health-related characteristics likely to have an impact on women's transition into older age, and will extend observation of the participants to incorporate additional cardiovascular, musculoskeletal, mental health, and quality-of-life outcomes.

This groundbreaking study is expected to advance the understanding of how modifiable risk factors related to the menopause transition are linked to health outcomes later in life. These findings may in turn lead to improved strategies for prevention of disease and maintenance of robust health in older women.

Funding for SWAN has been provided by NIA, NHLBI, NICHD, NIMH, NINR, NCCAM, and ORWH. (NIA)

Reference:

http://www.swanstudy.org/publications.asp

Exploring Genetic Variation and the Menopausal Transition—SWAN:

A series of 13 articles published from the Study of Women's Health Across the Nation (SWAN) site at the University of Michigan highlighted the importance of genetic variation in women's health using as examples single nucleotide polymorphisms (SNPs) from six genes in the sex steroid pathway. Twenty-six SNPs were found to be related to daily sex hormone levels across the menstrual cycle as well as measures of bone mineral density, glucose levels and diabetes, cognition, lipids, circulating sex hormone levels, and hormone metabolites. Further, the studies demonstrated that significant racial/ethnic differences exist in allele frequency and these differences appear to be associated with health outcomes. (NINR)

Reference:

A special supplement to the American Journal of Medicine (Volume 119S, Issue 9A, Pages S1-S102, September 2006) included 13 articles on the SWAN project.

Dietary and Serum Phytoestrogens and Women's Health Conditions in Midlife

Rates of some estrogen-associated diseases, such as breast cancer, and hip fracture are lower in regions where diets high in phytoestrogens are consumed. However, there have been few studies measuring phytoestrogen exposures relative to these outcomes. An NIH-supported study will use data from the Study of Women's Health Across the Nation (SWAN) to explore the relations between plant estrogen consumption and four outcomes that are important to the health of women: bone density, hot flashes, urinary incontinence, and cognitive performance. This study will serve as a translational research step, either encouraging or dissuading the future development of plant estrogen-based interventions for the treatment of conditions (e.g., hot flashes) or the maintenance of health (e.g., bone density preservation). (ODS)

The Women's Health Initiative (WHI)

The Women's Health Initiative is a long-term national health study that focuses on strategies for preventing heart disease, breast and colorectal cancer, and fracture in postmenopausal women. The first participants were enrolled in 1993, two years after then-NIH Director Dr. Bernadine Healy announced the program. WHI represents the most definitive, far-reaching program of research on women's health ever undertaken in the United States. More than 191,000 women of diverse race and ethnicity aged 50-79 were enrolled at 40 clinical centers across the country. The women agreed to participate in one or more of three clinical trials or an observational study, and follow-up has continued to date—for up to 17 years in the case of the earliest participants.

The WHI hormone trial is a landmark study that has changed medical practice. It included two randomized clinical trials of postmenopausal hormone therapy (MHT)—a study of estrogen plus progestin 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 risk of coronary heart disease (CHD). Contrary to the universal recommendation at the time that postmenopausal women at any age should be encouraged to take hormone therapy to prevent coronary heart disease, the trial findings were the opposite. In fact, the combination of oral estrogen and progestin was so adverse for coronary heart disease, stroke, blood clots in the legs and lungs, and breast cancer that the trial was halted ahead of schedule in July 2002 to protect participants from further harm and to inform the general public. 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. Because it overturned conventional wisdom, the 2002 publication of the trial findings received widespread publicity. More importantly, these findings led to the FDA mandating a "black box" warning on package inserts that postmenopausal hormone therapy should not be used for prevention of cardiovascular disease, changes in the recommendations of professional bodies, and a two-thirds reduction in prescriptions for hormone therapy.

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 CHD risk, but increased risk of stroke and blood clots in the legs. Unlike estrogen plus progestin, estrogen alone did not increase the risk of breast cancer, and a favorable effect on bone health emerged. Both types of hormone therapy increased the risk of memory problems and dementia, again contrary to expectation. On balance, however, the trial indicated that postmenopausal hormone therapy should not be prescribed for chronic disease prevention.

Follow-up studies and data analyses, and investigations using biological samples and clinical data from WHI participants, are ongoing and continue to generate many publications on a wide variety of women's health issues.

- The impact of these findings is illustrated by the national reduction in breast cancer incidence following 2002, in parallel with the reduction in hormone prescriptions. This phenomenon was confirmed in follow-up studies within WHI showing similar reductions in breast cancer risk after participants stopped taking estrogen plus progestin, and this reduction was not due to any change in the frequency of mammograms. The risk of blood clots also diminished, as did the benefit for hip fractures. Continued analyses of the WHI trials indicated that the excess risk of coronary heart disease was concentrated in older women, and particularly those with persistent hot flashes or night sweats (however, the increased risks of strokes and blood clots were independent of age). The finding that overall health risks due to short-term hormone therapy are less marked in younger women is important, because the current recommendations are that hormone therapy primarily be used in the short term for relief of hot flashes and night sweats.
- The WHI trial of low-fat dietary pattern (published in 2006) showed a nonsignificant reduction in breast cancer overall, but a significant reduction in the subset of women who started at the highest levels of fat intake. This is consistent with the public health message to avoid high-fat diets. Interestingly, a low-fat diet is also a high-carbohydrate diet, and in spite of consuming a high-carbohydrate diet the participants lost rather than gained weight, and had a slightly reduced risk of diabetes.
- The trial of calcium and vitamin D, also published in 2006, showed no overall benefit for fractures, but there was evidence of improvement in bone mineral density compared with placebo, and hip fractures were reduced in women over age 60. Again, these findings are consistent with the public health message of maintaining an adequate intake of calcium and vitamin D.
- The observational study has yielded important findings, such as the fact that even moderate regular exercise such as walking is associated with reduced risk of breast cancer and cardiovascular disease.
- These and other contributions of the program were celebrated at The WHI Legacy to Future Generations of Women, a conference on the past, present, and future of WHI, held February 28 - March 1, 2006 at NIH and cosponsored by NHLBI and ORWH.

The WHI program will continue until at least 2015; during this next phase the study will address the causes of cardiovascular conditions in older women (including heart failure, atrial fibrillation, and valvular heart disease in addition to coronary heart disease, peripheral arterial disease, and stroke) and conversely what determines healthy aging, including the absence of cardiovascular disease. The WHI is uniquely suited to study the important health demographic of older women since it has very large numbers of older women (one-third of participants are now over age 80). The program will intensify its efforts to mentor new investigators and serve as a resource for studies of the causes and mechanisms of disease including genomic, epigenetic, proteomic, and metabolomic studies using the stored bloods. (NHLBI)

References:

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288(3):321-33.

Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA*. 2004;291(14):1701-12.

http://www.nhlbi.nih.gov/whi/references.htm

Hormone Therapy and the Brain: A Question of Timing?

Postmenopausal women have a higher risk of developing Alzheimer's disease (AD) than do men, and some studies have suggested that the drop in estrogen levels post menopause may be a factor. Estrogen has been shown to have neuroprotective effects in laboratory studies, and results of some population studies have suggested that use of menopausal hormone therapy (MHT) may be associated with a reduced risk of cognitive decline and dementia. However, other studies have not shown such an association.

NIH has supported or been a part of several major studies of MHT's effects on cognitive health. For example:

- The Women's Health Initiative Memory Study (WHIMS), an ancillary study to the Women's Health Initiative clinical trials of MHT, tested the hypothesis that MHT protects against dementia and global cognitive decline in women age 65 and older. Contrary to expectation, WHIMS showed that MHT increased the risk for probable dementia and resulted in poorer global cognition over time.
- In the WHIMS-MRI study, a subgroup of WHIMS participants underwent magnetic resonance imaging of the brain in an attempt to determine the reason for the unexpected MHT-associated increase in risk for dementia. The investigators found that women who had received MHT as part of the study had smaller brain volumes in areas important in maintenance of normal memory function, but similar volumes of tissue showing abnormal vascular changes, when compared with women who had received a placebo.
- The Women's Health Initiative Study of Cognitive Aging (WHISCA) was an ancillary study to WHIMS to determine whether postmenopausal MHT influenced age-related change in memory and other specific cognitive functions in older women without dementia. Once again contrary to prediction, MHT had, at best, no effect on cognitive function, although one regimen (combination estrogen plus progestin) was associated with greater verbal memory decline over time compared with placebo.
- Most recently, in the Prevention of Postmenopausal Alzheimer Disease and Cognitive Loss with Replacement Estrogen (PREPARE) trial, women ages 65 and older with a family history of dementia were randomized to receive MHT or placebo. The medication was discontinued following reports from WHIMS, but investigators continued to follow the participants. The investigators found that according to predefined criteria on cognitive testing, there was significantly more worsening of cognitive function from baseline in the MHT group, and the composite memory score in the treatment group was significantly lower than in the placebo group at the first two annual follow-ups, with no differences noted in the subsequent three years.

These results demonstrate that use of certain forms of menopausal hormone therapy is associated with an increased risk of cognitive decline and dementia in older women. However, a majority of the participants in these studies were over age 65—a decade or more past the menopausal transition. Other research has suggested that when used at younger ages (i.e., around perimenopause), MHT may have a protective effect on the brain. Ongoing NIH-supported studies, including the Kronos Early Estrogen Protection Study/Cognitive and Affective Study (KEEPS/CA), are focused on determining whether a "window of opportunity" for optimal timing of MHT with regard to cognition may exist, and whether women experiencing significant perimenopausal symptoms may use MHT without risk of adverse cognitive effects. (NIA)

References:

WHIMS:
Espeland MA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291(24):2959-68.

Shumaker SA, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291(24):2947-58

WHIMS-MRI:
Coker LH, Hogan PE, Bryan NR, Kuller LH, Margolis KL, Bettermann K, Wallace RB, Lao Z, Freeman R, Stefanick ML, Shumaker SA. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology*. 2009;72(2):125-34.

Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, Ockene J, Davatzikos C. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study *Neurology*. 2009;72(2):125-34.

WHISCA:
Resnick SM, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab*. 2006;91(5):1802-10.

Resnick SM, et al. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab*. 2009;94(11):4152-61.

PREPARE:
Sano M, Jacobs D, Andrews H, Bell K, Graff-Radford N, Lucas J, Rabins P, Bolla K, Tsai WY, Cross P, Andrews K, Costa R, Xiaodong Luo. A multi-center, randomized, double blind placebo-controlled trial of estrogens to prevent Alzheimer's disease and loss of memory in women: design and baseline characteristics. Clin Trials. 2008;5(5):523-33.

Sano M, et al. Prevention of Postmenopausal Alzheimer Disease And Cognitive Loss With Replacement Estrogen (PREPARE) Study Results. Presented at the International Conference on Alzheimer's Disease; 2010 Jul 14; Honolulu, Hawaii.

KEEPS:
http://www.keepstudy.org/index.cfm

WHI has been funded by NHLBI with additional funding for WHIMS provided by NIA.

WOMEN GROWING OLDER

Pelvic Organ Prolapse and Urinary Incontinence

Pelvic organ prolapse is a condition in which the pelvic muscles and connective tissue of the pelvic cavity are weakened or damaged. Lack of support allows the uterus, bladder, and bowel to press on the vagina, which may cause it to invert, and the organs may protrude through the vaginal opening. In some cases this can lead to chronic pain, surgery, and greatly diminished quality of life. Previously, surgery to correct pelvic organ prolapse involved only a single procedure, and a second surgery would be performed only if incontinence developed. Research conducted by the NICHD Pelvic Floor Disorders Research Network found that the incidence of incontinence was reduced by half when two procedures were performed during the same operation. A more effective surgical approach could benefit the more than 200,000 women who undergo prolapse surgery each year in addition to reducing health care costs.

Another urinary issue that may be treated surgically is stress urinary incontinence. This is a common condition in which activities such as coughing, laughing, and sneezing cause leakage of urine. In some cases this can be bothersome; in others, it is extremely debilitating. The results of a recent comparative effectiveness trial supported by NICHD, NIDDK, and ORWH suggest that two common, minimally invasive surgeries for stress urinary incontinence, known as midurethral-sling surgeries, are equally effective treatments. However, the two procedures were found to have different side effects. This information may help women to weigh the benefits and risks of surgical options to treat stress urinary incontinence.

Some women may wish to explore nonsurgical approaches to treating urinary incontinence. Research supported by NICHD found that weight loss of 5 to 10 percent was as effective as other nonsurgical treatments in correcting urinary incontinence among overweight and obese women. The authors of the study concluded that weight loss should be considered as an initial treatment approach for these women. (NICHD)

References:

Brubaker L, et al. Abdominal sacrocolpopexy with burch colposuspension to reduce urinary stress incontinence. *N Engl J Med*. 2006 Apr 13;354(15):1557-66.

Rogers RG. What's best in the treatment of stress urinary incontinence? *N Engl J Med*. 2010 Jun 3;362(22):2124-5.

Subak LL, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS. Weight loss: a novel and effective treatment for urinary incontinence. *J Urol*. 2005 Jul;174(1):190-5.

A Novel Program Enhances Quality of Life for Caregivers of Alzheimer's Patients

Family caregivers of people with Alzheimer's disease (AD) are disproportionately female. NIA-supported investigators have demonstrated that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for AD caregivers. Subsequent research has shown that caregivers who receive this intervention report better self-rated health, sleep quality, physical health, and emotional health than caregivers not receiving the intervention. The study, Resources for Enhancing Alzheimer's Caregiver Health II (REACH II), was funded by NIA and the NINR and is the first randomized controlled trial to look at the effectiveness of an AD caregiver support intervention for ethnically diverse populations. The first national clinical translation of REACH II, REACH VA, has been implemented by the Veterans Health Administration Geriatrics and Extended Care Unit in partnership with the Memphis VA Medical Center. NIA is also working with the AoA to translate the REACH intervention at the community level. (NIA)

References:

Belle SH, et al. Enhancing the quality of life of dementia caregivers from different ethnic or racial groups: a randomized, controlled trial. *Ann Intern Med*. 2006;145(10):727-38.

Elliott AF, Burgio LD, Decoster J. Enhancing caregiver health: findings from the resources for Enhancing Alzheimer's Caregiver Health II intervention. *J Am Geriatr Soc*. 2010;58(1):30-7.

Ginkgo Biloba Does Not Reduce Risk of Alzheimer's Disease

Important scientific insights have been obtained from a major, long-term clinical trial, the Ginkgo Evaluation of Memory Study (GEMS). This study found that the dietary supplement Ginkgo biloba was ineffective in reducing the development of dementia and Alzheimer's disease in older people. In addition to funding from NCCAM, the GEMS received support from four other NIH components: NIA, NHLBI, NINDS, and ODS. (NCCAM)

Reference:

DeKosky ST, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA*. 2008;300(19):2253-62. Erratum in: *JAMA*. 2008 Dec 17;300(23):2730.

Vitamin D and Calcium Supplementation Reduce Fall Risk in Older Women

According to data from the CDC, more than one-third of U.S. adults ages 65 and older fall each year. Among older adults, falls are the leading cause of deaths due to injury and are also the most common cause of nonfatal injuries and hospital admissions for trauma. In a groundbreaking 2006 study, dietary supplementation with vitamin D and calcium was shown to reduce risk of falling by 46 percent in ambulatory older women overall and by 65 percent in women who were ambulatory but less physically active. No significant effects of this regimen were observed in men. Because supplementation with calcium and vitamin D is one of the least burdensome and expensive treatment strategies and is associated with relatively few side effects, efforts to reduce falls and improve skeletal health in older women have increasingly incorporated an emphasis on calcium and vitamin D supplementation. (NIA)

Reference:

Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med*. 2006;166(4):424-30.

Determination of RDA for Vitamin D in Caucasian and African-American Women

The prevalence of osteoporosis is high in United States, with about 10 million people over the age of 50 already having the disease and another 34 million at risk for developing osteoporosis. However, optimal daily intake for postmenopausal women has not been scientifically established. NIH-supported investigators are conducting studies to establish the RDA for vitamin D in older women, which will have important implications for efforts to prevent osteoporosis in this population. (ODS)

Examples of Cancer in Women

CERVICAL CANCER

The HPV Cervical Cancer Vaccine and HPV-based Cervical Cancer Screening

Cervical cancer is the second most common cause of death from cancer among women worldwide. Since 1990, epidemiologic studies have validated the fact that human papillomavirus (HPV) infection is the main cause of virtually all cases of cervical cancer. These results have led to the development of a highly effective vaccine to prevent cervical cancer and other HPV-associated diseases, and to HPV-based cervical cancer screening procedures. NCI has been involved in all of these etiology-based advances, and vaccine development was strongly supported by the ORWH. The vaccine can reduce the incidence of cervical cancer by about 70 percent, and second generation vaccines under development have the potential to reduce it even further. HPV-based testing can improve current cervical cancer screening programs in the United States and other industrialized nations. Its relatively low cost also makes HPV testing a feasible and effective screening test for use in developing nations, where increasing screening rates has the potential to reduce the incidence of cervical cancer sooner than by immunizing with the vaccine. (NCI)

References:

Muñoz N, Kjaer SK, Sigurdsson K, et al. Impact of the human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst*. 2010;102(5):325-39.

Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301-14.

Plummer M, et al. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis.* 2007;195(11):1582-9.

BREAST CANCER

Genes and Other Risk Factors

***BRCA1* and *BRCA2* Identification in Familial Breast and Ovarian Cancer**

Inactivating mutations of the *BRCA1* and *BRCA2* genes have been linked to an elevated risk of developing breast and ovarian cancer. They are the first genes identified as causing familial breast cancer. Their discovery has enabled better-informed genetic counseling for members of families that carry mutant alleles, contributed to the management of these patients, and brought insight to the normal function of these genes and how their inactivation in patients

can contribute to the development of cancer. Surgery that removes the ovaries and fallopian tubes, called salpingo-oophorectomy, has been demonstrated to decrease a woman's risk of breast and ovarian cancer if she carries a *BRCA1* or *BRCA2* gene mutation. The research studies that led to these advances were strongly supported by NCI. (NCI)

References:

Breast Cancer Linkage Consortium. Cancer risks in *BRCA2* mutation carriers. *J Natl Cancer Inst*. 1999;91(15):1310-6.

Kadouri L, Hubert A, Rotenberg Y, Hamburger T, Sagi M, Nechushtan C, Abeliovich D, Peretz T. Cancer risks in carriers of the *BRCA1/2* Ashkenazi founder mutations. *J Med Genet.* 2007;44(7):467-71.

Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers. *J Natl Cancer Inst*. 2009;101(2):80-7.

Thompson D, Easton DF, et al. Cancer incidence in *BRCA1* mutation carriers. *J Natl Cancer Inst*. 2002;94(18):1358-65.

Discovery of the *BRCA1* Gene

For millions of women whose lives have been affected by breast cancer, the 1994 discovery of the first breast cancer gene by researchers from NIEHS was a welcome sign of progress in the fight against this dreaded disease. Diagnostic tests can now identify women who have inherited defective copies of the gene and are more likely to develop breast cancer. (NIEHS)

Reference:

Futreal PA, Cochran C, Marks JR, Iglehart JD, Zimmerman W, Barrett JC, Wiseman RW. Mutation analysis of the *THRA1* gene in breast cancer: deletion/fusion of the gene to a novel sequence on 17q in the BT474 cell line. *Cancer Res*. 1994 Apr 1;54(7):1791-4.

Studies of *BRCA1* and Other Breast Cancer Genes

An intramural NHGRI laboratory investigates mutations in two known breast-cancer-linked genes, breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*), and their roles in inherited breast and ovarian cancer susceptibility. In 1994, this laboratory was among the first to report that women carrying *BRCA1* or *BRCA2* mutations have a higher risk of developing both breast and ovarian cancer than women without such mutations. The group also discovered an unusually high frequency of specific *BRCA1* mutations in the Jewish population. They recently helped identify eight distinct protein-shortening mutations and another six rare variations of *BRCA2* in a group of African-American breast and ovarian cancer patients.

The team is continuing to study these two populations to better understand the risk of cancer associated with specific mutations and is collecting information on all identified mutations in these two genes worldwide. Currently, more than 2,000 distinct *BRCA1* and *BRCA2* mutations have been identified. Because women with *BRCA1* mutations account for only 5 percent of all

breast cancer cases diagnosed every year, there is a growing scientific consensus that not all *BRCA* mutations carry the same risk of cancer.

The group also is investigating how normal *BRCA* genes help maintain healthy cells. They previously demonstrated that the normal BRCA1 protein regulates key effectors that control the G2/M DNA damage checkpoint, a cell-cycle checkpoint that prevents cells with genomic damage from entering mitosis and reproducing. The carboxyl terminus of BRCA1 contains two motifs found in several DNA-repair and cell-cycle checkpoint proteins. The laboratory also demonstrated that these motifs also bind to a number of other nuclear proteins critical to DNA replication. This segment of BRCA1 also interacts with several histone deacetylases, proteins that modulate the transcriptional activity of genes leading to cell growth arrest, cellular differentiation, and apoptosis (programmed cell death).

Research has found that the amino terminus of BRCA1 is a RING finger protein, a class of proteins that have ligase activity. This ligase catalyzes a key enzymatic step in the ubiquitination pathway, a cellular pathway that recognizes misfolded proteins and targets them for degradation, thus keeping the cell functioning normally. Defects in the normal ubiquitination pathway are implicated in a range of illnesses, including cancer. This particular team is working to identify all the molecules in the ubiquitination pathway that interact with BRCA1.

In addition, NHGRI funds numerous extramural projects related to breast cancer. These include development of an interactive CD-ROM on cancer genetics for Hispanic populations, analysis of parent communication of *BRCA1/2* testing results to children, economic evaluations of emerging genomics tests for early-stage breast cancer, and the development of many high-throughput cancer genome sequencing and mapping centers. (NHGRI)

Genes Associated With Aggressive Breast Cancer in African Women

Although incidence rates of breast cancer are lower in African-Americans than in Caucasians overall, African-American women have a higher incidence under 40 years of age, are diagnosed with more advanced disease, and have poorer prognoses. Groundbreaking NIH research in West Africa revealed evidence of a genetic predisposition to more aggressive forms of breast cancer. In Nigeria, researchers identified three genes that may contribute to high fatality rates and insensitivity to treatment of breast cancer in African women compared with Caucasian women. These findings underscore the urgent need for research into the etiology and treatment of the aggressive molecular subtypes that disproportionately affect young African women in the United States and globally. This study was funded by NCI. (NCI, FIC)

Reference:

Huo D, Ikpatt F, Khramtsov A, Dangou JM, Nanda R, Dignam J, Zhang B, Grushko T, Zhang C, Oluwasola O, Malaka D, Malami S, Odetunde A, Adeoye AO, Iyare F, Falusi A, Perou CM, Olopade OI. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol*. 2009 Sep 20;27(27):4515-21.

Large Surveys Explored Various Risk Factors for Breast Cancer

Approximately 200,000 women are diagnosed with breast cancer each year. Of women born in the United States since 1945, approximately 80 percent have used oral contraceptives. Previous research suggested a slightly elevated risk of breast cancer among women who had recently taken oral contraceptives. The NICHD Women's Contraceptive and Reproductive Experiences Study (Women's CARE) included interviews with more than 9,000 white and black women between the ages of 35 and 64 in various cities across the United States. Women in this study were asked about their use of oral contraceptives and other hormones as well as their reproductive, family, and health histories. The researchers concluded that there was no association between use of oral contraceptives and breast cancer among women between the ages of 35 and 64.

Information collected as part of NICHD's Women's CARE Study was also used by researchers at NICHD, NHGRI, and other institutions to estimate the prevalence in the United States of two genetic mutations that confer a greatly increased risk of breast cancer. The data suggested that the prevalence of *BRCA1* mutations among women ages 35-64 is approximately 0.06 percent, and the prevalence of *BRCA2* mutations is 0.4 percent. These inherited mutations, known as Breast Cancer 1 (*BRCA1*) and Breast Cancer 2 (*BRCA2*), may be involved in between 5 and 27 percent of all breast cancer cases. The researchers also identified factors that increase the likelihood that a woman carries a *BRCA1* or *BRCA2* mutation, such as early age of onset of breast cancer in the patient or family members. The study was also notable because it included understudied groups, such as African-Americans and older women, in its analysis. (NICHD)

References:

Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, Marchbanks PA, Simon MS, McDonald JA, Norman SA, Strom BL, Burkman RT, Ursin G, Deapen D, Weiss LK, Folger S, Madeoy JJ, Friedrichsen DM, Suter NM, Humphrey MC, Spirtas R, Ostrander EA. Prevalence and predictors of *BRCA1* and *BRCA2* mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res*. 2006 Aug 15;66(16):8297-308.

Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, Bernstein L, Malone KE, Ursin G, Strom BL, Norman SA, Wingo PA, Burkman RT, Berlin JA, Simon MS, Spirtas R, Weiss LK. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002 Jun 27;346(26):2025-32.

Breast Density in Mammography and Cancer Risk

Multiple studies have established that breast density is directly linked to breast cancer risk. Women with the highest densities are estimated to have a threefold or greater risk compared with women with the lowest densities. Though this risk can be influenced by lifestyle factors, twin studies show that the underlying causes of breast density are mostly inherited. Higher breast density is more common in some ethnic groups, including white women. It is also more common in younger women, beginning with increased hormone production during puberty

and continuing through the childbearing years. To identify women at higher risk for breast cancer, NCI's Breast Cancer Surveillance Consortium developed and published risk prediction models. (NCI)

References:

Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst*. 2010 Aug 18;102(16):1224-37.

Kerlikowske K, Ichikawa L, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J Natl Cancer Inst.* 2007;99(5):386-95.

Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *J Natl Cancer Inst*. 2007;99(5):386-95.

Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. *Breast Cancer Res Treat*. 2005;94(2):115-22.

The NIEHS/NCI Breast Cancer and the Environment Research Program

The NIEHS/NCI Breast Cancer and the Environment Research Program is one of the first attempts designed to determine how local environmental factors and genetics predispose young women to breast cancer later in life and to share the findings with the breast cancer community and the public at large. Among its accomplishments to date are pilot biomarker studies on blood and urine from girls—conducted in collaboration with CDC—that indicate the presence of a wide spectrum of hormonally active exposure biomarkers. Several of these chemicals had not been previously reported for school-age girls and may have important effects on their development through puberty.

A recent study by the program shows some association of common environmental exposures, such as phthalates, with changes in early childhood development. The thought is that these exposures may accelerate the beginning of puberty in girls, an event that is a risk factor for breast cancer in adult women. These seemingly small advances can prove to be significant in allowing girls and their families to take steps to change their risk profile for breast cancer. (NIEHS and NCI)

References:

Wolff MS, Teitelbaum SL, Windham G, Pinney SM, Britton JA, Chelimo C, Godbold J, Biro F, Kushi LH, Pfeiffer CM, Calafat AM. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. *Environ Health Perspect*. 2007;115(1):116-21.

Wolff MS, Teitelbaum SL, et al. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environ Health Perspect*. 2010 Jul;118(7):1039-46.

The Sister Study Examines Environmental and Genetic Risk Factors for Breast Cancer in a Diverse Population of Women

The Sister Study, a unique public-private partnership, seeks to identify some of the genetic and environmental causes of breast cancer. The Sister Study is cofunded by NCMHD and led by NIEHS. The Sister Study is the only long-term study in the United States and Puerto Rico of women ages 35 to 74 whose sisters have had breast cancer. Begun in 2003, the study prospectively examines the environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Initial research of the Sister Study has found that women who maintain a healthy weight and who have lower perceived stress seem to slow the aging process and live healthier lives. NCMHD support has assisted in the recruitment and retention of a diverse cohort of women, including African-Americans, Asians, American Indians/Alaska Natives, Hispanics, and seniors (age 65 and older). (NIEHS and NCMHD)

References:

Kim S, Parks CG, DeRoo LA, Chen, H, Taylor JA, Cawthon RM, Sandler DP. Obesity and weight gain in adulthood and telomere length. *Cancer Epidemiol Biomarkers Prev*. 2009 Mar;18(3):816-20.

Parks CG, Miller DB, McCanlies EC, Cawthon RM, Andrew ME, DeRoo LA, Sandler, DP. Telomere length, current perceived stress, and urinary stress hormones in women. *Cancer Epidemiol Biomarkers Prev*. 2009 Feb;18(2):551-60.

http://www.niehs.nih.gov/news/releases/2009/sister-study.cfm

Breast Cancer Prevention

Breast Cancer Prevention Trial Study of Tamoxifen and Raloxifene

The Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) demonstrated that half of breast cancers can be prevented with a medical intervention and provided a beginning from which a new paradigm for breast cancer prevention is evolving. Women at increased risk of this common disease now have preventive options where none had existed. Cohorts of women at increased risk for breast cancer who could derive a net benefit from receiving tamoxifen or raloxifene have been identified and are being studied. Neither tamoxifen nor raloxifene is without risk of side effects, but these studies have shown that premenopausal women are likely to derive benefit from tamoxifen with few serious side effects, and postmenopausal women have fewer risks with the drug raloxifene. Analyses of blood, tissue, and clinical data from these studies continue to answer vital questions about breast cancer biology, risk, and prevention, and about who is most likely to benefit from these drugs. (NCI)

References:

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 1998;90(18):1371-88.

Vogel VG, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res* (Phila PA). 2010 Jun;3(6):696-70.

Vogel VG, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006 Jun 21;295(23):2727-4.

Physical Activity Reduces Breast Cancer Risk and Improves Survival

Research shows that women who exercise are less likely to develop breast cancer than their sedentary peers; physical activity can also improve outcomes for those patients who do develop breast cancer. One of the largest surveys administered found an 18 percent drop in the risk of the disease for women who walked briskly for 75 to 150 minutes each week compared with women who were less active. While researchers continue to study how exercise reduces cancer risk, they hypothesize that it may be related to the amount of body fat; fat cells tend to release more estrogen, which is known to promote some types of breast cancer. Other studies have provided evidence that physical activity improves survival and reduces negative treatment side effects. (NCI)

References:

Alfano CM, Smith AW, Irwin ML, Bowen DJ, Sorensen B, Reeve BB, Meeske KA, Bernstein L, Baumgartner KB, Ballard-Barbash R, Malone KE, McTiernan A. Physical activity, long-term symptoms, and physical health-related quality of life among breast cancer survivors: a prospective analysis. *J Cancer Surviv*. 2007;1(2):116-28.

Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293(20):2479-86.

Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB, Bernstein L. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the Health, Eating, Activity, and Lifestyle study. *J Clin Oncol*. 2008;26(24):3958-64.

Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst*. 2008;100(10):728-37.

Artificial Light at Night Stimulates Breast Cancer Growth

Results from a study in laboratory mice show that nighttime exposure to artificial light stimulates the growth of human breast tumors by suppressing the levels of a key hormone called melatonin. The study also showed that extended periods of nighttime darkness greatly slowed the growth of these tumors. The study results might explain why female night shift workers have a higher rate of breast cancer. It also offers a promising new explanation for the epidemic rise in breast cancer incidence in industrialized countries like the United States. (NIEHS)

References:

Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, Sauer LA, Rivera-Bermudez MA, Dubocovich ML, Jasser SA, Lynch DT, Rollag MD, Zalatan F. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res*. 2005 Dec 1;65(23):11174-84.

http://www.niehs.nih.gov/news/releases/news-archive/2005/cancerlight.cfm

Timing of Dietary Exposure and Breast Cancer Risk

Epidemiological studies have not consistently linked any specific dietary component to either increased or reduced breast cancer risk. However, some researchers believe that timing of dietary exposures might be more important in affecting risk than an exposure shortly before or at diagnosis, and that the breast is most sensitive to dietary factors at times when diet-induced biological changes can alter its development and function. These sensitive periods include fetal life, puberty, and pregnancy, when the breast undergoes extensive proliferation following a natural exposure to high levels of hormones and growth factors, which are known to play a central role in breast cancer. NIH-supported investigators are currently studying the timing of exposures to various nutritional components that interact with nuclear hormone receptors, with the ultimate aim of developing novel means to prevent some breast cancers by dietary modifications that take place during pregnancy and puberty. (ODS)

Declines in Breast Cancer Incidence Linked to Reduced Use of Menopausal Hormone Therapy

After rising for more than two decades, the incidence of breast cancer in the United States decreased sharply in 2003 and has remained at the lower level. Researchers attribute the drop to a decrease in the use of menopausal hormone therapy (MHT) that occurred at about the same time. Starting in mid-2002, millions of women stopped using MHT after an NIH study linked certain hormones to health risks, including breast cancer. These studies relied heavily on data from the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. The declines were more significant in breast cancers that were estrogen receptor positive, the specific type of cancer whose growth can be fueled by the use of MHT. (NCI)

References:

Ross RK, Paganini-Hill A, Wan PC, Pike MC. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670-4.

Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst*. 2000;92(4):328-32.

Screening, Detection, and Diagnosis of Breast Cancer

Early Breast Cancer Detection—Breast CT Scanner

Breast cancer is the second most common cancer found among American women, with approximately 200,000 new cases reported each year. One method of early detection of breast cancer is getting women screened for breast cancer regularly. Mammograms, or x-rays of the breast, are used to detect breast cancer in women with no signs or symptoms of the disease in order to find and treat small lesions before cancer spreads. However, the pinch that occurs when breasts are squeezed between two plates during a mammogram is enough to make some women avoid this potentially life-saving screening procedure. A new approach to breast imaging—a dedicated breast scanner based on computed tomography (CT)—may someday offer women pain-free screening as well as more precise diagnosis and treatment options. Using x-rays taken from many different angles, breast CT provides a three-dimensional image of the breast using the same amount of radiation as that used for a mammogram. The scanner system, developed by researchers at the University of California, Davis, images and exposes only the breast to radiation, using cone beam geometry. This scanner protects the surrounding tissue in the lungs, heart, and back from radiation exposure. As a potential screening tool, the breast CT scanner surpasses conventional mammography in several ways: it provides three-dimensional images of the breast compared with just two-dimensional images for mammography, eliminates compression of the breast between two plates, and eliminates image artifacts (suspicious areas that result from normal breast structures overlaying each other when the breast compresses). Women with dense breasts may particularly benefit from this more detailed imaging, since dense breast tissue can obstruct lesions. (NIBIB)

Reference:

Lindfors KK, Boone JM, Nelson TR, Yang K, Kwan AL, Miller DF. Dedicated breast CT: initial clinical experience. *Radiology*. 2008 Mar;246(3):725-33.

Self-hypnosis Reduces Anxiety and Pain during Core Needle Breast Biopsy

An NCCAM-funded trial found that women who used self-hypnosis during a type of core needle breast biopsy experienced anxiety relief and reduced pain when compared with standard care. Specifically, the study found that both self-hypnosis and empathic attention reduced pain and anxiety during the procedure with self-hypnosis providing greater anxiety relief. Neither intervention increased procedure time or significantly increased cost. As a result, the researchers suggest that self-hypnosis appears attractive for outpatient pain management. (NCCAM)

Reference:

Lang EV, Berbaum KS, Faintuch S, Hatsiopoulou O, Halsey N, Li X, Berbaum ML, Laser E, Baum J. Adjunctive self-hypnotic relaxation for outpatient medical procedures: a prospective randomized trial with women undergoing large core breast biopsy. *Pain.* 2006 Dec 15;126(1-3):155-64.

Magnetic Resonance Spectroscopy Imaging (MRSI) for Characterizing Breast Cancers

MRI is increasingly being used as an imaging tool for management of breast cancer, for such purposes as local staging and screening for high-risk patients. Researchers at the NCRR-supported Biomedical Research Center at the University of Minnesota have explored the use of Magnetic Resonance Spectroscopy Imaging (MRSI) for characterizing breast cancers and demonstrated its efficacy in improving diagnostic accuracy and monitoring response to therapy. Specifically, they have shown that the concentration of choline-containing compounds, measured by MRSI, can serve as sensitive biomarkers for breast malignancies. (NCRR)

Classifying Breast Cancers by Gene Expression Profiling

In the last decade, the development of microarrays and the ability to carry out gene expression profiling have resulted in a new way of classifying breast cancers and have established the heterogeneity among breast cancers at the molecular level. Gene profiling has led to identification of four subtypes of breast cancers: luminal A (ER+/PR+/Her2-), luminal B (ER+/PR+/Her2+), Her2+ (ER-/Her2+) and basal (ER-/PR-/Her2-). The information from gene profiling is now being used to determine treatment decisions. (NCI)

References:

Liu X, Holstege H, van der Gulden H, Treur-Mulder M, Zevenhoven J, Velds A, Kerkhoven RM, van Vliet MH, Wessels LF, Peterse JL, Berns A, Jonkers J. Somatic loss of BRCA1 and p53 in mice induces mammary tumors with features of human *BRCA1*-mutated basal-like breast cancers. *Proc Natl Acad Sci USA*. 2007;104(29):12111-6.

Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumors. *Nature*. 2000; 406(6797):747-52.

Turner NC, Reis-Filho JS, Russell AM, Springall RJ, Ryder K, Steele D, Savage K, Gillett CE, Schmitt FC, Ashworth A, Tutt AN. BRCA1 dysfunction in sporadic basal-like breast cancer. *Oncogene*. 2007;26(14):2126-32.

Weigelt B, Baehner FL, Reis-Filho JS. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: a retrospective of the last decade. *J Pathol*. 2010 Jan;220(2):263-80.

NIH Consensus Development Conference: Breast Cancer Screening for Women Ages 40-49, January 21-23, 1997

NCI and OMAR convened an independent panel in 1997 to assess the available scientific data on the effectiveness of mammography screening for women ages 40-49. Panel members took into consideration the risks versus the benefits of mammography screening and found that the available evidence for a breast cancer mortality reduction for women in their forties was inconsistent, while the risks of false-positive and false-negative mammograms and radiation-induced breast cancers appeared greater in this age group. As such, they did not think that the data supported a recommendation for universal mammography screening for all

women in their forties and concluded that each woman should be able to individually decide whether to undergo mammography.[1] They noted the decision should be based upon access to the best possible information regarding benefits and risks, presented in an understandable and usable form. The panel believed that the costs of mammograms for all women in their forties choosing to undergo mammography should be reimbursed by third-party payors or covered by health maintenance organizations. The panel identified a number of critical research questions, including the optimal screening interval for women of various ages, the relationship between the magnitude of breast-cancer mortality reduction and the age of the woman beginning mammography, and the impact of menopause on the effectiveness of mammography. (OMAR)

Advances in Treatment of Breast Cancer

Treatment for HER-2-Positive Invasive Breast Cancer

Results from two large, randomized clinical trials conducted by the NCI-sponsored Clinical Trials Cooperative Group Program for patients with HER-2-positive invasive breast cancer demonstrated that women with early-stage breast cancer who received Herceptin® (trastuzumab, a monoclonal antibody to the HER-2 protein) in combination with chemotherapy reduced their risk of recurrence by 52 percent after three years compared with women who received the same chemotherapy regimen without trastuzumab. For women with this type of aggressive breast cancer, the addition of trastuzumab to chemotherapy appears to virtually reverse prognosis from unfavorable to good. These findings represent a triumph for molecularly targeted cancer treatment and a noteworthy advance in breast cancer treatment that has changed the standard of care for the 25 to 30 percent of women whose tumors express the HER-2 protein. (NCI)

Reference:

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-84.

Aromatase Inhibitors

Since the mid-1990s there has been a series of clinical trials of third-generation aromatase inhibitors demonstrating their effectiveness in treating breast cancer. Both anastrozole and letrozole have been approved as first-line endocrine therapy for postmenopausal estrogen-receptor-positive advanced breast cancer patients. Several studies have shown that about 60 percent of breast tumors have significant levels of aromatase and thus are able to carry out local synthesis of estrogens. An intratumoral aromatase model in nude mice which simulates

1 The NIH Consensus Statement on Breast Cancer Screening for Women Ages 40-49 contains a minority report. While a consensus was initially achieved by the entire panel at the end of the conference, 2 of the 12 panel members subsequently decided that the risks of mammography were overemphasized by the majority and concluded the data did support a recommendation for mammography screening for all women in this age group.

the postmenopausal breast cancer patient was found to be extremely useful in determining the efficacy of aromatase inhibitors and accurately predicting clinical response. This model was used in investigating the efficacy of combining tamoxifen with an aromatase inhibitor and demonstrated that the aromatase inhibitor alone was more effective than either tamoxifen alone or tamoxifen combined with the aromatase inhibitor. This was found to be true in clinical trials as well. (NCI)

References:

Baum M, et al. Anastrazole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer: results of the ATAC trial efficacy and safety update analyses. *Cancer*. 2003;98(9):1802-10.

Long BJ, Jelovac D, Handratta V, Thiantanawat A, MacPherson N, Ragaz J, Goloubeva OG, Brodie AM. Therapeutic strategies using the aromatase inhibitor letrozole and tamoxifen in a breast cancer model. *J Natl Cancer Inst*. 2004;96(6):456-65.

Understanding Racial Disparities in Underuse of Treatment for Early-Stage Breast Cancer

Reducing Underuse of Early-stage Breast Cancer Treatment in Minority Communities is a project measuring the extent of underuse of efficacious breast cancer treatments among patients of six hospitals serving East and Central Harlem and other minority communities in lower Manhattan with the intent of solving problems of underuse of effective interventions in patients with early-stage breast cancer. This study has generated new knowledge about racial disparities in treatment for early-stage breast cancer and patient and physician reasons for underuse, and is exploring the effectiveness of a simple, sustainable intervention to improve rates of efficacious cancer treatment. To date, they have completed chart abstraction of over 1,000 identified breast cancer cases from six different hospitals. In a study of the records of nearly 700 women, they found an overall disparity in underuse of 19 percent, with the following breakdown: 14 percent underuse for whites, 23 percent for Hispanics, and 30 percent for African-Americans. They are currently looking for the factors that may explain this underuse data and have completed a small number of patient and surgeon surveys. A computer-based intervention is currently ongoing at three of the six participating hospitals. (NCMHD)

Hypnosis May Reduce Hot Flashes in Breast Cancer Survivors

NCCAM-supported researchers investigated the effects of hypnosis on hot flashes in a study of 60 women with a history of primary breast cancer, no current evidence of detectable disease, and at least 14 hot flashes per week over a one-month period. They concluded that hypnosis not only appears to reduce perceived hot flashes in breast cancer survivors, but may also have additional benefits such as improved mood and sleep. They are now conducting a randomized clinical trial with 200 participants. (NCCAM)

Reference:

Elkins G, Marcus J, Stearns V, Perfect M, Rajab MH, Ruud C, Palamara L, Keith T. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol.* 2008 Nov 1;26(31):5022-6.

Antidepressants for Hot Flashes May Interfere with Tamoxifen

Women with breast cancer often take the drug tamoxifen to treat the cancer and antidepressants to ease the depression and hot flashes that are side effects of the cancer drug. However, a study led by a clinical pharmacologist at the Indiana University School of Medicine in Indianapolis and a member of the NIH Pharmacogenetics Research Network, shows that a common class of antidepressants, called selective serotonin reuptake inhibitors, can hinder the effectiveness of tamoxifen. The findings also point to genetic differences that may explain why tamoxifen works well in some women and not others, and why some people respond better to certain antidepressants. The new information could help doctors make more informed choices about what drugs are likely to work best for different patients. (NIGMS)

Reference:

Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF, Desta Z, Flockhart DA. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003 Dec 3;95(23):1758-64.

Genes Influence Response to Breast Cancer Treatment

A major focus in pharmacogenetics research is on a large group of enzymes that process many medications in the body. Researchers supported by the Pharmacogenetics Research Network studying women with breast cancer found that individuals with a specific genetic variation in one such enzyme (CYP2D6) do not respond as well as those without the variation to tamoxifen, a widely prescribed drug used to treat breast cancer. On average, breast cancer survivors with the CYP2D6 variation live disease free for only four years after treatment, whereas those without the variation average eleven years disease free. This discovery may lead to greater use of genetic tests to determine which women are most likely to benefit from tamoxifen. (NIGMS)

References:

Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH, Skaar T, Storniolo AM, Li L, Araba A, Blanchard R, Nguyen A, Ullmer L, Hayden J, Lemler S, Weinshilboum RM, Rae JM, Hayes DF, Flockhart DA. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*. 2005 Jan 5;97(1):30-9.

Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, Reynolds C, Couch FJ, Lingle WL, Flockhart DA, Desta Z, Perez EA, Ingle JN. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol*. 2005 Dec 20;23(36):9312-8.

Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, Jin Y, Storniolo AM, Nikoloff DM, Wu L, Hillman G, Hayes DF, Stearns V, Flockhart DA. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. *Clin Pharmacol Ther*. 2006;80(1):61-74.

NIH State-of-the-Science Conference: Diagnosis and Management of Ductal Carcinoma in Situ, September 22–24, 2009

NCI and OMAR cosponsored the NIH State-of-the-Science Conference: Diagnosis and Management of Ductal Carcinoma *in Situ* in September 2009. Ductal carcinoma *in situ* of the breast, or DCIS, represents a spectrum of abnormal cells confined to the breast duct and is a risk factor for invasive breast cancer development. The independent State-of-the-Science Panel convened to weigh the available evidence associated with DCIS in 2009 found that because of the noninvasive nature of DCIS and its favorable prognosis, strong consideration should be given to removing the anxiety-producing term "carcinoma" from the description of DCIS. The outcomes in women treated with available therapies are excellent. Thus, the primary question for future research must focus on the accurate identification of patient subsets diagnosed with DCIS, including those persons who may be managed with less-invasive intervention, without sacrificing the excellent outcomes presently achieved. (OMAR)

OVARIAN CANCER

Genetic Research on Ovarian Cancer

About one-fifth of ovarian cancers are found at an early stage. Early detection improves the chances that it can be treated successfully. Nine out of 10 women treated for early ovarian cancer will live longer than five years after the cancer is found. Unfortunately, there is no reliable test for finding this cancer early, but several large studies are in progress to learn how best to find ovarian cancer in its earliest stages.

Currently, NHGRI researchers are in the pilot phase of a collaborative project to identify locations in the genome that are important for the regulation of gene expression in ovarian cancers. By using sequencing to identify sites of abnormal methylation (a DNA modification) in promoter regions, this project hopes to determine which regulatory regions and which genes are factors in the occurrence of ovarian cancer. Investigators at NHGRI were among the first to report that women carrying *BRCA1* or *BRCA2* mutations have a higher risk for Hereditary Breast Ovarian Cancer (HBOC) Syndrome. NHGRI noticed a lack of studies regarding knowledge, attitudes, and behaviors related to cancer genetics among Hispanic women at increased risk for HBOC among various Hispanic ethnic groups.

NHGRI has awarded a grant to better understand cultural differences that may affect utilization of *BRCA1/2* testing for HBOC among three major U.S. Hispanic ethnic groups (Mexicans, Puerto Ricans, and Cubans). Study findings will serve as the basis for a larger intervention trial based in a public health department setting to educate Hispanic women at increased risk for HBOC about genetic counseling and testing for HBOC and possibly other hereditary cancers. (NHGRI)

Mifepristone Reduces Ovarian Cancer Cell Growth between Rounds of Chemotherapy

The majority of ovarian cancer patients require surgery to remove as much of the tumor as possible, followed by chemotherapy that includes a platinum compound such as cisplatin or carboplatin. However, platinum-based chemotherapy is hindered by the elevated toxicity of the drug, the development of chemoresistance, and the capacity to regenerate tumors of surviving tumor cells (repopulation) between rounds of chemotherapy. One strategy to stop tumor cell repopulation is to use a selective compound between courses of chemotherapy to inhibit repopulation of tumor cells. Researchers at the NCRR-supported Sanford School of Medicine of The University of South Dakota are investigating the use of mifepristone (commonly known as "RU-486") to reduce either the number of cisplatin cycles or the dose of cisplatin without losing efficacy in inhibiting tumor growth. Consequently, scheduling mifepristone treatment between courses of platinum-based therapy for ovarian cancer has potential to improve treatment success. (NCRR)

UTERINE/ENDOMETRIAL CANCER

Genetics of Endometrial Cancer

Endometrial cancer, which affects the endometrium (the lining of the uterus), is the most common gynecological malignancy in the United States. There are 41,200 new cases of endometrial cancer diagnosed each year, along with 7,350 deaths attributable to this disease. Most patients present with "type I" tumors and have a good prognosis, but around 15 percent are diagnosed with "type II" tumors that are clinically aggressive. Patients with type II tumors have a five-year survival rate of less than 40 percent.

Over the past few years, it has become evident that certain types of chromosomal and genetic alterations may be exploited as therapeutic targets in the treatment of certain cancers. For example, the drug imatinib is highly effective in the treatment of chronic myelogenous leukemia caused by a chromosome translocation. Similarly, a subset of non-small cell lung cancers with specific mutations that affect the catalytic domain of the epidermal growth factor receptor (EGFR) responds to the drugs gefitinib and erlotinib. An NHGRI team of investigators aims to identify the genetic alterations that cause serous and clear-cell tumors of the endometrium en route to developing new therapies for type II endometrial cancers.

Towards that end, the research group is using high-density, single-nucleotide polymorphism genotyping to identify genome-wide copy-number changes and other genetic events in type II endometrial tumors. Parallel studies include extensive collaborations with the NIH Intramural Sequencing Center for performing mutational screens of all exons that encode the catalytic domains of 90 known tyrosine kinases. In addition, these efforts include searching for structural chromosomal alterations in endometrial tumors. Once specific genetic alterations are found to be associated with tumor development, more extensive examination of the clinicopathologic features of mutation-harboring tumors will be performed in an attempt to implicate individual genes or functional pathways that could be targeted for therapeutic intervention. (NHGRI)

Endometrial Cancer and HNPCC

An inherited susceptibility to endometrial cancer is usually associated with increased risk for hereditary nonpolyposis colorectal cancer (HNPCC). In fact, endometrial cancer is the second most common form of malignancy diagnosed in women with HNPCC. Susceptibility to endometrial cancer is also associated with an increased risk for Cowden syndrome, which first produces symptoms in the late twenties and causes multiple noncancerous growths called hamartomas on the skin and mucous membranes. Cowden syndrome is also linked to the development of breast, thyroid, and endometrial malignancies. There are a few families that lack either the clinical manifestations or molecular characteristics of HNPCC or Cowden syndrome, yet still have a clustering of endometrial cancer cases, which suggests a tissue-specific etiology. It is possible that predisposition to endometrial cancer in these families is linked to one or more mutations that have varying risk, rather than a single mutation that always results in disease.

In an effort to learn about the influence of genetic education, counseling, and the option of genetic testing on psychological and behavioral outcomes in individuals at risk for inherited HNPCC, another NHGRI research project explores how patients perceive their risk of developing cancer, and monitors the influence of education and counseling on mood, behavior, and family relationships. (NHGRI)

LUNG CANCER

Smokefree Women

The popular Smokefree.gov Web site has spun off a new section, Smokefree Women (*http://women.smokefree.gov*) and a companion Facebook page with information, tools, and discussion forums specifically developed to help female smokers quit. Women who smoke experience the same health hazards as men but they also face hazards unique to women, including endangering the life and health of a developing child if they smoke during pregnancy. The new site focuses on helping women integrate smoking cessation into daily life and family matters to help women stay smokefree. It was designed with the knowledge that different women need different resources to quit.

The Web site and Facebook page contain interactive features, as well as tools that users can download to their personal Facebook profiles. For example, the “Talk to an Expert” feature allows users to receive information and advice about quitting smoking through real-time telephone-based or online LiveHelp messaging with an NCI smoking cessation counselor. A step-by-step Quit Guide is also provided, and the “Topics that Interest You” section includes information on smoking and pregnancy, depression, weight management, and relationships.

Smokefree Women was developed by the Tobacco Control Research Branch in NCI’s Division of Cancer Control and Population Sciences, with assistance from CDC, Health Canada, the American Legacy Foundation, the Robert Wood Johnson Foundation, the American Cancer Society, and NCI’s Office of Communications and Education. (NCI)

Chronic Diseases and Conditions in Women

Stressed-Out DNA

Numerous studies have demonstrated links between chronic stress and poor health, including cardiovascular disease and diminished immune function, but scientists are not sure why. Elizabeth Blackburn, Ph.D., who shared in the 2009 Nobel Prize in Physiology or Medicine, has investigated the hypothesis that stress impacts health by modulating the rate of cellular aging. She and collaborators have provided evidence that psychological stress—both perceived stress and chronicity of stress—is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity, in peripheral blood mononuclear cells from healthy premenopausal women. Women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared with low-stress women. These findings have implications for understanding how, at the cellular level, stress may promote earlier onset of age-related diseases. (NIGMS)

Reference:

Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA*. 2004 Dec 7;101(49):17312-5.

DIABETES

Prevention or Delay of Type 2 Diabetes

The Diabetes Prevention Program (DPP) randomized clinical trial demonstrated for the first time that type II diabetes can be prevented or delayed in women and men through intensive lifestyle intervention to induce modest weight loss. Treatment with an oral diabetes medication (metformin) was also effective. Further, both strategies are effective in women with a history of gestational diabetes, who are at greatly increased risk of developing diabetes after pregnancy. A ten-year follow-up study has demonstrated sustained benefits of the DPP. (NIDDK)

References:

Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002 Feb 7;346(6):393-403.

Diabetes Prevention Program Research Group, Knowler WC, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009 Nov 14;374(9702):1677-86.

Gestational Diabetes

Gestational diabetes mellitus (GDM) affects at least 200,000 pregnancies in the United States each year (7 percent).[2] Having GDM can lead to large babies, birth injuries, and other pregnancy and delivery complications. However, research has shown that the effects of GDM last long past pregnancy. Women with a history of GDM have a 40 to 60 percent risk of developing diabetes, mostly type II diabetes, in the five to ten years after delivery. Moreover, the children of GDM-affected pregnancies are at greatly increased risk of future obesity and type II diabetes. For girls born to GDM pregnancies, this may increase their risk of having or developing diabetes while pregnant themselves, perpetuating diabetes health risks through future generations.

To address this important health issue for women and their families, ORWH and the National Diabetes Education Program (NDEP) have partnered to significantly expand a GDM outreach and awareness initiative. Jointly sponsored by NIDDK and CDC with over 200 public and private partners, NDEP seeks to reduce the burden of diabetes in the United States by facilitating adoption of proven approaches to prevent or delay the onset of diabetes and its complications. Since 2003, NDEP has been conducting a national, multicultural campaign called *"Small Steps. Big Rewards. Prevent type 2 Diabetes"* to disseminate the positive results of the landmark Diabetes Prevention Program (DPP) clinical trial—that type II diabetes can be prevented or delayed in people at high risk through lifestyle change or use of the medication metformin. The campaign employs materials tailored to specific high-risk audiences, including women with a history of GDM. ORWH provided funding to facilitate recruitment of women with a history of GDM into the DPP trial, enabling DPP researchers to determine that both trial interventions were highly and equally effective in these women, who were at even greater risk of developing diabetes than other high risk, prediabetic women enrolled in the trial.

Now, ORWH has joined NDEP to expand and extend the reach of the tailored GDM campaign. Called *"It's Never Too Early To Prevent Diabetes. A Lifetime of Small Steps for a Healthy Family,"* goals of the expanded campaign are to decrease the incidence of diabetes among women with a history of GDM, increase the awareness of health risks among affected families, and improve the reach of information and delivery of health care professional counseling regarding future health risks and the importance of adopting and maintaining healthy behaviors among these families. Through this effort, ORWH and NDEP hope to see the DPP results translated into positive health outcomes for women who have had GDM and their families. (NIDDK)

2 Recent data from the NIH-supported Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study have shown that pregnancy complications occur at glucose levels lower than those currently used for gestational diabetes diagnosis, which in turn has led to recommendations to change the diagnostic definition of gestational diabetes. This change would potentially increase the burden of gestational diabetes to nearly 18 percent of pregnancies. These recommendations are currently under consideration. (International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33(3):676-82.)

Diabetes and Maternal Health

The University of Oklahoma Center for American Indian Diabetes Health Disparities (OCAIDHD) aim to reduce and eventually eliminate the excess mortality, morbidity, and quality of life and culture lost due to diabetes. The primary impact of the Center focuses on diabetes, maternal health, infant mortality, and obesity. The OCAIDHD confronts health disparities by focusing the expertise of a multidisciplinary, multicollege team of diabetes researchers on specific biological, physiological, behavioral, and cultural stressors of the disease in studies such as 1) *Early Markers of Preeclampsia in American Indians with Type 2 Diabetes*, 2) *Insulin Resistance and Glucocorticoid Treatment of Inflammatory Diseases of High Prevalence Among AI*, and 3) *American Indian Diabetes Beliefs and Practices: Maternal Care, Infant Mortality, and Adherence*. (NCMHD)

EYE DISEASE

Age-Related Macular Degeneration

Studies show that the incidence of age-related macular degeneration (AMD) continues to rise in the population as the result of the increasing percentage of elderly persons, with women at 50 percent greater risk than men. A study looking at AMD in women participating in the Nurses' Health Study indicated a preliminary association between AMD and use of menopausal hormone therapy after menopause. These findings suggest a role for estrogen in the pathogenesis of AMD that requires further research in specific early and late signs of disease. (NEI)

Reference:

Cho E, Seddon JM, Rosner B, Willett WC, Hankinson SE. Prospective study of intake of fruits, vegetables, vitamins, and carotenoids and risk of age-related maculopathy. *Arch Ophthalmol*. 2004 Jun;122(6):883-92

Optic Neuritis

The Optic Neuritis Treatment Trial (ONTT) and the Longitudinal Optic Neuritis Study (LONS) showed that intravenous corticosteroids delay the short-term progression of optic neuritis, an acute, debilitating inflammation of the optic nerve primarily affecting women with multiple sclerosis. This study also demonstrated that the presence of lesions on the brain on MRI scans performed at the time optic neuritis was diagnosed was the single most important predictor of the development of multiple sclerosis within five years. (NEI)

References:

Beck RW, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol*. 2003 Jul;121(7):944-9.

Beck RW, Gal RL, et al. Visual function more than 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Am J Ophthalmol*. 2004;137(1):77-83.

Beck RW, Smith CH, Gal RL, et al. Neurologic impairment 10 years after optic neuritis. *Arch Neurology*. 2004;61(9):1386-9.

Optic Neuritis Study Group. Long-term brain magnetic resonance imaging changes after optic neuritis in patients without clinically definite multiple sclerosis. *Arch Neurology*. 2004;61(10):1538-41.

Keratoconus

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study provided evidence demonstrating an association between corneal scarring and decreased vision in keratoconus, which is more common in women than in men. This association may be linked to wearing contact lenses, suggesting that modifying lens fit can reduce this risk factor. (NEI)

Reference:

Barr JT, Wilson BS, Gordon MO, Rah MJ, Riley C, Kollbaum PS, Zadnik K; CLEK Study Group. Estimation of the incidence and factors predictive of corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Cornea*. 2006 Jan;25(1):16-25

Idiopathic Intracranial Hypertension

The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) is organizing a clinical study on idiopathic intracranial hypertension (IIH), a neuro-ophthalmology-related disease that occurs predominantly in women. The objective is to provide a unique opportunity to recruit and study statistically significant numbers of hard-to-find patients in order to evaluate different diagnostic and treatment options. (NEI)

Reference:

Kupersmith MJ, Miller N, Balcer L, Gordon L, Wall M, Keltner J, Friedman D, Feldon S, McDermott M, Kieburtz K. The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC). *J Neuroophthalmol*. 2009 Sep; 29(3):259-61.

HEART DISEASE

Causes and Symptoms of Coronary Heart Disease in Women

The Women's Ischemia Syndrome Evaluation (WISE), a multicenter study initiated in 1996, has greatly increased understanding about coronary heart disease (CHD) in women and about gender-specific symptoms, risk factors, and pathology. The study enrolled and studied over 900 women who had symptoms of CHD (e.g., chest pain, shortness of breath) and were referred for diagnostic angiography. It found that approximately 50 percent of enrollees did not, in fact, have blockages in their large coronary arteries, yet many of them continued to experience debilitating symptoms or went on to have heart attacks. Microvascular dysfunction (impaired functioning of the small arteries of the heart, which is generally not detected by angiography) was often associated with the ischemia experienced by this large group of women. These findings indicate that CHD risk factors should be addressed aggressively in women with symptoms, even in the absence of a positive angiogram, and that better approaches to evaluate cardiac ischemia in women should be developed and used. (NHLBI)

Reference:

A special supplement to the Journal of the American College of Cardiology on CHD in women (Volume 47, Issue 3, Supplement 1, Pages S1-S72, February 7, 2006) included a number of papers from the WISE.

The Jackson Heart Study: Epidemiology of Cardiovascular Disease in African-American Women

The Jackson Heart Study is the largest single-site, prospective, epidemiologic investigation of cardiovascular disease among African-Americans ever undertaken. It is a population-based longitudinal cohort study. The Jackson Heart Study exemplifies a unique collaborative model among Jackson State University, Tougaloo College, the University of Mississippi Medical Center, the Jackson community, and NIH to discover and test best practices for eliminating health disparities. Since 1998, NCMHD has worked with NHBLI to initiate the study and, more recently, assess success in meeting milestones, including ensuring adequate participation by key stakeholders and advice on scientific direction, including the identification of genetic, biological, and environmental risk factors in African-American women. (NCMHD)

Vitamin E and Aspirin Have Little Protective Effect on the Cardiovascular System in Women

The Women's Health Study found that low-dose aspirin and vitamin E supplements play a minor role, if any, in protecting women from cardiovascular disease (CVD). Aspirin use did not prevent first heart attacks or CVD deaths. It did, however, reduce strokes by 17 percent in the overall study cohort and lower the risk of major CVD events by 26 percent among women who were 65 years of age or older. The study also showed that vitamin E supplementation had no effect on heart attacks, strokes, or total deaths and—with regard to another hypothesized benefit—did not reduce rates of breast, lung, colon, or other cancers. NIH continues to recommend that women focus on other well-proven approaches for reducing their risk of heart disease and stroke—eating healthfully; engaging in regular physical activity; maintaining a healthy weight; abstaining from smoking; and controlling high cholesterol, high blood pressure, and diabetes. (NHLBI)

References:

Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005 Mar 31;352(13):1293-304.

Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005 Jul 6;294(1):56-65.

Women's Cholesterol Levels Vary with Phase of Menstrual Cycle

In recent data, NICHD researchers have shown that women and their physicians need to consider the phase of a women's menstrual cycle when measuring cholesterol. In an in-depth study assessing blood samples taken from healthy women between 18 and 44 years of age over two menstrual cycles, researchers showed that women's cholesterol levels

correspond with monthly changes in estrogen levels. On average, the total cholesterol level of the women in the study varied 19 percent over the course of the menstrual cycle. A small subset of obese women over age 40 showed greater fluctuation in cholesterol levels during their cycles than did the rest of the group. While previous studies have shown that taking drugs that contain estrogen—oral contraceptives or menopausal hormone therapy—can affect cholesterol levels, other studies examining the effects of naturally occurring hormone levels on cholesterol have been inconclusive. The researchers found that as the level of estrogen rises, high-density lipoprotein (HDL) cholesterol also rises, peaking at the time of ovulation. HDL cholesterol is believed to be protective against heart disease. In contrast, total cholesterol and low-density lipoprotein (LDL) cholesterol levels—as well as another form of blood fat known as triglycerides—declined as estrogen levels rose. The decline was not immediate, beginning a couple of days after the estrogen peak at ovulation. Total cholesterol, LDL cholesterol, and triglyceride levels reached their lowest just before menstruation began. This finding lays the groundwork for clarifying the optimal point in the cycle for doctors to measure women's cholesterol levels and for helping to develop standardized procedures for measuring cholesterol in premenopausal women and determining their heart disease risk. (NICHD)

Women and the Subtle Symptoms of a Heart Attack

A study assessed the symptoms experienced by women who had suffered a heart attack in the previous four to six months. Virtually all of the women reported having early symptoms within the weeks prior to their attack, the most common being unusual fatigue and sleep disturbance. Less than a third of the women reported any early warning signs involving chest pain or discomfort, the signs most commonly associated with a heart attack. Likewise, the acute symptoms experienced by women during the attack included shortness of breath, weakness, and fatigue, but, in contrast with men, fewer than half of the women reported some degree of pressure, pain, or tightness of the chest during the critical time of attack onset. (NINR)

Reference:

McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ. Women's early warning symptoms of acute myocardial infarction. *Circulation*. 2003;108(21):2619-23.

Long-term Effects of a Multiple Health Behavior Intervention for Postmenopausal Women

Postmenopausal women with type II diabetes are at high risk for heart disease. The Mediterranean Lifestyle Program, an intervention featuring a weekend retreat followed by regular meetings over 24 months to enhance healthful eating, physical activity, and stress management, and to support behaviors, was undertaken with 279 women. At five years postintervention, long-term analyses indicated that significant improvements made in the targeted behaviors during the active treatment phase of the study (up to 24 months) were partially maintained during the nontreatment phase of the study. Overall, cardiac risk factors decreased and women maintained dietary behavior and stress management levels for the entire follow-up period, and physical activity levels remained significantly higher for the first year of follow-up. These results suggest that sustained health behavior improvement is

possible with a moderate-intensity group-based intervention, but that additional support may be needed to sustain all of the desired program effects for the long term. Funding for the research was provided by NHLBI and OBSSR. (OBSSR)

Reference:

Toobert DJ, Strycker LA, et al. Seven-year follow-up of a multiple-health-behavior diabetes intervention. *Am J Health Behav*. 2010 Nov-Dec;34(6):680-94.

Studies of Metabolic Syndrome among Native Hawaiians, Alaska Natives, and Pacific Islanders

The NCMHD Center for Native and Pacific Health Disparities Research at the University of Hawaii provides a regional focal point for research, research training, and community engagement aimed at cardiometabolic health and health disparities among Native Hawaiians (NH), Alaska Natives (AN), and other Pacific Islanders (PI) including Filipinos, Samoans, and Tongans, among other NH and PI communities. The Center conducts a *Metabolic Syndrome* study, an epidemiological study involving Filipino, NH, and Samoan youth.

A novel community-based participatory research project called *The Partnerships for Improving Lifestyle Interventions (PILI)* has been formed between five community groups, the medical school, and the state department of health to focus on reducing and eliminating obesity health disparities. It is anticipated that women will constitute 80 percent of the participants in this study. Community engagement projects in Hawaii and California will assess optimal strategies for health information dissemination and participation among NH, AN, and PI communities to improve cardiometabolic health and eliminate health disparities. (NCMHD)

Cardiovascular Disease Risk Factors and 25-Hydrocyvitamin D Serum Levels

Researchers at the NCMHD Center of Excellence, established between the Charles Drew University of Medicine and University of California at Los Angeles, analyzed secondary data from the Third National Health and Nutrition Examination Survey (NHANES) to examine the association between serum levels of 25-hydroxyvitamin D and select cardiovascular disease factors in U.S. adults. Findings showed lower levels of 25-hydroxyvitamin D in women, elderly persons, racial/ethnic minorities, and participants with obesity, hypertension, and diabetes mellitus. (NCMHD)

OBESITY

Prevention of Obesity in Girls

Results from the NHLBI Growth and Health Study—an observational study that followed cohorts of white and black girls from childhood to early adulthood—highlight the importance of teaching girls as young as age 9 about behaviors to maintain a healthy weight. Rates of overweight increased through adolescence from 7 percent to 10 percent among white girls in the study and from 17 percent to 24 percent among black girls, with the greatest jump in weight gain occurring at ages 9 to 12 years. Girls who were overweight during childhood were

11 to 30 times more likely to be obese in young adulthood. Moreover, overweight was significantly associated with elevated systolic and diastolic blood pressures and detrimental levels of high-density lipoprotein cholesterol and triglycerides. The findings underscore that efforts to reduce cardiovascular disease risk in women should begin early in life. (NHLBI)

Reference:

Thompson DR, Obarzanek E, Franko DL, Barton BA, Morrison J, Biro FM, Daniels SR, Striegel-Moore RH. Childhood overweight and cardiovascular disease risk factors: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 2007 Jan;150(1):18-25.

Behavioral Modifications for Reducing Obesity in African-American Women

The Uniform Services University (USU) Center for Health Disparities Research, a partnership between USU and the University of Maryland, Eastern Shore, conducts research on long-term behavioral modification aimed at reducing and preventing obesity among African-American women and applies the results of this research experience toward building a program on cardiovascular disease and the metabolic syndrome, both of which disproportionately affect minority populations. Research includes issues related to lifestyle and health, health care access, health status, and health disparities. The Healthy Lifestyles among African-American Women through Weight Loss and Exercise project is exploring ways for women within faith-based communities to sustain weight reduction and maintenance efforts using different exercise regimes and different behavioral therapies. The results from the successful treatment combination could be applicable, with the appropriate cultural modification, to faith-based groups from different racial and ethnic groups. The long-term expectation for this project is a decrease in the risk and incidence of obesity and associated conditions (e.g., hypertension, diabetes, metabolic syndrome, and cardiovascular disease). (NCMHD)

Cultural Attitudes towards Weight, Diet, and Physical Activity in African-American Girls

The Carolina-Shaw Partnership for the Elimination of Health Disparities and the University of North Carolina published findings on NCMHD cofunded research on cultural attitudes toward weight, diet, and physical activity among overweight African-American girls. The study examined attitudes and perceptions toward weight, diet, and physical activity among African-American youth, and particularly among young African-American females. Weight and body size preferences were found to be primarily determined by the individual and her immediate social circle and were less influenced by opinions of those outside of the social circle. Food choices depended on texture, taste, appearance, and context more than on nutritional value. Engagement in recreational physical activity was influenced by time constraints from school and extracurricular activities and by neighborhood safety. Celebrities were not perceived as role models for diet and physical activity habits. The findings imply that perceptions of weight and healthy lifestyle behaviors are largely determined by environmental and personal influences. These factors should be considered in the development of healthy-weight interventions for African-American girls. (NCMHD)

Educational Attainment and Metabolic Syndrome in Latina Women

Researchers at San Diego State University recently published their research on metabolic syndrome in Latina women. The effects of educational attainment as a measurement of socio-economic status and psychosocial resources on metabolic syndrome variables were examined. Latina women with less educational attainment reported fewer psychosocial resources and showed a higher risk profile on measures of blood pressure, waist circumference, and plasma glucose as compared with Latina women with higher educational attainment. (NCMHD)

Obese Mothers Are Twice as Likely to Have Obese Children

In a study conducted at the NCMHD Center of Excellence established at University of Texas, M.D. Anderson Cancer Center, researchers evaluated the relationship between the weight status of mothers and their children, 5-18 years old, at baseline in a cohort study of Mexican origin, low-socioeconomic status families residing in inner-city Houston, TX. This is highly relevant given that obesity is a risk factor for several chronic conditions later in life, including cardiovascular disease, type II diabetes, and some cancers. The study found obese mothers were twice as likely to have an overweight and/or at-risk-for-overweight child compared with normal-weight mothers. Women born in the United States were twice as likely to have an overweight and/or at-risk-for-overweight child compared with women born in Mexico. In addition, women with less than a high school education were twice as likely to have an overweight child compared with their more educated peers. (NCMHD)

Obesity-Disease Risk Guidelines in Various Populations

The Body Composition, Hormones, and Health Risk Factors in Middle-Aged Hispanic, African-American and Caucasian Women study being conducted at the Hispanic Health Disparities Research Center at the University of Texas, El Paso, examines the obesity-disease risk relationship among racial/ethnic groups in the development of healthy-weight guidelines. Analyses include determination of body fat ranges related to dyslipidemia, hypertension, and elevated glucose and insulin concentrations in each group and the obesity-hormone relationship among the racial/ethnic groups. These interrelationships are critical in developing an understanding of the etiology of diseases. (NCMHD)

Gender and the Effect of Obesity on Asthma

A finding from NIAID's Inner City Asthma Consortium suggests that obesity makes asthma harder to control in adolescent females but not in males. The Inner City Asthma Consortium studies asthma risk factors and promising therapies to reduce the severity and prevent disease onset among children and adolescents living in the inner city. (NIAID)

Reference:

Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, Kercsmar CM, Visness CM, Matsui EC, Steinbach SF, Szefler SJ, Sorkness CA, Morgan WJ, Teach SJ, Gan VN. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol.* 2010;125(3):584-92.

Gender, Obesity, C-Reactive Protein, and Oxidative Stress

The long-term objective of this project is to identify nutritional factors that can reduce the inflammatory component of obesity, a major risk factor for many chronic diseases of aging. Therapies to minimize obesity-related comorbidities are needed, and targeting inflammation may help slow the progression of obesity towards cardiovascular disease and insulin resistance. C-reactive protein (CRP) is a key marker of inflammation. Previous research has demonstrated that supplementation with vitamin C reduces CRP in active and passive smokers and in nonsmokers, particularly among individuals whose CRP levels place them at elevated risk of cardiovascular disease. NIH-supported investigators are now performing a clinical trial of the effects of supplementation with vitamin C on CRP levels in obese individuals. The investigators also plan to characterize the pathways through which any effect takes place by measuring cytokines and oxidative stress. If supplementation with vitamin C is effective in this population, it could offer a low-cost alternative to use of statins to reduce inflammation in persons without other risk factors. (ODS)

OSTEOARTHRITIS

Knee Osteoarthritis and Sports Injuries in Women

Traumatic knee injury often leads to osteoarthritis (a painful condition characterized by cartilage degeneration) in the joint several years later. Injuries to the anterior cruciate ligament of the knee occur in girls and women who participate in high-risk sports, such as soccer and basketball, at a four- to sixfold greater rate than in their male counterparts. Researchers are beginning to appreciate that structural differences of the knee joint and thigh muscles, differences in the ways male and female athletes move, and other sex differences explain why women are more susceptible to injuries than men. They are also developing strategies to identify young female athletes who could benefit from interventions to prevent these injuries. (NIAMS)

References:

Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. *Am J Sports Med*. 1995 Dec;23(6):694-701.

Griffin LY, Albohm MJ, Arendt EA, Bahr R, Beynnon BD, Demaio M, Dick RW, Engebretsen L, Garrett WE Jr, Hannafin JA, Hewett TE, Huston LJ, Ireland ML, Johnson RJ, Lephart S, Mandelbaum BR, Mann BJ, Marks PH, Marshall SW, Myklebust G, Noyes FR, Powers C, Shields C Jr, Shultz SJ, Silvers H, Slauterbeck J, Taylor DC, Teitz CC, Wojtys EM, Yu B. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. *Am J Sports Med*. 2006 Sep;34(9):1512-32.

Myer GD, Ford KR, Barber Foss KD, Liu C, Nick TG, Hewett TE. The relationship of hamstrings and quadriceps strength to anterior cruciate ligament injury in female athletes. *Clin J Sport Med*. 2009 Jan;19(1):3-8.

Myer GD, Ford KR, Paterno MV, Nick TG, Hewett TE. The effects of generalized joint laxity on risk of anterior cruciate ligament injury in young female athletes. *Am J Sports Med*. 2008 Jun;36(6):1073-80.

Myklebust G, Steffen K. Prevention of ACL injuries: how, when and who? *Knee Surg Sports Traumatol Arthrosc*. 2009 Aug;17(8):857-8.

Acupuncture Relieves Knee Pain from Osteoarthritis

A landmark study has shown that acupuncture provides pain relief and improves function for people with osteoarthritis of the knee. This was the first clinical trial with sufficient rigor, size, and duration to show that acupuncture reduces the pain and functional impairment of osteoarthritis of the knee. The study results also indicated that acupuncture can serve as an effective addition to a standard regimen of care and improve quality of life for knee osteoarthritis sufferers. This study was funded by NCCAM and NIAMS. (NCCAM)

Reference:

Berman BM, Lao L, Langenberg P, Lee WL, Gilpin AM, Hochberg MC. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med*. 2004;141(12):901-10.

Glucosamine plus Chondroitin Relieves Pain for Some, but Not All, Arthritis Patients

The Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) found that, overall, the combination of glucosamine plus chondroitin sulfate did not provide significant relief from osteoarthritis pain among all study participants. However, a smaller subgroup of individuals with moderate-to-severe pain showed significant relief with the combined supplements. The trial was funded by NCCAM and NIAMS. (NCCAM)

References:

Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO 3rd, Weisman MH, Jackson CG, Lane NE, Cush JJ, Moreland LW, Schumacher HR Jr, Oddis CV, Wolfe F, Molitor JA, Yocum DE, Schnitzer TJ, Furst DE, Sawitzke AD, Shi H, Brandt KD, Moskowitz RW, Williams HJ. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *New Engl J Med*. 2006;354(8):795-808.

Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the Glucosamine/Chondroitin Arthritis Intervention Trial. *Arthritis & Rheum*. 2008;58(10):3183-91.

The Osteoarthritis Initiative

Because osteoarthritis affects over 27 million individuals in the United States, NIH has long supported research to improve methods for assessing disease onset and progression. Knee osteoarthritis is associated with significant pain and development of disability over time. People who are severely compromised have few effective treatment options other than joint replacement. It has long been noted that there are differences in the prevalence, incidence, and severity of osteoarthritis between men and women. Women have higher incidence of osteoarthritis of the knee, hip, and hand. Severity of disease is significantly worse in women and women are less willing to undergo joint replacement surgery than are men. Thus, the course of disease in women is associated with significant morbidity and disability. There are currently no disease modifying agents for the treatment of osteoarthritis. The discovery of osteoarthritis biomarkers—including structural characteristics that can be observed with MRI—could lead to identification of new treatment targets and mechanisms for shorter, more efficient trials of disease-modifying agents.

The Osteoarthritis Initiative (OAI) is a multicenter, longitudinal, prospective observational study of knee osteoarthritis (OA) that was launched by NIH in 2002. The overall aim of the OAI is to develop a public-domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. The goals of the OAI are to enroll approximately 5,000 subjects with risk factors for or early knee osteoarthritis and collect clinical and imaging data and biological specimens from these participants for eight years of follow-up. No details are provided here with regard to study startup, protocol development, or recruitment and enrollment. These details are available on the OAI website (*www.oai.ucsf.edu/datarelease/StudyOverview.asp*).

The OAI research team consists of the following centers and their principal investigators: University of Maryland School of Medicine, Baltimore, and Johns Hopkins University: Marc Hochberg, M.D., M.P.H.; The Ohio State University, Columbus: Rebecca Jackson, M.D.; University of Pittsburgh: C. Kent Kwoh, M.D.; Memorial Hospital of Rhode Island, Pawtucket: Charles Eaton, M.D.; University of California, San Francisco (data coordinating center): Michael Nevitt, Ph.D. A Steering Committee advises on the scientific aspects of the study. The FDA provides a representative to serve as a liaison to the Steering Committee in an advisory manner.

The OAI cohort of 4,796 subjects is 58 percent female and ranged in age from 45-79 at the time of recruitment. As of summer 2010, the entire OAI cohort has completed their baseline, 12-, 24-, and 36-month visits. About 99 percent of the 48-month visits have been completed. The 60-month visit is by telephone and is approximately 71 percent complete. The 72-month visits are in-clinic and well under way at all sites. Eighty-four-month telephone and mail visits and 96-month in-clinic visits are planned. A subset of participants in the progression cohort were also seen at 18 months (n=288) or 30 months (n=494) for knee MRI, blood draw,

exam, and questionnaire data to allow for analysis of change over shorter intervals. Retention remains high. The rate of no-contact has stabilized at 10 percent.

Seventy-three percent of participants have a knee x-ray and 70 percent have a knee MRI for all five time points. Sixty-seven percent of participants are estimated to have knee x-rays and MRIs at all time points. Any bias regarding those who do not have an MRI will be addressed in the analysis.

There are four separate NIH-funded (R01 and R21 mechanisms) ancillary studies to the OAI, which are well under way. One of the most recent ancillary studies addresses the effects of physical activity on disability progression. Physical activity is measured using an accelerometer to see whether participants who meet the recommended activity guidelines can slow disability progression.

The OAI is supporting some analyses of the MRI and x-ray data, which are being annotated with the source and posted to the Web site. Since the preferred method for reading the MRIs is unclear, there are no efforts to read the MRIs for the entire cohort at this time. Selected readings are posted to allow researchers to test their own hypotheses for what components and methods of reading provide the best diagnostic variable for predicting progression. It is proposed that funds from the American Revitalization and Recovery Act (ARRA) will be used to read the OAI x-rays. Other OAI investigators are requesting supplemental funding from the ARRA to support ancillary studies.

Data are released on a regular basis to OAI-online. As of June 2010, there were 1,649 registered users of OAI Online from 71 countries, with over 5,606 datasets downloaded and 232 image sets distributed. Data are currently being released in a single bolus for the entire visit. Recent releases have included the 36-month questionnaire and exam data and images for the full cohort, as well as the 30-month questionnaire and exam data and images for a subset of the progression cohort. An increasing number of abstracts and papers are being produced from the data (see *www.oai.ucsf.edu/datarelease/Publications.asp*).

This groundbreaking study is expected to advance the understanding of how modifiable and nonmodifiable risk factors are linked to development and worsening of knee osteoarthritis. These findings may in turn lead to improved strategies for prevention of disease, identification of novel treatment targets, and ways to prevent later-life disability.

Funding for the OAI has been contributed by both NIH and private-sector participants. The private-sector funding was initially provided from Pfizer, Merck, GlaxoSmithKline, and Novartis. The Foundation for the National Institutes of Health (FNIH) has coordinated private-sector participation. Funding from the NIH Institutes and Centers initially included NIAMS and NIA, NCCAM, NCMHD, NIDCR, NIBIB, and ORWH. ORWH has been and continues to be a major contributor to the OAI.

OSTEOPOROSIS

Preventing Hip Fracture Due to Osteoporosis

Once thought to be a normal consequence of aging, hip fractures due to osteoporosis can be prevented. Health care providers now know that bone mineral density of the hip is one of the best predictors of future fractures, and that certain lifestyle changes (such as improving nutrition or exercising) can reduce a person's fracture risk. Clinicians have an arsenal of bone-preserving drugs that they can prescribe; because of NIH-funded research, they understand how to combine the different medications to preserve bone health. These advances—along with other NIH-sponsored activities to improve osteoporosis prevention, diagnosis, and treatment—are having a positive effect on bone health. Specifically, the overall age-adjusted hospitalization rate for hip fractures among older women is decreasing (down 24.5 percent from 1995 until 2005), and the percent whose bone mineral density tests show that they are at risk of osteoporotic fractures also has decreased. (NIAMS)

References:

Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Eng J Med*. 1995 Mar 23;332(12):767-73.

Black DM, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Eng J Med*. 2003 Sep 25;349(13):1207-15.

Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *JAMA*. 2009 Oct 14;302(14):1573-9.

Looker AC, Melton LJ 3rd, Harris TB, Borrud LG, Shepherd JA. Prevalence and trends in low femur bone density among older US adults: NHANES 2005-2006 compared with NHANES III. *J Bone Miner Res*. 2010 Jan;25(1):64-71.

A Reference Model to Understand Osteoporosis

Osteoporosis is a skeletal disorder in which bones weaken due to the loss of bone mineral density, and the risk of fracture is increased. The disease affects both men and women of all ages, although women over 50 have more than twice the prevalence of low bone density than men. The chance of fracture increases with age. While any fracture is a serious occurrence, hip fractures are of greatest public health concern because the consequences are often devastating. For example, those who experience hip fractures have an increased risk of death during the first 12 months after the fracture. Among those who survive, many experience loss of mobility and may have to enter long-term care facilities. Finally, hip fractures cost more to repair than any other type of osteoporotic fracture. Current projections indicate that the prevalence of this disease will grow dramatically over the next decade from the current 10 million individuals affected, considering the aging American population. Osteoporosis is a complex, multifactorial disorder with multiple causes, including hormonal, genetic, and lifestyle-related factors. Prediction of who is at risk and who will respond to an intervention is, therefore, difficult and requires an understanding of the interplay of a

multitude of parameters. Investigators at UCLA are developing a Bayesian Belief Network (BBN) model of bone density and quality at the peak of skeletal development in order to provide a tool for better understanding the genesis of osteoporosis. The model is based on quantitative data from a reference population consisting of healthy volunteers aged 20-30 years old. The patient population to be studied suffers from chronic renal diseases that result in osteoporotic conditions. The BBN along with visualization tools, also under development, will make it easier for researchers to examine cause and effect of numerous variables on bone development. (NIBIB)

References:

Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol Metab*. 2010 Feb;95(2):471-8.

http://www.cdc.gov/nchs/data/nhanes/databriefs/osteoporosis.pdf

Efficacy of Turmeric Extract in Prevention of Postmenopausal Osteoporosis

The identification of a dietary supplement that effectively inhibits bone resorption could offer a particularly attractive approach to the prevention of postmenopausal osteoporosis, a disease with extremely high prevalence that is essentially irreversible yet readily preventable by early interventions that inhibit bone resorption. Recent studies in an animal model of arthritis have demonstrated that curcuminoid-containing turmeric extracts (C-CTEs) are potent inhibitors of inflammation-associated bone resorption. Because the same inflammatory pathways mediate bone loss in arthritis and in menopause, researchers have hypothesized that C-CTEs may be similarly efficacious in the prevention of postmenopausal osteoporosis. NIH-supported investigators are now exploring this hypothesis using models of surgical and natural menopause in rats. Evidence obtained in this study supporting (or refuting) the efficacy of turmeric dietary supplements in osteoporosis prevention and/or treatment will: (1) begin to help guide the public's use of turmeric supplements for the preservation of bone health, (2) aid in the design of preclinical trials comparing the efficacy and identifying turmeric's mechanism of action on bone, and (3) provide necessary information for the design of future clinical trials. (ODS)

Bone Response to Soy Isoflavones in Women

Soy protein rich in isoflavones (estrogen-like compounds) has been shown to prevent bone loss in ovariectomized rats, and preliminary study results suggest a bone-sparing effect of isoflavones in perimenopausal women. However, the long-term efficacy of isoflavones on bone in humans is unknown. NIH-supported investigators are currently conducting a three-year study to establish the efficacy of isoflavone-rich soy extract in attenuating bone loss in postmenopausal women. This study will provide valuable data on whether isoflavones impact bone in early postmenopausal women and help elucidate potential mechanisms, thereby contributing to the understanding of isoflavones as an alternative to traditional menopausal hormone therapy. (ODS)

Folic Acid and B Vitamins to Prevent Fracture in Women

Prospective studies have found that women with elevated plasma homocysteine have a substantially increased risk of osteoporotic fractures, including hip fractures. Investigators are currently studying, within the context of an ongoing randomized trial (the Women's Antioxidant Cardiovascular Study), whether reducing plasma homocysteine levels by dietary supplementation with folic acid, vitamin B6, and vitamin B12 will reduce the risk of non-spine fractures in women. This study will be instrumental in determining whether a safe and inexpensive nutritional intervention substantially reduces the risk of fracture and in understanding the mechanism of this effect. (ODS)

Impact of a Protein Supplement on Bone Mass in Older Women

Nutrition plays a critical role in bone health, but its role in the pathogenesis and prevention of bone loss is incompletely understood. Investigators have found that dietary protein is a major regulator of calcium homeostasis, yet its impact on skeletal health remains controversial. Increasing dietary protein is known to increase urinary calcium excretion, and a widely held view is that this extra calcium originates in part from bone, but recent epidemiologic studies have found that higher protein intakes are associated with higher (not lower) bone mineral density and lower (not higher) rates of bone loss. NIH-supported investigators have found that when dietary protein is increased in healthy women, intestinal calcium absorption increases significantly and accounts for almost all of the increase in urinary calcium, and that when women consume a high-protein diet, the percentage of urinary calcium originating from bone is reduced and bone turnover is also slightly reduced. The investigators are currently performing a clinical trial of protein supplementation in older women who typically consume a low-normal protein diet in order to assess the effects of protein supplementation on bone mass. This study will better inform dietary protein recommendations for optimal skeletal health and potentially suggest a new therapeutic approach to age-related bone loss. (ODS)

PAIN

Gender-Based Differences in Pain Response

Researchers tested the effects of nalbuphine, a member of a little-used class of medications called kappa-opioids, on women and men after surgery for wisdom tooth extraction. They found that women gained relief of their postoperative pain from a moderate dose of nalbuphine, while both higher and lower doses had little effect when compared with a placebo. In men, only a high dose offered slight, short-term pain relief, while a low dose actually intensified the pain. Kappa-opioids have fewer negative side effects, such as nausea, confusion, and constipation, than the more commonly used mu-opioids like morphine. The difference in pain perceptions and responses between women and men uncovered in this study was an unexpected result and revealed the importance of considering gender in developing pain management strategies. (NINR)

Reference:

Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain*. 1999;83(2):339-45.

Irritable Bowel Syndrome

New Insights into the Pain Associated With Irritable Bowel Syndrome

Researchers at a specialized center of research cofunded by ORWH and NIDDK found that women with irritable bowel syndrome (IBS) perceive visceral pain associated with IBS differently than do healthy volunteers, and exhibit altered brain activity responses to both pain and the anticipation of pain. They also found that a history of physical abuse heightens visceral pain responses in women with IBS. Moreover, researchers have identified sex/gender-specific differences in brain activity in women and men with IBS. These findings may lead to improved treatment strategies and outcomes for IBS-related pain. (NIDDK)

References:

Berman SM, Naliboff BD, Suyenobu B, Labus JS, Stains J, Ohning G, Kilpatrick L, Bueller JA, Ruby K, Jarcho J, Mayer EA. Reduced brainstem inhibition during anticipated pelvic visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. *J Neurosci*. 2008 Jan 9;28(2):349-59.

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Labus JS, Naliboff BN, Fallon J, Berman SM, Suyenobu B, Bueller JA, Mandelkern M, Mayer EA. Sex differences in brain activity during aversive visceral stimulation and its expectation in patients with chronic abdominal pain: a network analysis. *Neuroimage*. 2008 Jul 1;41(3):1032-43.

Temporomandibular Joint Disorders

Temporomandibular Joint and Muscle Disorders

Pain conditions, particularly temporomandibular joint (TMJ) and muscle disorders (TMJMDs), have been an active area of NIDCR-supported research for many years. Data from the 2002 U.S. National Health Interview Survey confirm that TMJMD-type pain is 2.25 times more prevalent in women than in men. Other studies indicate that gender-based differences in pain conditions may be due to hormonal influences and genetic susceptibilities. In addition to clinical studies, multiple investigators supported by NIDCR have studied basic mechanisms related to orofacial pain. Another significant program examining new TMJMD is *Orofacial Pain: Prospective Evaluation and Risk Assessment* (OPPERA), a prospective study of 3,200 healthy subjects designed to identify risk factors contributing to TMJMD onset. (NIDCR)

References:

Isong U, Gansky SA, Plesh O. Temporomandibular joint and muscle disorder-type pain in U.S. adults: the National Health Interview Survey. *J Orofac Pain*. 2008 Fall;22(4):317-22.

Kramer PR, Bellinger LL. The effects of cycling levels of 17beta-estradiol and progesterone on the magnitude of temporomandibular joint-induced nociception. *Endocrinology*. 2009 Aug;150(8):3680-9.

Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, Higgins TJ, Sama S, Belfer I, Goldman D, Max MB, Weir BS, Maixner W. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2006 Jul 5;141B(5):449-62.

https://www.oppera.org/

NIH Technology Assessment Conference: Management of Temporomandibular Disorders, April 29-May 1, 1996

OMAR and the National Institute of Dental Research (now known as NIDCR) convened an independent panel in 1996 to assess the available scientific evidence on the management of temporomandibular disorders (TMD). The panel found significant problems with diagnostic classifications of TMD and recommended that validated diagnostic methods be developed. The panel further concluded that the preponderance of the data did not support the superiority of any method for initial management of most TMD problems. Moreover, the superiority of such methods to placebo controls or no treatment controls was undetermined. Because most individuals experience improvement or relief of symptoms with conservative treatment, the panel concluded that the vast majority of TMD patients should receive initial management using noninvasive and reversible therapies. They believed surgical intervention should be considered in the small percentage of patients with persistent and significant pain and dysfunction who show evidence of pathology, or internal derangement of the temporomandibular joint, and for whom more conservative treatment has failed. An identified area of future research is the underlying etiology behind the gender difference inherent in this disorder (with an observed predominance in women in their 30s and 40s). (OMAR)

URINARY INCONTINENCE

Weight Loss in Overweight and Obese Women Reduces Urinary Incontinence

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) clinical trial demonstrated that weight loss significantly reduces episodes of urine leakage in overweight and obese women who experience incontinence. Evidence of this additional health benefit of weight loss expands the options physicians and their patients can consider for treating incontinence in women. (NIDDK)

Reference:

Subak LL, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med.* 2009 Jan 29; 360(5):481-90.

Sling Surgery Is More Effective Than Burch for Bladder Control in Women

The Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr), conducted by NIDDK's Urinary Incontinence Treatment Network, found that a sling procedure for stress urinary incontinence (SUI) helps more women achieve dryness than the Burch technique. This rigorous trial also provided insights into surgical therapy outcomes, such as differences in side effects from the two procedures, that will help women with SUI and their health care providers make better-informed treatment decisions. (NIDDK)

Reference:

Albo ME, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med*. 2007 May 24; 356(21):2143-55.

NEUROSCIENCE AND THE FEMALE BRAIN

Sexual Differentiation of the Brain and Behavior

Sex Chromosomes Affect Sexual Differentiation of the Brain and Behavior

Research on mammalian sexual differentiation exploded in the second half of the 20th century. This work built on an "organizational-activational" hypothesis which posited that gonadal hormone actions during critical periods of development were responsible for sex differences in brain structure and in behavioral responses to gonadal hormones during adulthood (often reproductive behavioral responses). More recently, however, the ability to manipulate the genome independently of gonadal hormones has changed the understanding of sexual differentiation. Specifically, studies using transgenic mice have demonstrated that many sexually dimorphic phenotypes—ranging from the molecular to the behavioral—are caused primarily by differences in the sex (i.e., X and Y) chromosomes, independent of or in addition to, the actions of hormones (reviewed by Arnold in 2009). Examples of these primary sex chromosome effects include sexual dimorphisms in the response to nociceptive stimuli, habit formation, and autoimmune responses and disease progression in mouse models of multiple sclerosis and systemic lupus erythematosus. This more comprehensive view of sexual differentiation has important implications for general understanding of sex differences in health and disease. Funding for this research was provided by NICHD, NIDA, NIDDK, and NINDS. (OBSSR and NIMH)

References:

Arnold AP. The organizational–activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. *Horm Behav*. 2009;55(5):570-8.

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Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology*. 1959 Sep;65:369-82.

Quinn JJ, Hitchcott PK, Umeda EA, Arnold AP, Taylor JR. Sex chromosome complement regulates habit formation. *Nat Neurosci*. 2007 Nov;10(11):1398-400.

Females Fight Differently

Most studies of aggression, in humans or animal models, focus on males. However, a Harvard Medical School team discovered that Drosophila (fruit fly) females fight, and that the circumstances that trigger aggression, the flies' fighting behaviors, and the effects of being a winner or loser of previous fights are all sex-specific. Subsequently, the team demonstrated that they can induce male flies to fight like females, and vice versa, by manipulating expression of sex determination genes in the brain. Recently, the team made a counterintuitive discovery: genetically feminizing a subset of the neurons in the brain, during development, makes male flies significantly more aggressive. Given the similarity in human and fly brains in terms of how they develop and function, it would be surprising if female aggression in the two species shared no common substrates. Accordingly, the team's studies may illuminate efforts to determine the biological basis for aggression in women and identify environmental, developmental, and social factors that affect women's aggression. (NIGMS)

References:

Nilsen SP, Chan YB, Huber R, Kravitz EA. Gender-selective patterns of aggressive behavior in *Drosophila melanogaster*. *Proc Natl Acad Sci USA*. 2004 Aug 17;101(33):12342-7.

Chan YB, Kravitz EA. Specific subgroups of FruM neurons control sexually dimorphic patterns of aggression in *Drosophila melanogaster*. *Proc Natl Acad Sci USA.* 2007 Dec 4;104(49):19577-82.

Mundiyanapurath S, Chan YB, Leung AK, Kravitz EA. Feminizing cholinergic neurons in a male Drosophila nervous system enhances aggression. *Fly* (Austin). 2009 Jul-Sep;3(3):179-84.

Stroke

Estrogen Replacement Does Not Protect Against Recurrent Stroke

Results of a clinical trial evaluating the impact of menopausal hormone therapy on recurring stroke in postmenopausal women were announced in October 2001. The Women's Estrogen for Stroke Trial (WEST), supported by NINDS, was the first randomized, controlled clinical trial of estrogen therapy for secondary prevention of cerebrovascular disease. Investigators found that estrogen menopausal hormone therapy did not reduce the risk of stroke or death in postmenopausal women who had already had a stroke or transient ischemic attack and, therefore, suggested that this therapy should not be prescribed. (NINDS)

Reference:

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001 Oct 25;345(17):1243-9.

Preeclampsia Increases Risk of Stroke over Lifetime

Stroke in pregnancy is associated with several factors including preeclampsia, a serious complication of pregnancy marked by high blood pressure, weight gain, and protein in the urine. An analysis of the data from the Stroke Prevention in Young Women Study (a large NINDS-funded clinical study of the genetic and environmental risk factors for ischemic stroke) showed

that, over their lifetime, women with a history of preeclampsia are 60 percent more likely to have a nonpregnancy-related stroke. A history of preeclampsia should therefore be considered a risk factor for stroke. (NINDS)

Reference:

Brown DW, Dueker N, Jamieson DJ, Cole JW, Wozniak MA, Stern BJ, Giles WH, Kittner SJ. Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. *Stroke*. 2006 Apr;37(4):1055-9.

Women with Visual Aura during Migraine Are at Higher Risk for Ischemic Stroke

Researchers from the Stroke Prevention in Young Women Study (SPYWS), a large clinical study of the genetic and environmental risk factors for ischemic stroke funded by NINDS, examined clinical features of migraine that place women at a greater risk for stroke. This study showed that women who frequently had a visual aura during migraine had 1.5 greater odds of having an ischemic stroke than women without migraine or women with migraines and without auras. Furthermore, the combined use of oral contraceptives and smoking placed women with visual auras during migraine at the highest risk for stroke, increasing the odds of suffering ischemic stroke by sevenfold compared with women with visual aura that did not smoke or use oral contraceptives. This study was also supported in part by the VA, CDC, ORWH, NIA, and NCRR. (NINDS)

Reference:

MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke*. 2007 Sep;38(9):2438-45.

Strong Relationship between Smoking and Stroke in Young Women

While cigarette smoking is a known risk factor for ischemic stroke (the type caused by blood clots), the relationship between cigarette dose and stroke risk had not been examined in a young (15- to 50-year-old), ethnically diverse population of women. Researchers from the Stroke Prevention in Young Women Study (SPYWS), a large clinical study of the genetic and environmental risk factors for ischemic stroke funded by NINDS, found a strong relationship between the number of cigarettes smoked per day and the probability of ischemic stroke in young women. The study also found that black women were more likely than white women to smoke, therefore placing them at greater risk. The findings support the need to target smoking as a preventable and modifiable risk factor for cerebrovascular disease in young women. This study was also supported in part by the VA, CDC, ORWH, NIA, and NCRR. (NINDS)

Reference:

Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008 Sep;39(9):2439-43.

Substance Abuse

Sex and Gender Differences in Drug Addiction

Research supported by NIDA has shown that antecedents, consequences, and mechanisms of drug addiction differ in males and females, which in turn often affects treatment and prevention outcomes differently for males and females. Further, mounting evidence shows that animal models of addiction based solely on males are incomplete and ignore both the effects of gonadal hormones and sexual dimorphism in the brain. (NIDA)

References:

Wetherington CL. Sex-gender differences in drug abuse: a shift in the burden of proof? *Exp Clin Psychopharmacol*. 2007 Oct;15(5):411-7.

Wetherington CL. Sex differences and gonadal hormone influences in drug addiction and sexual behavior: progress and possibilities. *Horm Behav*. 2010;58(1):2-7

Gender Differences in Response to Nicotine Replacement

Men and women respond differently to nicotine replacement therapy, highlighting the importance of including gender analyses in medication trials for substance abuse. A meta-analysis of 14 placebo-controlled trials of nicotine patch therapy for smoking cessation revealed poorer long-term (6 months) outcomes in women than in men. The odds ratio for quitting with the patch versus placebo was 2.20 for men and 1.61 for women. Reasons underlying this differential response may include that (a) women metabolize nicotine more quickly than men, potentially decreasing the effectiveness of nicotine replacement therapy and (b) smoking-related cues play a larger role in motivating women to smoke than they do men, a gender-sensitive relapse factor that may need to be addressed to optimize treatment effectiveness. (NIDA)

References:

Perkins KA, Scott J. Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine Tob Res*. 2008;10(7):1245-50.

Lerman C, Tyndale R, Patterson F, Wileyto EP, Shields PG, Pinto A, Benowitz N. Nicotine *metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. Clin* Pharmacol Ther. 2006;79(6):600-8.

Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther.* 2006;79(5):480-8.

Perkins KA, Gerlach D, Vender J, Grobe J, Meeker J, Hutchison S. Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine Tob Res*. 2001;3(2):141-50.

Gender Differences in the Abuse of Prescription Drugs

Gender is a key factor in understanding the problem of prescription drug abuse and addiction. While the prevalence of prescription drug abuse overall in the United States is higher among males than among females, young girls (12- to 17-year-olds) exceed boys in the nonmedical use of *all* psychotherapeutics, including pain relievers, tranquilizers, and stimulants, and females in general show a faster progression to dependency. Growing evidence suggests that, compared with males, females' motivations to abuse prescription drugs tend more toward self-"improvement" (e.g., weight loss, performance enhancement), self-medication, and coping than to get high. These differences demand research and interventions that take gender into account. (NIDA)

References:

Teter CJ, McCabe SE, LaGrange K, Cranford JA, Boyd CJ. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. *Pharmacotherapy*. 2006;26(10):1501-10.

McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. *Addict Behav*. 2007;32(3):562-75.

Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. *Psychiatr Clin North Am*. 2010 Jun;33(2):339-55.

Lynch WJ. Acquisition and maintenance of cocaine self-administration in adolescent rats: effects of sex and gonadal hormones. *Psychopharmacology*. 2008;197(2):237-46.

Sex Differences in Vulnerability to Rewarding Effects of Drugs of Abuse

Preclinical studies show that females are more vulnerable than males to the rewarding effects of abused drugs at all stages of drug abuse: initiation, maintenance, escalation, bingeing, extinction of drug-seeking behavior (when drug access is removed), and relapse. These sex differences remain even in the absence of circulating gonadal hormones. Studies also reveal sex differences in neurotransmitter systems underlying drug reward. Researchers are beginning to investigate how gonadal hormones affect these behavioral outcomes and neurotransmitter systems compared with independent sex chromosomal effects on brain organization, neurochemistry, and function. (NIDA)

References:

Evans SM, Foltin RW. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? *Horm Behav*. 2010;58(1):13-21.

Kuhn C, Johnson M, Thomae A, Luo B, Simon SA, Zhou G, Walker QD. The emergence of gonadal hormone influences on dopaminergic function during puberty. *Horm Behav*. 2010;58(1):122-37.

Quinn JJ, Hitchcott PK, Umeda EA, Arnold AP, Taylor JR. Sex chromosome complement regulates habit formation. *Nat Neurosci*. 2007 Nov;10(11):1398-400.

Effect of the Menstrual Cycle on Drug Abuse Treatment

Findings from human and animal studies show that the menstrual cycle (estrus cycle in animals) influences the reinforcing and positive subjective effects of abused drugs, and that estradiol facilitates these effects while progesterone opposes them. This line of research is providing evidence that synchronizing drug addiction treatment (e.g., nicotine cessation) with the menstrual cycle may improve treatment outcomes, and that progesterone or progesterone-like compounds could prove useful in treating drug addiction. (NIDA)

References:

Evans SM, Foltin RW. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? *Horm Behav*. 2010;58(1):13-21.

Carroll ME, Anker JJ. Sex differences and ovarian hormones in animal models of drug dependence. *Horm Behav*. 2010;58(1):44-56.

Mello NK. Hormones, nicotine, and cocaine: clinical studies. *Horm Behav*. 2010;58:57-71.

Alcohol Use and Abuse

Brain Development and Maternal Alcohol Use

Normal development of the brain requires ordered migration of immature neurons, a process that is disrupted by neonatal exposure to alcohol. In an animal model of fetal alcohol syndrome, scientists found that alcohol alters neuronal migration through its effects on the levels of specific signaling molecules in the cell (calcium ions and cyclic nucleotides). Reversing the effects of alcohol on these signaling processes also reversed its effects on neuronal migration, suggesting potential avenues for preventing alcohol's harmful effects in early development. (NIAAA)

Reference:

Kumada T, Lakshmana MK, Komuro H. Reversal of neuronal migration in a mouse model of fetal alcohol syndrome by controlling second-messenger signalings. *J Neurosci*. 2006 Jan 18;26(3):742-56.

Fetal Alcohol Exposure and Future Alcohol Use

Studies conducted in humans have shown that fetal alcohol exposure may increase susceptibility to adolescent alcohol abuse. A study investigated the mechanisms by which fetal alcohol exposure might influence the desire for alcohol later in life. Researchers gave alcohol to pregnant rats, and then tested their pups for taste and olfactory responses to alcohol and quinine. Rat pups that were exposed to alcohol before birth had a greater preference for the taste of both alcohol and quinine hydrochloride (bitter) than did animals that had not been exposed to alcohol before birth. A significant proportion of the increased alcohol taste preference could be attributed directly to the weakened aversion to alcohol's quinine-like taste quality. Fetal alcohol exposure also increased the pups' alcohol intake and the behavioral response to alcohol odor. Thus, fetal alcohol exposure can affect the developing sensory (smell and taste) systems of the brain in a way that enhances alcohol preference later in life. (NIAAA)

Reference:

Youngentob SL, Glendinning JI. Fetal ethanol exposure increases ethanol intake by making it smell and taste better. *Proc Natl Acad Sci USA*. 2009 Mar 31;106(13):5359-64.

Excessive Alcohol Consumption during Puberty May Affect Development of the HPA

Maternal alcohol consumption during critical periods of fetal brain development leads to devastating long-term consequences on adult reproductive physiology, cognitive function, and social behaviors. However, very little is known about the long-term consequences of alcohol consumption during puberty, which is perhaps an equally dynamic and critical period of brain development. An important neurological system that undergoes extensive plasticity during pubertal development is the hypothalamo-pituitary-adrenal (HPA) axis. A study contrasted the HPA axis effects of binge alcohol exposure in rats during the peripubertal period to that of acute exposure. The effects of alcohol on the HPA axis are sex-specific and are dependent on repeated high-dose exposures. This contribution provides the first characterization of the impact of binge alcohol exposure during adolescence on the HPA axis. Binge exposure produces a lasting effect on HPA reactivity and an effect different from that induced by acute alcohol exposure. (NIAAA)

Reference:

Przybycien-Szymanska MM, Rao YS, Pak, TR. Binge-pattern alcohol exposure during puberty induces sexually dimorphic changes in genes regulating the HPA axis. *Am J Physiol Endocrinol Metab*. 2010 Feb;298(2):320-8.

Treatment with Phosphodiesterase Inhibitors May Counteract the Effects of FASD

Fetal alcohol spectrum disorders (FASD) are the leading cause of mental retardation in the Western world and children with FASD present altered somatosensory, auditory, and visual processing. There is growing evidence that some of these sensory processing problems may be related to altered cortical maps caused by impaired developmental neuronal plasticity. Using the ferret visual cortex as a model, investigators previously established that fetal alcohol impairs neuronal plasticity, which could account for altered sensory processing associated with FASD. This impaired plasticity in the visual cortex is accompanied by sustained reductions in the levels of active, phosphorylated CREB (pCREB), an established mediator of plasticity. Furthermore, subsequent treatment with a phosphodiesterase (PDE) inhibitor, vinpocetine, corrected pCREB levels and, more importantly, dramatically restored neuronal plasticity. These findings suggest that PDE inhibition might be an effective therapeutic strategy for correcting sensory and possibly other neuronal functional deficits in individuals affected by FASD. (NIAAA)

Reference:

Krahe TE, Wang W, Medina AE. Phosphodiesterase inhibition increases CREB phosphorylation and restores orientation selectivity in a model of fetal alcohol spectrum disorders. *PLoS One*. 2009 Aug 14;4(8):e6643.

Gender Differences in Age of Onset of Drinking Accounts for Gender Differences in Lifetime Prevalence of Alcohol Dependence

Researchers evaluated secular trends in ages at onset of drinking to determine whether they can account for secular changes in alcohol dependence, using data from the combined National Longitudinal Alcohol Epidemiologic Survey (NLAES) and National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), two nationally representative surveys that were conducted 10 years apart. Both men and women born between 1944 and 1963 had earlier ages of onset of drinking (AOD) than did the earliest birth cohort analyzed (1934-1943). However, the net decrease in AOD was twice as large for women (3.2 years) than for men (1.6 years). After adjusting for AOD, differences in lifetime prevalence between different birth cohorts of women were rendered nonsignificant, indicating that AOD accounts for a substantial portion of change in the lifetime prevalence of alcohol dependence. These results suggest that a decrease in AOD accounts for much of the increase in lifetime alcohol dependence among women. AOD is likely to be an indicator of dynamic, and therefore modifiable, risk behaviors impacting risk for alcohol dependence. (NIAAA)

Reference:

Grucza RA, Norberg K, Bucholz KK, Bierut LJ. Correspondence between secular changes in alcohol dependence and age of drinking onset among women in the United States. *Alcohol Clin Exp Res*. 2008 Aug;32(8):1493-501.

Employment and Abstinence Outcomes for Women May Depend on Treatment Type

Among substance-dependent women receiving Temporary Assistance for Needy Families (TANF), investigators compared abstinence rates and employment outcomes for those who entered intensive case management (ICM) and those assigned to a screen-and-refer program (i.e., usual care). Abstinence rates were higher for the ICM group than for the usual care group through 24 months of follow-up. Additionally, women in the ICM group were more likely to be employed full time than women in the usual care group. Thus, ICM appears to be a promising intervention for managing substance dependence among women receiving TANF and for improving employment rates among this vulnerable population. (NIAAA)

Reference:

Morgenstern J, Neighbors CJ Kuerbis A, Riordan A, Blanchard KA, McVeigh KH, Morgan TJ, McCrady B. Improving 24-month abstinence and employment outcomes for substance-dependent women receiving temporary assistance for needy families with intensive case management. *Am J Public Health*. 2009 Feb;99(2):328-33.

The Correlation between Sexual Abuse, Alcohol Use, and Risky Behavior in Women

Correlational studies have established that sexually abused (SA) women, particularly women abused in childhood (CSA), are at higher risk of contracting HIV/sexually transmitted infections (STIs) than are non-SA women. An experimental evaluation of potential differences in women's likelihood of sexual risk undertaken in a laboratory setting based on alcohol intoxication and sexual abuse history demonstrated that intoxicated CSA women reported significantly more likelihood of unprotected oral sex and less likelihood of condom use relative to intoxicated non-sexually abused women and those sexually abused in adulthood and sober CSA women. CSA women's increased risk of STIs may be driven by lack of condom use and behavioral changes while intoxicated. These findings provide preliminary insight into situational influences affecting CSA women's increased STI risk. (NIAAA)

Reference:

Schacht RL, George WH, Davis KC, Heiman JR, Norris J, Stoner SA, Kajumulo KF. Sexual abuse history, alcohol intoxication, and women's sexual risk behavior. *Arch Sex Behav*. 2010 Aug;39(4):898-906.

Modeling Can Help Shape and Test Interventions to Curb Drinking on College Campuses

The misuse and abuse of alcohol among college students remain persistent problems. Using a systems approach to understand the dynamics of student drinking behavior and thus forecast the impact of campus policy to address the problem represents a novel approach. Toward this end, researchers developed a deterministic, compartmental model of college drinking incorporating three processes: (1) individual factors, (2) social interactions, and (3) social norms. The model quantified these processes in terms of the movement of students between drinking compartments characterized by five styles of college drinking: abstainers, light drinkers, moderate drinkers, problem drinkers, and heavy episodic drinkers. Predictions from the model were first compared with actual campus-level data and then used to predict the effects of several simulated interventions to address heavy episodic drinking. The model was found to adequately predict the actual drinking patterns of students from a variety of campuses surveyed in the Social Norms Marketing Research Project study. The model predicted the impact on drinking patterns of several simulated interventions to address heavy episodic drinking on various types of campuses. These findings provide a novel method for testing the likely effectiveness of preventive policy interventions prior to campuses having to expend resources on a trial-and-error basis. Thus, employment of such methods has great potential to contribute to future research on prevention effectiveness. (NIAAA)

Reference:

Scribner R, Ackleh AS, Fitzpatrick BG, Jacquez G, Thibodeaux JJ, Rommel R, Simonsen N. A systems approach to college drinking: development of a deterministic model for testing alcohol control policies. *J Stud Alcohol Drugs*. 2009;70(5):805-21.

Adolescent Alcohol-Related Sexual Aggression May Predict Adult Alcoholism and Aggression

A Web-based survey administered to 1,220 7th- to 12th-grade students from a middle school and high school in southeastern Michigan demonstrated that youth reporting alcohol-related sexual assault aggression represent a high-risk group for both sexual perpetration and alcoholism during adulthood. The fact that distinctions can be identified in youth suggests that targeted interventions during middle school and high school may be feasible. (NIAAA)

Reference:

Young AM, King L, Abbey A, Boyd CJ. Adolescent peer-on-peer sexual aggression: characteristics of aggressors of alcohol and non-alcohol-related assault. *J Stud Alcohol Drugs*. 2009 Sep;70(5):700-3.

Correlation between Heavy Alcohol Use and Educational Attainment Varies by Gender

Although teenage alcohol use is well correlated with school failure and reduced educational attainment, it is unclear whether this relationship is causal or spurious. Using data from the National Child Development Study, an ongoing longitudinal birth cohort study of British youth born in 1958 (N = 9,107), the authors of this study investigated the long-term impact of heavy alcohol use at age 16 years on educational qualifications in adulthood. Drawing on a lifespan developmental contextual approach, they found that heavy teenage alcohol use and disadvantaged social origins combined to diminish male educational attainment. In contrast, heavy alcohol use had little effect on female educational attainment. Future long-term longitudinal research is needed to replicate these findings for more recent birth cohorts and for populations outside of Britain. (NIAAA)

Reference:

Staff J, Patrick ME, Loken E, Maggs JL. Teenage alcohol use and educational attainment. *J Stud Alcohol Drugs*. 2008 Nov;69(6):848-58.

MENTAL HEALTH

Sex Differences in Mental Health

Women Are More Likely Than Men to Develop Some Mental Health Disorders

Epidemiological research demonstrates that women are more likely than men to develop certain mental health disorders, such as depression, eating disorders, panic disorder, and post-traumatic stress disorder (PTSD). Men are more likely to develop attention deficit/hyperactivity disorder, impulse-control disorders, and alcohol dependence and drug dependence. Investigators, through the ORWH Building Interdisciplinary Careers in Women's Health (BIRCWH) program, are also studying fetal antecedents to depression and schizophrenia in men and women. These findings offer insight into differences in brain development between men and women and possible crucial periods of development in men and women, which may lead to more accurately targeted prevention and treatment efforts. (NIMH)

References:

Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, Caviness VS Jr, Faraone SV, Tsuang MT. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch Gen Psychiatry*. 2002 Feb;59(2):154-64.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005 Jun;62(6):593-602.

Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: lifetime prevalence, chronicity and recurrence. *J Affect Disord*. 1993 Oct-Nov;29(2-3):85-96.

Walder DJ, Seidman LJ, Cullen N, Su J, Tsuang MT, Goldstein JM. Sex differences in language dysfunction in schizophrenia. *Am J Psychiatry*. 2006 Mar;163(3):470-7.

Epigenetic and Preclinical Research on Mental Health in Women

Ongoing studies are examining how environmental factors like diet, stress, and others can alter gene function. These studies are helping to identify factors that may also influence men's and women's different risks for developing depression and other disorders, and are revealing potential new molecular targets for treating mental health disorders in women. (NIMH)

References:

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004;7(8):847-54.

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*. 2009;12(3):342-8.

Post-Traumatic Stress Disorder

Women and Post-Traumatic Stress Disorder

Post-traumatic stress disorder is an anxiety disorder that can develop after exposure to a terrifying event or ordeal in which grave physical harm occurred or was threatened. Traumatic events that may trigger PTSD include violent personal assaults, natural or human-caused disasters, accidents, or military combat. Women experience PTSD at twice the rate of men.

In 2008, NIMH facilitated the launch of a major study of the genetics of PTSD in women. This project is embedded within the Nurses' Health Study II (NHS), a large prospective epidemiologic cohort of women. Identification of genes responsible for PTSD would represent a major advance in understanding the pathophysiology of the disorder. Such understanding could lead to the development of new PTSD treatments and preventive interventions as well. It would also help identify those at high risk for developing PTSD, making it possible to provide early intervention to those most in need. (NIMH)

References:

Cornelis MC, Nugent NR, Amstadter AB, Koenen KC. Genetics of post-traumatic stress disorder: review and recommendations for genome-wide association studies. *Curr Psychiatry Rep*. 2010 Aug;12(4):313-26.

Koenen KC, De Vivo I, Rich-Edwards J, Smoller JW, Wright RJ, Purcell SM. Protocol for investigating genetic determinants of posttraumatic stress disorder in women from the Nurses' Health Study II. *BMC Psychiatry*. 2009 May; 9:29.

Koenen KC, Nugent N, et al. Gene-environment interaction in posttraumatic stress disorder: review, strategy and new directions for future research. *J Trauma Stress*. 2008 Feb;21(1):49-57.

Koenen KC, Widom CS. A prospective study of sex differences in the lifetime risk of posttraumatic stress disorder among abused and neglected children grown up. *J Trauma Stress*. 2009 Dec;22(6):566-74.

Kubzansky LD, Koenen KC, Jones C, Eaton WW. A prospective study of posttraumatic stress disorder symptoms and coronary heart disease in women. *Health Psychol*. 2009 Jan; 28(1):125-30.

Maikovich AK, Koenen KC, Jafee SR. Posttraumatic stress symptoms and trajectories in child sexual abuse victims: an analysis of sex differences using the National Survey of Child and Adolescent Well-being. *J Abnorm Child Psychol*. 2009 Jul;37(5):727-37.

Depression

Advances in Diagnosis and Treatment of Postpartum Depression

Research demonstrates that postpartum depression is a serious and debilitating disorder that affects up to 15 percent of new mothers. Women with depression who stop antidepressant treatment during pregnancy are at higher risk for relapse, and their risk of postpartum depression is significantly elevated as well. Several forms of treatment, including cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and medication treatment are effective in treating this disorder. Research continues into prevention efforts and improved service delivery of treatments based on individual needs. (NIMH)

References:

Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry*. 1993 Jul;163:27-31.

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1;295(5):499-507. Erratum in: *JAMA*. 2006 Jul 12;296(2):170.

Dimidjian S, Goodman S. Nonpharmacologic intervention and prevention strategies for depression during pregnancy and the postpartum. *Clin Obstet Gynecol*. 2009 Sep;52(3):498-515.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, Brody S, Miller WC. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evidence

Report/Technology Assessment no. 119. Prepared by the RTI-University of North Carolina Evidence-based Practice Center, under contract no. 290-02-0016. AHRQ Publication No. 05-E006-2. Rockville, MD: Agency for Healthcare Research and Quality; 2005 Feb.

O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry* 2000;57(11):1039-45.

Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, Perel JM, Jones-Ivy S, Bodnar LM, Singer LT. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry*. 2009 May;166(5):557-66.

Sex Differences in Nerve Growth Factors May Impact Depression

Research has found sex-related differences in the role of the nerve growth factor BDNF (brain-derived neurotrophic factor), which is believed to play a role in depression and in the response to antidepressants. Acute and chronic stress decreases levels of BDNF. In studies using mice in which the BDNF gene is turned off, females showed decreases in anxiety-like behaviors relative to controls, but males did not. These results support a possible specific role of BDNF in anxiety- and depression-related behaviors in females. They further demonstrate the importance of examining both sexes for potential genetic effects on mood behaviors. (NIMH)

Reference:

Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, Parada LF, Nestler EJ. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol Psychiatry*. 2007 Jan 15;61(2):187-97.

Depression Is Often Comorbid with Other Mental Illnesses

Depression often coexists with eating disorders such as anorexia nervosa, bulimia nervosa, and others, especially among women. Anxiety disorders, such as post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, social phobia, and generalized anxiety disorder, also sometimes accompany depression, especially among women. Women suffering from post-traumatic stress disorder are especially prone to also having depression. (NIMH)

References:

Devane CL, Chiao E, Franklin M, Kruep EJ. Anxiety disorders in the 21st century: status, challenges, opportunities, and comorbidity with depression. *Am J Manag Care*. 2005 Oct;11(Suppl. 12): S344-53.

Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, Howes MJ, Normand SL, Manderscheid RW, Walters EE, Zaslavsky AM. Screening for serious mental illness in the general population. *Arch Gen Psychiatry*. 2003 Feb; 60(2):184-9.

Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *Br J Psychiatry Suppl*. 1998;(34):24-8.

Depression Is Often Comorbid with a Range of Medical Illnesses

Depression also often coexists with medical illnesses such as heart disease, stroke, cancer, HIV/AIDS, diabetes, Parkinson disease, thyroid problems, and multiple sclerosis, and may make symptoms of the illness worse. A study conducted by the NIMH and NIDDK Intramural Research Programs showed that premenopausal women with even mild depression have less bone mass than their nondepressed peers. The level of bone loss is at least as high as that associated with recognized risk factors for osteoporosis, including smoking, low calcium intake, and lack of physical activity. Studies have also shown that both women and men who have depression plus a serious medical illness tend to have more severe symptoms of both illnesses. They also have more difficulty adapting to their medical conditions and more medical costs than those who do not have coexisting depression. Research has shown that treating the depression along with the coexisting illness will help ease both conditions. (NIMH)

References:

Cassano P, Fava M. Depression and public health, an overview. *J Psychosom Res*. 2002 Oct;53(4):849-57.

Eskandari F, et al. Low bone mass in premenopausal women with depression. *Arch Intern Med*. 2007 Nov 26;167(21):2329-36.

Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. *J Psychosom Res*. 2002 Oct;53(4):859-63.

Use of Medications to Treat Depression Has Increased in Women

Over the past 20 years, progress has been made in standardizing effective psychotherapy interventions such as cognitive behavioral therapy and interpersonal therapy (IPT), and in trials of medication treatment. The class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) has come into widespread use and improves the quality of life for many women. Researchers have also learned that women are much more likely to seek treatment than men. (NIMH)

Reference:

Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005 Jun;62(6):629-40.

Neuroimaging and the Menstrual Cycle

Neuroimaging research has revealed a unique reward-related pattern of brain activation during different phases of the menstrual cycle. These data demonstrate that sex hormones affect the function of the reward system. These hormones regulate areas of the brain involved with mood and emotion and are implicated in depression. (NIMH)

Reference:

Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci USA*. 2007;104(7):2465-70.

Estrogen and Depression

Studies have demonstrated the antidepressant role of estradiol (estrogen) therapy during perimenopause. Other researchers have shown the effectiveness of antidepressant medications, given premenstrually, in reducing symptoms. The NIMH Intramural Research Program also has shown that lower levels of estradiol can precede depression but only in women with a past history of perimenopausal depression. Other studies have found that mood changes may be associated with low hormonal levels in women who have a past history of major depression, but not in those without such a history. (NIMH)

References:

Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry*. 2000;157(6):924-30.

Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, Rubinow DR. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gyn*. 2000;183(2):414-20.

Depression and Premature Ovarian Insufficiency

Lifetime prevalence of depression in women with premature ovarian insufficiency is significantly greater than that in the general population. First episodes of major depression preceded a POI diagnosis in more than 70 percent of women studied. A better understanding of this association could identify physiological and genetic processes that underlie depression and POI, as well as the association between depression and the menopause transition in the typical menopause experience. (NIMH)

Reference:

Schmidt PJ, Cardoso GM, Ross JL, Haq N, Rubinow DR, Bondy CA. Shyness, social anxiety, and impaired self-esteem in Turner Syndrome and premature ovarian failure. *JAMA*. 2006;295(12):1374-6.

Onset of Depression during Perimenopause

Two large NIMH- and NIA-funded studies in the past decade have confirmed that women are significantly more likely to experience a first-time major depressive episode in the perimenopausal period than at other life stages. In a study that was part of the Harvard Study of Moods and Cycles, researchers showed that premenopausal women with no lifetime history of major depression who then entered the perimenopause were twice as likely to develop significant depressive symptoms compared with women who remained premenopausal during the study. The researchers also found that high rates of depression were four times more likely to occur during a women's menopausal transition compared with when she was in premenopause. (NIMH)

References:

Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry*. 2006 Apr;63(4):385-90.

Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry*. 2006 Apr;63(4):375-82.

Reproductive Hormones and Mood Disorders

The reproductive endocrine system may play a major role in mood disorders among women. NIMH's Intramural Behavioral Endocrinology Program is working to better understand the neurobiology of these conditions. Researchers have found that changes in reproductive hormones can cause mood disorders. Age, ovarian hormones, and the extent to which hormone level varies across the menstrual cycle can influence whether a woman develops a mood disorder. The same hormonal changes could cause different effects on mood and behavior at different stages of the same woman's life. (NIMH)

References:

Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. Concordant restoration of ovarian function and mood in perimenopausal depression. *Am. J. Psychiatry*. 2003;160(10):1842-6.

Morrison JH, Brinton RD, Schmidt PJ, Gore AC. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. *J. Neurosci*. 2006;26(41):10332-48.

Schmidt PJ, Daly RC, Bloch M, Smith MJ, Danaceau MA, St Clair LS, Murphy JH, Haq N, Rubinow DR. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch. Gen. Psychiatry*. 2005;62(2):154-62.

Schmidt PJ. Mood, depression, and reproductive hormones in the menopause transition. *Am. J. Med*. 2005;118(12B):54S-58S.

Hormonal Transitions and Depression

The NIMH Intramural Research Program's scientists and other researchers have been investigating why women are more prone to depression throughout life, and what prevention and treatment efforts can be brought to bear upon this high burden. Scientists are studying why and how some women are more sensitive to hormonal changes, which may help explain why depression rates among women tend to rise during puberty, around pregnancy, and before and during menopause. It also may lead to a better understanding of premenstrual dysphoric disorder, a very severe form of premenstrual syndrome. (NIMH)

References:

Bloch M, Rubinow DR, Berlin K, Kevala KR, Kim HY, Schmidt PJ. Monoamines and neurosteroids in sexual function during induced hypogonadism in healthy men. *Arch Gen Psychiatry*. 2006;63(4):450-6.

Huo L, Straub RE, Roca C, Schmidt PJ, Shi K, Vakkalanka R, Weinberger DR, Rubinow DR. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biol Psychiatry*. 2007;62(8):925-33.

Richards M, Rubinow DR, Daly RC, Schmidt PJ. Premenstrual symptoms and perimenopausal depression. *Am J Psychiatry*. 2006;163(1):133-7.

Roca CA, Schmidt PJ, Altemus M, Deuster P, Danaceau MA, Putnam K, Rubinow DR. Differential menstrual cycle regulation of hypothalamic-pituitary-adrenal axis in women with premenstrual syndrome and controls. *J Clin Endocrinol Metab*. 2003;88(7):3057-63.

Roca CA, Schmidt PJ, Deuster PA, Danaceau MA, Altemus M, Putnam K, Chrousos GP, Nieman LK, Rubinow DR. Sex-related differences in stimulated hypothalamic-pituitary-adrenal axis during induced gonadal suppression. J Clin Endocrinol Metab. 2005 Jul;90(7):4224-31. Erratum in: *J Clin Endocrinol Metab*. 2005 Sep;90(9):5522

Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry*. 2004;161(12):2238-44.

Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med*. 1998;338(4):209-16.

Yonkers KA, Holthausen GA, Poschman K, Howell HB. Symptom-onset treatment for women with premenstrual dysphoric disorder. *J Clin Psychopharmacol*. 2006 Apr;26(2):198-202.

Immunity, Autoimmunity, and Infectious Diseases

Microorganisms and Early Immune Responses Involved in the Development of Inflammation and Autoimmune Disease

NIAID-funded investigators showed that mice with a defect in a specific gene called SHP1, which is involved in dampening immune responses, developed chronic inflammation in their feet, lungs and salivary glands. In addition, the mice produced self-reactive antibodies, a sign of autoimmune disease. The observed inflammatory and autoimmune response in the SHP-1 mutant mice did not occur when the mice were kept in a germ-free environment. Inflammation was also prevented when specific signaling genes of the early, or innate, immune system were deleted in the SHP-1 mutant mice. Studies in this mouse model define a mechanism for the development of inflammation and autoimmunity: a dependence on both the presence of microbial pathogens and signaling through innate immune pathways. (NIAID)

Reference:

Croker BA, Lawson BR, et al. Inflammation and autoimmunity caused by SHP1 mutation depend on IL-1, MyD88, and a microbial trigger. *Proc Natl Acad Sci USA*. 2008:105(39):15028-33.

Gender Differences in Response to Stress

Researchers in one study found that 30 minutes after experiencing a stressful event, production of pro-inflammatory cytokines were elevated in both men and women. However, from before to immediately post-stress, men demonstrated a significant drop in cytokine production compared with women. Further, postmenopausal women demonstrated greater subsequent increases in the production of certain cytokines compared with men. These data bolster existing evidence that stress causes the immune system in postmenopausal women to produce larger inflammatory responses than in either premenopausal women or men. The results also demonstrate gender differences in stress-related cytokine activity, and suggest a possible reason for an observed increased susceptibility of postmenopausal women for developing inflammatory disease. (NINR)

Reference:

Prather AA, Carroll JE, Fury JM, McDade KK, Ross D, Marsland AL. Gender differences in stimulated cytokine production following acute psychological stress. *Brain Behav Immun*. 2009;23(5):622-8.

Candidate GBS Vaccine Shown To Be Safe

A group B Streptococcus (GBS) serotype III polysaccharide tetanus toxoid vaccine was found to be safe, elicit a strong immune response, and significantly reduce bacterial colonization (36 percent in the vagina and 43 percent in the rectum) in 650 women studied. This response indicates that such a candidate vaccine may prevent invasive infections by decreasing colonization at mucosal sites. (NIAID)

Reference:

Hillier, et al. Women receiving group B Streptococcus serotype III tetanus toxoid (GBS III-TT) vaccine have reduced vaginal and rectal acquisition of GBS type III. Presented at the 47th Annual Meeting of the Infectious Diseases Society of America; 2009 Oct 30; Philadelphia, PA.

Newborn Screening for CMV

A study funded by NIDCD has found that the traditional "heel stick" test is not an effective screening tool for congenital cytomegalovirus (CMV) infection, a leading cause of hearing loss in children. Researchers compared the effectiveness of a common molecular diagnostic technology using dried blood samples to the standard method for detecting CMV in newborns, which is labor-intensive and not conducive to a widespread screening program. The researchers are now assessing whether analysis of saliva samples using the same diagnostic technology can do a better job than dried blood spots when compared with the standard method. (NIDCD)

Reference:

Boppana SB, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. 2010 Apr 14;303(14):1375-82.

HEPATITIS

Development of a Hepatitis E Vaccine with Potential to Reduce Maternal Mortality

Infection by the food- and waterborne pathogen hepatitis E virus (HEV) can cause 10 to 25 percent fatality rates among HEV-infected pregnant women, and can adversely affect pregnancy outcomes among survivors. An HEV vaccine developed by NIAID scientists, in collaboration with GlaxoSmithKline (GSK), has been proven safe and effective in field trials supported by the U.S. Army Medical Research and Materiel Command, NIAID, and GSK. Distribution of this vaccine in endemic areas could have an important effect on public health, especially the health of pregnant women. (NIAID)

References:

Robinson RA, Burgess WH, Emerson SU, Leibowitz RS, Sosnovtseva SA, Tsarev S, Purcell RH. Structural characterization of recombinant hepatitis E virus ORF2 proteins in baculovirus-infected insect cells. *Protein Expr Purif*. 1998;12(1):75-84.

Shrestha MP, Scott RM, Joshi DM, Mammen MP Jr, Thapa GB, Thapa N, Myint KS, Fourneau M, Kuschner RA, Shrestha SK, David MP, Seriwatana J, Vaughn DW, Safary A, Endy TP, Innis BL. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med*. 2007;356(9):895-903.

Tsarev SA, Tsareva TS, Emerson SU, Govindarajan S, Shapiro M, Gerin JL, Purcell RH. Recombinant vaccine against hepatitis E: dose response and protection against heterologous challenge. *Vaccine*. 1997;15(17-18):1834-8.

H1N1 (SWINE) FLU

H1N1 Vaccine Trials in Pregnant Women

NIAID, through its Vaccine and Treatment Evaluation Units, has recently conducted several studies evaluating influenza vaccines in pregnant women. Because pregnant women were disproportionately affected by the 2009 H1N1 pandemic, NIAID launched studies to assess whether higher vaccine dosages or more than one dose should be recommended for this population. Early results—indicating that a single 15 mg dose produces a robust immune response in this population—helped shape treatment guidelines. Studies looking at HIV-infected pregnant women are also under way. (NIAID)

LUPUS

Gene Expression in Lupus Patients

Using a new global gene expression analysis approach, researchers discovered a gene expression pattern of interferon-regulated genes that correlated with disease activity in systemic lupus erythematosus patients. This molecular pattern is clinically important, as it may be a useful biomarker to predict the therapeutic efficacy of experimental drugs for lupus. This basic research finding also led to several studies in which clinicians are testing new treatments for lupus that block interferon alpha. (NIAID)

Reference:

Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, Pascual V. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med*. 2003;197(6):711-23.

Prevalence and Severity of Lupus in Various Populations of Women

Systemic lupus erythematosus, or lupus, is a chronic inflammatory disease that can affect many organs of the body, including the skin, joints, heart, lungs, kidneys, and brain. Substantial research accomplishments have been made to characterize this complex disease, which has diverse effects across the patient population, in efforts to treat individual patients. The Lupus in Minority Populations: Nature vs. Nurture (LUMINA) study revealed that female Hispanic and African-American lupus patients tend to develop the disease at a younger age than their Caucasian counterparts and experience greater disease activity and more severe manifestations of lupus. (NIAMS)

References:

Alarcón GS, Friedman AW, Straaton KV, Moulds JM, Lisse J, Bastian HM, McGwin G Jr, Bartolucci AA, Roseman JM, Reveille JD. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. Lupus in Minority populations: Nature vs. Nurture. Lupus. 1999;8(3):197-209.

Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus*. 2002;11(3):152-60.

Advances in Detection and Treatment of Lupus

The Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) clinical trial addressed concerns over the impact of estrogen-based oral contraceptives on disease activity and has shown they can be used safely without directly inducing lupus flares. Methods to analyze patients' blood samples are being developed to group variations in gene expression according to the different disease-causing molecular pathways in individual patients. This system may be used to predict flares of lupus activity in the future and guide personalized treatment. (NIAMS)

References:

Petri M, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Eng J Med*. 2005 Dec 15,353(24):2550-8.

Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, Baldwin N, Stichweh D, Blankenship D, Li L, Munagala I, Bennett L, Allantaz F, Mejias A, Ardura M, Kaizer E, Monnet L, Allman W, Randall H, Johnson D, Lanier A, Punaro M, Wittkowski KM, White P, Fay J, Klintmalm G, Ramilo O, Palucka AK, Banchereau J, Pascual V. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity*. 2008 Jul 18;29(1):150-64.

Lupus and Pregnancy

Ongoing studies from the Research Registry for Neonatal Lupus and the multicenter study called Predictors of Pregnancy Outcome, Biomarkers in Antiphospholipid Syndrome and Systemic Lupus Erythematosus (PROMISSE) are investigating the role of autoantibodies and other serum molecules from pregnant lupus patients in increasing the risk of neonatal lupus syndrome and associated cardiovascular complications. (NIAMS)

References:

Buyon JP, Hiebert R, Copel J, Craft J, Friedman D, Katholi M, Lee LA, Provost TT, Reichlin M, Rider L, Rupel A, Saleeb S, Weston WL, Skovron ML. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol*. 1998 Jun;31(7):1658-66.

Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, Salmon JE, Buyon JP. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis*. 2010 May 6 [Epub ahead of print].

RHEUMATOID ARTHRITIS

Potential Treatments for Rheumatoid Arthritis?

In the 1990s, researchers identified molecular mechanisms of inflammation and immune dysfunction that could be associated with disease pathways in rheumatoid arthritis. Biologics—drugs in the form of biological molecules—that block the activity of tumor necrosis factor, a key molecule in inflammatory processes, have brought relief to many rheumatoid arthritis patients, including children, with fewer side effects than other treatments. The North American

Rheumatoid Arthritis Consortium (NARAC), a multi-institutional group of researchers, is conducting ongoing studies, in collaboration with colleagues from other countries, to identify the genetic factors that contribute to rheumatoid arthritis susceptibility and that may affect responses to rheumatoid arthritis treatments. (NIAMS)

References:

Pisetsky DS. Tumor necrosis factor blockers in rheumatoid arthritis. *N Eng J Med*. 2000 Mar 16;342(11):810-1.

Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Eng J Med*. 2000 Mar 16;342(11):763-9.

Raychaudhuri S, Remmers EF, Lee AT, Hackett R, Guiducci C, Burtt NP, Gianniny L, Korman BD, Padyukov L, Kurreeman FA, Chang M, Catanese JJ, Ding B, Wong S, van der Helm-van Mil AH, Neale BM, Coblyn J, Cui J, Tak PP, Wolbink GJ, Crusius JB, van der Horst-Bruinsma IE, Criswell LA, Amos CI, Seldin MF, Kastner DL, Ardlie KG, Alfredsson L, Costenbader KH, Altshuler D, Huizinga TW, Shadick NA, Weinblatt ME, de Vries N, Worthington J, Seielstad M, Toes RE, Karlson EW, Begovich AB, Klareskog L, Gregersen PK, Daly MJ, Plenge RM. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat Genet*. 2008 Oct;40(10):1216-23.

Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FA, Zhernakova A, Hinks A, Guiducci C, Chen R, Alfredsson L, Amos CI, Ardlie KG; BIRAC Consortium, Barton A, Bowes J, Brouwer E, Burtt NP, Catanese JJ, Coblyn J, Coenen MJ, Costenbader KH, Criswell LA, Crusius JB, Cui J, de Bakker PI, De Jager PL, Ding B, Emery P, Flynn E, Harrison P, Hocking LJ, Huizinga TW, Kastner DL, Ke X, Lee AT, Liu X, Martin P, Morgan AW, Padyukov L, Posthumus MD, Radstake TR, Reid DM, Seielstad M, Seldin MF, Shadick NA, Steer S, Tak PP, Thomson W, van der Helm-van Mil AH, van der Horst-Bruinsma IE, van der Schoot CE, van Riel PL, Weinblatt ME, Wilson AG, Wolbink GJ, Wordsworth BP; YEAR Consortium, Wijmenga C, Karlson EW, Toes RE, de Vries N, Begovich AB, Worthington J, Siminovitch KA, Gregersen PK, Klareskog L, Plenge RM. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet*. 2010 Jun;42(6):508-14.

SCLERODERMA

Advances in the Treatment of Scleroderma

Scleroderma is a disease associated with excessive production of connective tissue proteins, a condition known as fibrosis, and tissue hardening. It affects women more often than men, and there is a higher prevalence in some Native American populations. The immunosuppressive drug cyclophosphamide may improve lung function, particularly in scleroderma patients with pulmonary alveolitis, and quality-of-life outcomes. The cancer drug Gleevec has been shown to target a molecular mediator of fibrosis, which inhibits the key process associated with scleroderma; Gleevec is currently being tested in clinical trials for scleroderma. (NIAMS)

References:

Zhou X, Tan FK, Wang N, Xiong M, Maghidman S, Reveille JD, Milewicz DM, Chakraborty R, Arnett FC. Genome-wide association study for regions of systemic sclerosis susceptibility in a Choctaw Indian population with high disease prevalence. *Arthritis Rheum*. 2003 Sep;48(9):2585-92.

Khanna D, et al. Impact of oral cyclophosphamide on health-related quality of life in patients with active scleroderma lung disease: results from the scleroderma lung study. *Arthritis Rheum*. 2007 May;56(5):1676-84.

Pannu J, Asano Y, Nakerakanti S, Smith E, Jablonska S, Blaszczyk M, ten Dijke P, Trojanowska M. Smad1 pathway is activated in systemic sclerosis fibroblasts and is targeted by imatinib mesylate. *Arthritis Rheum*. 2008 Aug;58(8):2528-37.

SJÖGREN'S SYNDROME

Hormone Levels and Sjögren's syndrome

Androgen deficiency was demonstrated in a study of patients with primary Sjögren's syndrome, a disease that occurs almost exclusively in women. There was no significant change in the levels of other hormones such as estrogen. These findings could not be linked to the use of oral contraceptives or menopausal hormone therapy. (NEI)

Reference:

Sullivan DA, Bélanger A, Cermak JM, Bérubé R, Papas AS, Sullivan RM, Yamagami H, Dana MR, Labrie F. Are women with Sjögren's syndrome androgen-deficient? *J Rheumatol*. 2003 Nov;30(11):2413-9.

URINARY TRACT INFECTIONS

The Interaction between Cranberry Juice and Antibiotics in the Treatment of Urinary Tract Infections

Cranberry juice is a popular home remedy for urinary tract infections (UTIs). Because little is known about the potential of cranberry juice to interact with drugs, NCCAM-funded researchers studied the effects of cranberries on two antibiotics frequently prescribed for UTI: amoxicillin and cefaclor. The data showed that cranberry juice did not significantly affect either antibiotic's oral absorption or renal clearance (i.e., how completely the body processed the drugs in the intestine and kidneys). Based on these results, the researchers concluded that cranberry juice cocktail, consumed in usual quantities, is unlikely to change the effects of these two antibiotics on UTIs. (NCCAM)

Reference:

Li M, Andrew MA, Wang J, Salinger DH, Vicini P, Grady RW, Phillips B, Shen DD, Anderson GD. Effects of cranberry juice on pharmacokinetics of beta-lactam antibiotics following oral administration. *Antimicrob Agents Chemother*. 2009 Jul;53(7):2725-32.

THE HUMAN MICROBIOME

The Human Microbiome Project (HMP)

Within the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, physiology, immunity, and nutrition.

The human microbiome consists of all of the DNA, or genomes, of all of the microorganisms present in or on the human body. Launched in 2007 as part of the NIH Roadmap for Medical Research, the Human Microbiome Project is a five-year effort that will produce a resource for researchers who are seeking to use information about the microbiome to improve human health.

Initially, researchers plan to sequence 600 microbial genomes, completing a collection that will total some 1,000 microbial genomes. The remaining microbial genomes are being contributed to the collection by individual NIH Institutes and internationally funded projects. Those data will then be used to characterize the microbial communities present in samples taken from healthy human volunteers. The samples will be collected from five areas of the body: the digestive tract, the mouth, the skin, the nose, and the vagina.

Following the precedents set by other large-scale genomics efforts, such as the Human Genome Project and the International HapMap Project, data from the Human Microbiome Project will be swiftly deposited in public databases. The HMP has the potential to transform understanding of human health and the prevention, diagnosis, and treatment of a wide range of conditions, particularly for women. (NHGRI)

Reference:
http://nihroadmap.nih.gov/hmp/

Women and HIV/AIDS

Trans-NIH Plan for HIV/AIDS Research

Each year, OAR develops the comprehensive Trans-NIH Plan for HIV-Related Research. The Plan includes chapters specifically devoted to Microbicides Research and to HIV Research for Women and Girls. The Plan is developed in collaboration with scientists from NIH, other government agencies, non-governmental organizations, and community representatives. The Plan serves as the framework for developing the annual AIDS research budget for each Institute or Center; determining the use of AIDS-designated dollars; and tracking and monitoring all NIH AIDS research expenditures. The Plan also is used to inform the scientific community, the public, and the HIV/AIDS-affected community about NIH priorities for HIV research. (OAR)

Federal Treatment and Prevention Guidelines

OAR provides funding and coordination for the development of U.S. Department of Health and Human Services Federal guidelines on the treatment of HIV infection. The guidelines are written, reviewed, and updated by Working Groups of HIV experts from across the country convened under the auspices of OAR. These working groups include HIV care physicians, pharmacists, researchers, and HIV treatment advocates. The guidelines on treatment of adults and adolescents include a section on the specific treatment of women, including evidence-based information. A second guidelines document addresses the treatment of pregnant women and the prevention of mother-to-child HIV transmission. These documents are widely considered to be the standard for HIV treatment nationally and internationally. The guideline documents can be accessed on the AIDS*info* Web site at *http://www.aidsinfo.nih.gov/Guidelines/Default.aspx?MenuItem=Guidelines*.

The Working Groups develop separate guidelines for: Treatment of Adults and Adolescents; Treatment of Children; Treatment of Pregnant Women and Prevention of Mother-to-Child HIV Transmission; and Prevention and Treatment of Opportunistic Infections.

Through all of these activities, OAR continues to demonstrate its leadership and commitment to the study of HIV in women. (OAR)

Safety of Contraception for HIV-infected Women: Depot Medroxyprogesterone Injectable Contraceptives (DMPA)

Until recently, the question of whether antiretroviral (ARV) agents affect or are affected by a widely used hormonal contraceptive—depot medroxyprogesterone (DMPA)—had not been thoroughly addressed. Safe and effective contraception is an important concern for reproductive-age women living with HIV/AIDS. Researchers conducted a study to examine the interactions between DMPA, a progesterone-based injectable contraceptive given every three months, and selected antiretroviral agents. Study results showed that DMPA remained at effective levels across groups for the 12 weeks after the injection. There were no pregnancies after DMPA injection. Plus, there were no significant changes in HIV RNA levels or in CD4+

cell counts after DMPA injection. The side effects of the DMPA were similar to those seen in women who are not infected with HIV. The study findings can reassure millions of women worldwide of reproductive age who are taking antiretroviral treatments that they may safely use DMPA as a contraceptive. (NICHD)

Reference:

Watts DH, Park JG, Cohn SE, Yu S, Hitti J, Stek A, Clax PA, Muderspach L, Lertora JJ. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. 2008 Feb;77(2):84-90.

Women's Interagency HIV Study (WIHS)

Established in 1994, this is the largest observational study (3,500) of HIV-infected women and uninfected women at high risk of HIV, the majority of whom are African-American and Latina. With study participants at sites in six U.S. metropolitan areas, the study has yielded major discoveries about how HIV is spread, how the disease progresses, and how it can best be treated. WIHS has produced 440 publications dealing with women and HIV and maintains 2 million specimens to support ongoing and future research. The study continues to support research on drug resistance, coinfections, therapy use and treatment effects, genetics, metabolic abnormalities and toxicities, hormonal factors, aging, risk of cardiovascular disease, neurocognitive functioning, and physical impairment. (NIAID and NICHD)

Reference:

http://statepiaps.jhsph.edu/wihs/

Women's HIV Seroincidence Study

Initiated in 2009, this observational study will enroll 2,000 women from 10 geographically distinct high-risk areas in the United States to estimate the overall incidence of HIV-1. This study will provide essential information about women's preferred recruitment and retention strategies for future intervention studies. (NIAID)

Reference:

http://www.hptn.org/research_studies/hptn064.asp

Support for Research on Microbicides to Help Stop the Spread of HIV

To further enhance research in the area of microbicides, OAR reorganized its scientific staff to add a new division specifically dedicated to planning, coordinating, budgeting, and facilitating trans-NIH microbicide research and other issues relevant to research on women and girls. This has resulted in elevating the scientific priority and funding for this important area within the overall HIV prevention research agenda. OAR has utilized its unique budgetary authority to ensure that funding for microbicide research continues to increase, even during these times of budgetary constraints. OAR also revised its AIDS Research Information System (ARIS) to code, track, and monitor all trans-NIH investments in and expenditures on microbicide research. (OAR)

Microbicide Innovation Program (MIP)

Topical microbicides are agents which when applied vaginally, rectally, and/or on the penis can result in inhibition of the transmission of HIV and/or other sexually transmitted infections that may be cofactors in HIV transmission and acquisition. A safe, effective, acceptable topical microbicide that prevents the sexual transmission of HIV could play a major role in worldwide reduction of the more than 7,000 new HIV infections per day, potentially saving millions of lives. The MIP supports the advancement of novel scientific ideas, models, tools, agents, targets, and technologies with the potential to advance microbicide science. (NIAID)

Reference:

http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-10-011.html

Microbicide and Pre-exposure Prophylaxis Trials

Research is under way to develop and test new chemical and biological compounds that women can apply before intercourse to protect themselves against HIV and other sexually transmitted infections. The VOICE study (Vaginal and Oral Interventions to Control the Epidemic) will enroll approximately 5,000 women in Africa to provide additional safety and effectiveness data for a tenofovir-based vaginal gel as an HIV prevention method. The study also will offer some insight as to the gel's acceptability as a product used once a day, rather than one that is used before and after sexual intercourse. The study also is examining oral antiretroviral tablets (tenofovir alone or tenofovir plus emtricitabine) as an HIV prevention method. If either regimen is found to be effective, it would give women an HIV prevention method they can control, and would increase the number of prevention tools available to curb the epidemic. (NIAID)

Reference:

http://www.niaid.nih.gov/news/newsreleases/2009/pages/voice.aspx

HIV Prevention during Pregnancy

NIAID is examining the safety of HIV prevention regimens during pregnancy, when women are more susceptible to HIV infection. A small Phase I study of tenofovir vaginal gel among healthy pregnant women found no safety concerns. An HIV Prevention Agent Pregnancy Exposure Registry (also known as EMBRACE) is enrolling women who become pregnant during a microbicide or PrEP trial, or who have had planned exposures to drugs in pregnancy safety studies. The babies resulting from these pregnancies will also be enrolled. If studies can demonstrate safety for the mother and infant, the women will be able to continue participating in large trials testing the efficacy of these prevention strategies. (NIAID)

Prevention of Mother-to-Child Transmission (MTCT) of HIV

In 1994, a landmark study cosponsored by NIAID demonstrated that the drug AZT, given to HIV-infected women who had little or no prior antiretroviral therapy, reduced the risk of MTCT by two-thirds. This and other findings have helped reduce perinatal HIV infections in the United States by more than 90 percent, according to the Centers for Disease Control and Prevention.

In 1999, a NIAID-funded study in Uganda found that single oral doses of the inexpensive drug nevirapine—one dose given to an HIV-infected mother at the onset of labor and one given to the infant soon after birth—reduced MCTC by nearly 50 percent. The World Health Organization now recommends this simpler, lower-cost regimen as a key component of MTCT prevention programs in resource-limited settings. Similar studies conducted by NICHD-supported researchers from Thailand, France, and the United States showed that transmission of HIV from a mother to her child can be reduced with shorter treatments of the drug AZT (zidovudine) at one-fifth the usual cost (in U.S. dollars). (NIAID and NICHD)

Iron Supplementation in HIV-infected Pregnant Women

Anemia is a major health problem in sub-Saharan Africa, affecting 35 to 75 percent of pregnant women, and is an important cause of maternal morbidity and mortality, fetal loss, and low birth weight. As part of a strategy to prevent anemia and its adverse effects, the World Health Organization recommends routine use of iron supplementation in all pregnant women living in areas with high prevalence of iron deficiency. However, there is little evidence showing that this intervention is effective in HIV-infected pregnant women, and some evidence suggesting that iron supplementation may increase the risk and density of malaria infection and be associated with increased viral load in these women. NIH-supported investigators are conducting a cross-sectional study of HIV-infected Malawian women in their third trimester of pregnancy to compare the prevalence of maternal anemia, the presence of malaria-associated parasites, viral load, and concentrations of certain blood markers among women who do and do not receive iron supplementation. Results from this study will inform standard clinical practice with regard to iron supplementation in this vulnerable population. (ODS)

Antiretroviral Drug Use during Pregnancy by HIV-infected Women does Not Result in an Increase in the Risk of Birth Defects

Antiretroviral drugs are routinely recommended for use during pregnancy to prevent the perinatal transmission of HIV. In addition, millions of HIV-infected women of childbearing age require antiretroviral therapy for their own health and may conceive while taking antiretroviral drugs. The safety of these drugs, especially regarding the potential for birth defects after exposure during early pregnancy, is often unknown. Using data from the Women and Infants Transmission Study, researchers assessed data from women who were enrolled during pregnancy and followed them and their infants over time. The rate of birth defects was compared among infants born to women with no antiretroviral exposure, with exposure only during the second and third trimester after the formation of the organs was almost complete, and with first-trimester exposure. The reassuring results showed no increase in overall risk of defects with first-trimester compared with later or no exposure. Major defects such as neural tube defects or heart defects were not increased with drug exposure. One defect, hypospadias, was potentially increased after first-trimester zidovudine exposure, and these data must be verified. However, overall data are reassuring to providers and patients who require antiretroviral therapy during pregnancy. Continued evaluation of the safety of newer antiretroviral agents in pregnancy is required. (NICHD)

Reference:

Watts DH, Li D, Handelsman E, Tilson H, Paul M, Foca M, Vajaranant M, Diaz C, Tuomala R, Thompson B. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. J Acquir Immune Defic Syndr. 2007 Mar 1;44(3):299-305.

HIV Risk Reduction Interventions Tailored to Hispanic Women

The University of Miami NCMHD Center of Excellence is conducting a three-year experimental study evaluating the effectiveness of a randomized HIV risk reduction intervention led by Hispanic women and culturally tailored to the specific needs of Hispanic women, who are disproportionally impacted by HIV/AIDS. The research study evaluates the effectiveness of a refined and culturally tailored specific intervention to increase HIV prevention behaviors for inner-city Hispanic women and explores the role of acculturation, family, stress, and family functioning as risk and/or protective factors in the prevention of HIV/AIDS among Hispanic women. (NCMHD)

Interventions to Reduce HIV Risk and Improve Outcomes for Pregnant African-American Women

The Virginia Commonwealth University (VCU) Center of Excellence in Health Disparities Research (CoEHDR) is conducting research on adverse pregnancy outcomes for African-American women and community health education interventions that increase safe-sex skills development among pregnant women at high risk for HIV infection. (NCMHD)

OAR-sponsored Research Activities

As an Office within the Office of the Director, NIH, OAR has convened, sponsored, or supported a number of activities to focus increased emphasis on microbicide research and to enhance research and prevention efforts in women and girls. These include, but are not limited to:

- Convened an Office of AIDS Research Advisory Council consultation on HIV prevention research for women and girls that outlined the research gaps and priorities that inform current NIH research.
- Established the Microbicides Research Working Group, an external group of expert advisors that provides guidance to NIH and the research field.
- Supports the Women's Research Institute, a group of external experts who meet annually to outline the important gaps in research on women.
- Convenes and chairs the Trans-NIH Microbicide Research Coordinating Committee composed of representatives from relevant NIH Institutes and Centers; and convenes and chairs the Trans-U.S. Government (USG) Microbicides Research Coordinating Committee including representatives from CDC, USAID, FDA, and DoD to share information, and facilitate collaboration, cooperation, and the efficient use of resources. This group will play a critical role in defining the next steps in USG microbicides research in response to the success of the first antiretroviral-based microbicide study (CAPRISA 004).

- Provides support for NIH-funded studies in the prevention of mother-to-child HIV transmission, microbicide trials, and the pathogenesis of HIV in women.
- Provides funding for and works with ORWH, NIAID, NICHD, and NIMH to implement an innovative microbicide research initiative designed to facilitate advancement in the field. The “Microbicides Innovation Program” provides funding to researchers with unique ideas that will further the science of microbicides research. Thus far, the MIP has funded 15 grants that address pressing scientific questions in microbicides development research.
- Provides support to the Microbicides Trials Network to conduct the first assessment of the impact of the use of ARV-based microbicides in clinical trials on the level of ARV resistance in communities and the first studies of the safety of antiretroviral-based microbicides used during pregnancy (OAR)

Rare Diseases

A rare disease is a condition that affects fewer than 200,000 people in the United States. Several rare diseases are known to proportionately affect women more than men. It is not known how many diseases affect women more than men. The following paragraphs provide a summary of research and research-related activities that have been supported by ORDR that relate to conditions that are known to affect women more than men.

THE RARE DISEASES CLINICAL RESEARCH NETWORK

Since FY 2003, ORDR has collaborated with NIH Institutes and Centers to support the Rare Diseases Clinical Research Network (RDCRN). The RDRCN is made up of 19 distinctive consortia that are working in concert to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities. A listing of consortia and diseases or disorders studied by each can be found at *http://rarediseasesnetwork.epi.usf.edu/*. (ORDR)

Rett Syndrome

Rett syndrome is known to affect girls almost exclusively. The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. Before the symptoms begin, however, the child appears to grow and develop normally. Then, gradually, mental and physical symptoms appear. Hypotonia (loss of muscle tone) is usually the first symptom. As the syndrome progresses, the child loses purposeful use of her hands and the ability to speak. Other early symptoms may include problems crawling or walking and diminished eye contact. The loss of functional use of the hands is followed by compulsive hand movements such as wringing and washing. The onset of this period of regression is sometimes sudden. The consortium, of which the study of Rett syndrome is an important part, is now in its second five-year cycle and focuses on a natural history study to establish a phenotype-genotype correlation over a broad spectrum of Rett syndrome phenotypes including the longitudinal pattern of progression of clinical features, quality of life, and longevity across this cohort. (ORDR)

Congenital Adrenal Hyperplasia

The most common form of congenital adrenal hyperplasia (CAH) results from a deficiency of the enzyme 21-hydroxylase. There are two forms of 21-hydroxylase congenital adrenal hyperplasia, a severe form termed “classical CAH,” with profound 21-hydroxylase deficiency, and a mild form called “nonclassical CAH,” which has a lesser deficiency of 21-hydroxylase. The classical form of CAH may be life-threatening if untreated. 21-hydroxylase deficiency in the classical forms, both salt-wasting and simple virilizing, results not only in reduced secretion of cortisol but also increased secretion of male-like hormones from the adrenal glands. These male-like hormones masculinize the female fetus *in utero* so that the genitalia are

ambiguous. CAH can be diagnosed prenatally following amniocentesis or chorionic villus sampling. Classical CAH can be treated prenatally to prevent masculinization of the genitalia of affected females.

11β-hydroxylase deficiency is the second most common form of CAH. Like 21-hydroxylase deficiency, it causes masculinization in the female fetus, but it also cause high blood pressure. It is diagnosed by hormone testing and DNA analysis and is treated by steroid hormone replacement. Like 21-hydroxylase deficiency, it can be prenatally diagnosed and treated, and has severe and mild forms. Studies to date have included a natural history study; a study to determine whether differences in other genes can modify the clinical course of adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency; and long-term outcome in offspring and mothers of dexamethasone-treated pregnancies to determine whether prenatal treatment with dexamethasone has any long-term effects on those who were treated as fetuses and who are now 12 years and older. (ORDR)

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) in a sporadic form affects almost exclusively women of childbearing age. LAM is typically slowly progressive. Treatments include the use of mTOR inhibitors (e.g., sirolimus), farnesyl transferase inhibitors, specific estrogen antagonists, endothelin receptor antagonists (e.g., Bosentan), statins (e.g., simvastatin), tyrosine kinase inhibitors (e.g., Gleevec), metalloproteinase inhibitors, and angiogenesis inhibitors (e.g., Avastin). When pulmonary function is no longer sufficient, a lung transplant may be needed, though the transplanted lung may eventually also be affected. The consortium assessed the safety of sirolimus administered orally or a placebo to assess the effect of sirolimus on biological and clinical markers of lung function, including spirometry findings, dyspnea, quality of life, lung volume, diffusion, oxygenation, and exercise tolerance. (ORDR)

Progressive Familial Intrahepatic Cholestasis

Progressive Familial Intrahepatic Cholestasis (PFIC) is passed from parents to children through genes. For a child to get PFIC they must receive two changed copies of a gene, one each from the mother and the father. These changes in genes are called mutations. Carrying one changed copy of a gene and one normal copy of a gene does not usually cause disease and is relatively common. Thus, parents of children with PFIC usually have no liver or other medical problems. One exception to this may be that women with one changed PFIC gene may develop liver disease during pregnancy. The purpose of a longitudinal study of genetic causes of intrahepatic cholestasis was to learn about the natural history and progression of PFIC and three other cholestatic liver diseases. (ORDR)

Takayasu Arteritis

Takayasu arteritis (TAK) is a rare form of vasculitis affecting medium-sized and large blood vessels, primarily the aorta. TAK generally affects people in their teens, twenties, or thirties, and primarily strikes young women. It is also more common in Asia. The cause of Takayasu arteritis is unknown. Inflammation of the large blood vessels may cause segments of vessels to weaken and stretch, resulting in an aneurysm (weakening of the vessel wall) or, more commonly, the inflammation of the vessel wall leads to thickening and subsequent partial

blockage or complete blockage of the artery. These blockages can result in the surrounding tissues being deprived of an adequate blood supply, which causes mild to very severe problems including cramping in the arms and legs, kidney damage with severe hypertension, strokes, or heart attacks. Many other symptoms and problems can be seen in TAK, including joint pains, fevers, and fatigue, among others. Three studies are currently under way: a longitudinal protocol for TAK **(***http://rarediseasesnetwork.epi.usf.edu/vcrc/takeaction/studies/TAK-5503.htm***);** an imaging protocol for magnetic resonance (MRI) and positron emission tomography (PET/CT) in TAK(*http://rarediseasesnetwork.epi.usf.edu/vcrc/takeaction/studies/TAK-5515.htm*), and a comparison of x-ray-like tests that are not a part of regular medical care (PET/CT) with x-ray-like tests that are a part of a regular care (MRI). The third study will determine if the medication abatacept is safe and effective in Takayasu arteritis as well as in giant-cell arteritis. (ORDR)

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) is an autoimmune disease, and 75 to 90 percent of people affected with this disease are women. In this disorder, antibodies that are found in the blood and normally fight off infections instead turn against the body's own normal clotting mechanisms. These antibodies make people more prone to certain problems, such as clots in the deep veins in the arms and legs, known as deep vein thrombosis (DVT), or in the lung, known as pulmonary embolism (PE). People with APS can also develop clots in their arteries that can cause heart attacks or strokes. In certain women, these antibodies can cause recurrent pregnancy loss. The treatment of choice for patients with APS who have had a blood clot is anticoagulant therapy (treatment with a blood thinner). For women with APS and recurrent miscarriages who have not had a prior blood clot, the use of anticoagulant therapy during the pregnancy may increase the likelihood of a successful outcome. Some individuals may have elevated antiphospholipid antibodies but have no clinical manifestations of the syndrome. These individuals do not need anticoagulant therapy, but studies are ongoing to evaluate whether an aspirin a day might be beneficial for these individuals. Diagnostic and/or therapeutic limitations exist and prospective studies have begun to more clearly define the syndrome and develop better therapies. (ORDR)

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare blood condition characterized by a low platelet count and the widespread formation of small blood clots throughout the circulatory system. Platelets are the smallest of the cells in the blood, and they function as tiny corks that form a plug to stop bleeding. In general, a very low platelet count, referred to as thrombocytopenia, is associated with bleeding problems, and these patients may present with large bruises. These patients can also develop clotting complications involving the brain, kidneys, and virtually any organ in the body.

TTP occurs more frequently in women than in men. The primary treatment for TTP is a process called "plasma exchange," during which a patient's plasma (the liquid part of the blood) is removed and replaced with plasma from blood donors. This treatment is very effective and life-saving in the majority of patients. Other treatments that have been used include steroids, aspirin, and certain chemotherapy agents. In a subset of patients, TTP may recur after

stopping treatment. These patients may require treatment to be restarted, or a different type of therapy may become necessary. The study of incidence of thromboembolic events in patients with antibodies to heparin-PF4 after cardiac bypass was begun to determine how often heart surgery patients who receive heparin develop an immune response (heparin-induced thrombocytopenia) that leads to clots forming in different parts of the body.

GENETIC AND RARE DISEASES INFORMATION CENTER

ORDR supports, with the National Human Genome Research Institute, the Genetic and Rare Diseases Information Center (GARD). GARD provides information to patients and their families, health professionals, researchers, and the public. A customer service satisfaction survey showed that, typically, information center customers are white, non-Hispanic, English-speaking women between the ages of 31 and 40 with a postgraduate education who request information for themselves and for family members or friends, who could be male or female. To reach an even wider audience, GARD now focuses on making available questions and answers on the ORDR Web site in addition to services by e-mail, telephone, or mail. In 2010, the GARD section of the ORDR Web site has receive an average of 75,000 visits per month in addition to continued inquiries by e-mail, telephone, and mail totaling over 27,000 since its inception. (ORDR)

SCIENTIFIC CONFERENCES

ORDR collaborates with Institutes, Centers, and Offices at NIH to stimulate rare diseases research by cosponsoring scientific conferences where research is lagging or to take advantage of scientific opportunities. Throughout the years, conferences cofunded by ORDR with a focus on women's health have included:

- *Profiling of Immune Response to Guide Cancer Diagnosis, Prognosis, and Prediction of Therapy,* which included sessions on T-regulatory T cells as predictors of survival in ovarian cancer and Interleukin-6 polymorphism as predictor of outcome in high-risk breast cancer. The meeting highlighted the clinical significance of immunologically regulated molecules as markers and validation approaches for basic and clinical researchers interested in marker development.
- *The Status and Future of Acupuncture Research: 10 Years Post-NIH Consensus Conference,* which synthesized the current status of the research evidence base for the efficacy of acupuncture for a number of diseases, including rare diseases, through plenary sessions, breakout sessions, and workshops. Overall, the goal was to strengthen the evidence base for acupuncture therapy. Sessions included Acupuncture in Female Infertility–Basic and Clinical Studies and Functional Neuroimaging of Acupuncture in Fibromyalgia: Insights into Mechanisms and Clinical Trial Design.
- *Stillbirth Definition and Classification System: Developing an International Consensus,* which gathered international experts and researchers to address the definition of stillbirth, the goals of a stillbirth classification system, and the necessary criteria for

assigning cause of death. The development of an agreed-upon classification system should facilitate analyses of larger amounts of stillbirth information with greater sample sizes, allowing for more robust conclusions from the international research currently conducted on stillbirth.

- *2010 NHLBI/LAM Foundation International Lymphangioleiomyomatosis) Research*, which reviewed research developments in lymphangioleiomyomatosis, aimed to attract new investigators to LAM research, identified promising new LAM research directions, and attempted to reach consensus on difficult clinical issues. The 2010 LAM Research Conference was needed to sustain the momentum that has brought the LAM field in a relatively short time from obscurity to trials based on molecular targets. The advances in understanding of the molecular and cellular basis of the disease have been remarkable, and the basic science community, the clinical science community, and LAM patients are all aligned to continue to address this problem in an aggressive, cooperative, and intelligent manner. The 2010 LAM Research Conference charted the course for new research directions in LAM, assisted the clinical community in arriving at consensus on the optimal management of LAM, and continued to provide hope to women affected by this ravaging disease.
- The *2007 LAM Foundation Lymphangioleiomyomatosis International Research Conference* brought together basic scientists working in different disciplines pertinent to lymphangioleiomyomatosis with pharmaceutical experts from industry, clinical investigators, patients, and other advocates to advance research on understanding and treating LAM. The ultimate goal was to identify new targets for therapeutic interventions.
- *Mental Health Promotion and Injury Prevention in the Context of a Diverse, Transforming China* addressed issues including: (1) risk factors for suicide and injury mortality in Chinese women, (2) the implications of rapid economic and technological development for risk of suicide and injury in men *and* women, and (3) ethnic differences.
- *Orphan Mechanisms of Primary Ovarian Insufficiency: Passion for Participatory Research.* Galactosemia is a rare metabolic disorder that is associated with the development of primary ovarian insufficiency. Despite appropriate dietary restriction of galactose, many girls and young women develop primary ovarian insufficiency. Participants addressed mechanisms of ovarian toxicity related to galactosemia, induction of puberty in girls with galactosemia who have primary ovarian insufficiency, hormone replacement in women with galactosemia who have primary ovarian insufficiency, mental health aspects of primary ovarian insufficiency as it relates to galactosemia, and pregnancy in women with galactosemia.
- *Cognitive and Neuroplastic Changes Following Surgical Hemispherectomy and In Utero Strokes Affecting an Entire Hemisphere*. The main goal of this conference was to ascertain the state of the art in hemispherectomy outcome as a precursor to preparing a protocol to test a number of assumptions. To that end, leading neurologists, neurosurgeons, and cognitive neuroscientists were invited to discuss their experience with patients receiving hemispherectomies.

- The *Preconception Care Research: Improving Birth Outcomes and Reproductive Health Conference,* which brought together a broad spectrum of experts, including clinicians and basic and behavioral scientists, to define a multidisciplinary framework for developing a research agenda in preconception care research.
- *Opsoclonus Myoclonus Syndrome (OMS) Workshop*. This disease is also more prevalent in women than in men. The goals of the OMS Workshop were to discuss the various issues and special challenges associated with the diagnosis, prognosis, and treatment of OMS; identify strategies to improve research and clinical collaborations and resource sharing in the United States and internationally; examine the disease course of pediatric and adult-onset OMS; discuss current therapeutic strategies; and look at immune mechanisms of OMS. The Workshop resulted in identification of basic and clinical research needs and setting of research priorities, and is expected to facilitate the development of clinical protocols.

National Toxicology Program

The National Toxicology Program, an interagency testing program headquartered at NIEHS, has listed more than 40 chemicals in its Report on Carcinogens because they have been found to cause tumors in laboratory animals. These include pharmaceutical products such as diethylstilbestrol, a synthetic form of estrogen that was used to prevent miscarriages, chemical solvents and flame retardants, and a variety of chemicals used in the manufacturing of dyes, rubber, vinyl, and polyurethane foams. (NIEHS)

Reference:
http://ntp.niehs.nih.gov/

Genetic Determinants of Sex

Sex Determination: More Subtle and More Precise Than Previously Thought

The Drosophila doublesex gene, a component of the genetic hierarchy that determines sex, is transcribed differently in males and females. The simplest model for how doublesex works is that downstream genes are repressed by male-specific doublesex transcripts and activated by female-specific doublesex transcripts, or vice versa. Although some genes are regulated in an "all or nothing" way by doublesex, a University of Southern California team discovered that most genes regulated by doublesex are expressed at different levels in males and females, rather than being on in one sex and off in the other. The team also demonstrated that many genes are expressed at different levels in males and females only during very limited periods during development. It would not be surprising if the conclusions drawn from these findings—that differences in gene expression that determine sex are more subtle and more ephemeral than previously thought—were also applicable to human sex determination, since the process in humans is also determined by a gene hierarchy, some components of which are expressed differently in males and females. (NIGMS)

Reference:

Lebo MS, Sanders LE, Sun F, Arbeitman MN. Somatic, germline and sex hierarchy regulated gene expression during Drosophila metamorphosis. *BMC Genomics*. 2009 Feb 13;10:80.

X Chromosome Genes More Active, Variable in Females

An analysis of the female X chromosome has led to surprising results showing that not only are genes on this bundle of DNA more active than once thought, but that their activity patterns vary greatly from woman to woman. Through sequencing, scientists have found that the X chromosome contains 1,098 protein-coding genes, compared with the male Y chromosome's 78. With females having a double dose of X-linked genes (they have two X chromosomes while males have an X and a Y), researchers have long believed that most genes on one of the X chromosomes are inactivated. But researchers have now shown that at least 15 percent of an X chromosome's genes escape this inactivation. The researchers also found that gene activity varies greatly from woman to woman. This new information could lead to a better understanding of individual health differences, as well as the 300-plus diseases linked to the X chromosome. (NIGMS)

Reference:

Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature*. 2005 Mar 17;434(7031):400-4.

Additional NIH Resources

NIH OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health, established in September 1990 within the Office of the Director, NIH:

(a) Advises the NIH Director and staff on matters relating to research on women's health

(b) Strengthens and enhances research related to diseases, disorders, and conditions that affect women

(c) Ensures that research conducted and supported by NIH adequately addresses issues regarding women's health

(d) Ensures that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH

(e) Develops opportunities for and supports recruitment, retention, re-entry, and advancement of women in biomedical careers

(f) Supports research on women's health issues.

ORWH works in partnership with the NIH Institutes and Centers to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community. ORWH works collaboratively with the Advisory Committee on Research on Women's Health, which comprises physicians, scientists, and other health professionals; and the Coordinating Committee on Research on Women's Health, which is composed of the NIH Institute and Center directors or their designees.

ORWH, in collaboration with NIH and the extramural scientific and public advocacy communities, has undertaken strategic planning and the resulting publication is entitled, Moving into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research.

WOMEN'S HEALTH RESOURCES WEB PORTAL

The NLM Division of Specialized Information Services, Outreach and Special Populations Branch has partnered with ORWH to create the Women's Health Resources Web Portal (*http://www.womenshealthresources.nlm.nih.gov*). This portal gives researchers and consumers access to the latest information in a centralized location about significant topics in women's health from scientific journals, peer-reviewed sources, NIH Institutes and Centers, and health news sources. The portal focuses on health topics and the NIH Priorities for Women's Health to identify research initiatives and overarching themes. The Health Topics section is organized by disease or condition categories, and an A to Z index is available to provide consumers with an easy way to locate specific health topics. The NIH Priorities for Women's Health section is created from the annual recommendations put forth by the CCRWH and ACRWH. The topics for this section include lifespan, sex/gender determinants, health disparities/differences and diversity, and interdisciplinary research. NLM has created specific user-friendly strategies for these topics to ease searching within ClinicalTrials.gov and PubMed. The portal is also using social media to connect with the public for health awareness campaigns. (NLM)

Appendix: NIH Reports on ORWH and NIH Support for Research on Women's Health

NIH Support for Research on Women's and Men's Health Issues: FY 1988, 1989, 1990.

NIH Support for Research on Women's and Men's Health Issues: FY 1991 and 1992.

NIH Support for Research on Women's Health Issues: FY 1993-1994.

Report of the Office of Research on Women's Health and of NIH Support for Women's Health Issues: FY 1995-1996.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY1997-1998.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY1999-2000.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY2001-2002.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY2003-2004.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY2005-2006.

Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health Issues: FY2007-2008.

To order copies of ORWH reports or other ORWH publications go to http://orwh.od.nih.gov/pubs.html

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