

40th Meeting of the Advisory Committee on Research on Women's Health (ACRWH)

October 20, 2015, 9 a.m. to 5 p.m.

Wilson Hall, Building 1

National Institutes of Health Main Campus, Bethesda, MD

Janine Austin Clayton, M.D., *Chairperson*

Terri L. Cornelison, M.D., Ph.D., *Executive
Secretary*

Jill B. Becker, Ph.D.

Chloe E. Bird, Ph.D.

Wen Jun Chen, M.D.

Geert de Vries, Ph.D.

Carmen R. Green, M.D.

Angela D. Kashuba, B.Sc.Pharm., Pharm.D., DABCP

Carolyn M. Mazure, Ph.D.

Valerie C. Montgomery-Rice, M.D.

Heidi Nelson, M.D., M.P.H.

David C. Page, M.D.

Mary H. Palmer, Ph.D., RNC, FAAN, AGSF

Judith G. Regensteiner, Ph.D.

Connie M. Weaver, Ph.D.

Gerson Weiss, M.D.

Teresa K. Woodruff, Ph.D., *via teleconference*

Call to Order

Introduction of New Members

Janine A. Clayton, M.D., NIH Associate Director for Women's Health

Director, Office of Research on Women's Health (ORWH)

Dr. Clayton opened the meeting with introductions and then read the confidentiality and conflict of interest procedures for special government employees. Committee members are classified as special government employees when they are at the meeting.

Dr. Clayton announced that Terri L. Cornelison, M.D., Ph.D., the ORWH associate director for clinical research, has been appointed the ACRWH executive secretary.

Committee members introduced themselves.

Dr. Clayton noted that two new members have joined the ACRWH: Carmen Green, M.D., and Connie M. Weaver, Ph.D.

Dr. Green is the University of Michigan Health System inaugural associate vice president and associate dean for health equity and inclusion. She is a professor of anesthesiology, obstetrics and gynecology, and health management and policy. Her expertise in pain management is expected to be helpful to the committee. She is a member of the National Academies.

Dr. Weaver is a distinguished professor and head of the Department of Nutrition Science at Purdue University and founder of the Purdue Women's Global Health Institute. She is a member of the National Academies. Dr. Weaver's research interests are in mineral bioavailability, calcium metabolism, and bone health, which are critical issues in girls' and women's health.

ORWH Director's Report

Dr. Clayton

Congressional recognition

U.S. Senators Barbara Mikulski (D-MD) and Susan Collins (R-ME) put forth Senate Resolution 242, congratulating ORWH on its 25th anniversary and the women's health advances it has supported. The U.S. House of Representatives passed a similar resolution, Resolution 458.

The resolutions encourage ORWH to continue to promote research that considers sex as a biological variable. Dr. Clayton encouraged the committee to read the resolutions, which can be found in the [25th anniversary](#) materials at the ORWH website.

Information about the 25th Anniversary Congressional Briefing, sponsored by Women's Policy, Inc., will also be uploaded to the ORWH website soon. Dr. Clayton expressed gratitude to the congresswomen and others who led the effort to establish the office in 1990 and to demand that women be included in clinical research.

New policy in preclinical research

The mission at NIH is to improve human health through research. This is not achievable for all people unless both sexes are studied. In the 1990s, NIH began working to have women included in clinical research. Women now account for more than half of all clinical research participants.

In 2014, Dr. Clayton and NIH Director Francis S. Collins, M.D., Ph.D., published an article in *Nature* regarding the need to include both sexes in preclinical research involving vertebrate animals and cells. Scientists, media, professional societies, industry, academia, journal editors, Congress, and nonprofits must all be involved to ensure success for the NIH policy. When the policy was announced, journalists who contacted Dr. Clayton were surprised that studying both sexes was not standard practice in preclinical research.

NIH issued a notice in October 2015 saying that applicants must explain how relevant biological variables such as sex will be included in research designs and analyses for studies in vertebrate animals and cells. Both sexes must be included unless there is strong justification from the scientific literature, preliminary data, or other relevant considerations to study only one sex. Reviewers must consider the inclusion of both sexes when evaluating grant applications due on January 25, 2016, and later.

The policy implementation includes the publication of new frequently asked questions (FAQs) on October 14, development of NIH internal staff training, and updating of application instructions and funding opportunity announcements. The first research and career development applications are due on January 25, 2016, and the first fellowship and training grant applications are due on May 25, 2016. The first round of scientific review takes place in the spring of 2016, and the first awards are made in the fall.

Rationale for policy

Improving women's health depends on having sex differences included in research. One example of a study of clinical importance is the Women's Health Initiative (WHI), launched in 1991, is a study that provided new information about women's health and overturned some commonly held beliefs that had never before been rigorously tested. The WHI still bears fruit and was an example of a smart investment in science that improved women's health.

U.S. women have the lowest probability of surviving to age 50 among women in 21 high-income countries. While the probability of living until age 50 is increasing in those other countries, it has plateaued in the United States. It is important to find out what factors are at play in producing these results.

ORWH sponsored the meeting "Raising the Bar—The Health of Women in America" in partnership with the National Academies of Sciences, Engineering, and Medicine. The meeting's purpose was to identify the factors that explain the comparative deficiency in the health of U.S. women. A report will be out in December.

ORWH research funding

ORWH awarded about \$32 million in fiscal year (FY) 2015:

- 29 percent on the Specialized Centers of Research (SCOR) program
- 24 percent on administrative supplements
- 20 percent on projects co-funded with other NIH Institutes and Centers (ICs)
- 18 percent on the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program
- 8 percent on the R56 program
- 1 percent on Women's Reproductive Health Research Career Development Award

Investigators used the funding to supplement funding they had already received from 17 NIH Institutes and one NIH Center. The funds extend the studies to include sex as a biological variable. The majority of the studies would not have looked at sex as a variable without the supplement. Other investigators used the money to analyze existing data by sex or to add subjects to increase the statistical power of the study to allow a sex analysis. Most of the supplement went to preclinical research projects.

Among the projects topics that received a supplement were the following:

- Notch signaling in osteocytes
- Sex differences in the cannabinoid regulation of energy homeostasis
- Mechanisms underlying persistent lentivirus replication in follicular T cells

During the current fiscal year (FY 2015), the NIH Common Fund also offered supplements for sex differences research. Some of the projects receiving supplements are Genotype-Tissue Expression (GTEx) and Human Health and Heredity in Africa (H3Africa).

Expectations for investigators

The NIH policy requires investigators to disaggregate and report data by sex to help provide greater knowledge about sex-specific differences. Investigators have asked ORWH how they get started in considering sex as a biological variable. The answer depends on the study's context. Investigators should start by doing a literature search on their topic, adding the terms "sex," "gender," "male," and "female" to their search. Investigators should include both females and males in test groups and should report sex-based data and any identified sex-based influences.

Even when a research project on a disease or condition shows no differences between males and females, there may still be a clinically relevant reason to do the study. For example, the mechanism underlying progression or treatment may be different for males and females, even if the outcome is the same.

Dr. Clayton provided some resources for studying both sexes using various research methods, including a randomized block design, a four-core genotype model, knockout mouse models, and a hormone depletion model. NIH is confident that investigators will develop appropriate ways to factor sex into their research. NIH has identified and collected a range of [online](#) resources for investigators.

This anniversary year has been a whirlwind, but it is only the beginning of the work to implement the policy, which is necessary because issues related to sex differences were not being addressed.

Dr. Clayton said that her hope is that in 10 years, investigators will automatically think about sex differences when designing their studies. The policy will trigger discoveries that will benefit everyone.

Discussion

Geert de Vries, Ph.D., asked whether there has been pushback on the policy from basic scientists.

Dr. Clayton said that many have said that the policy will require them to double the number of animals that they use and that it makes their work more costly. Including sex as a biological variable does not necessarily increase the number of animals the scientist must use, Dr. Clayton said. In many cases, the scientist could use the same number of animals, but half would be female and half would be male.

Although there have been complaints that the new policy makes studies more expensive, it is important to remember that not including both sexes also has a cost. Research has a less firm knowledge base when one sex is excluded from preclinical research. The results of the research could lead to patients being exposed to treatments that will not help or that could be harmful. Investigators must be transparent about their research, including reporting data disaggregated by sex.

Louise McCullough, M.D., said that ovariectomized animals do not provide a good model for conditions such as stroke. Aging and hormonal changes are important in stroke, and using ovariectomized young animals is not a good model. Investigators must select the most appropriate animals to model the disease. Dr. Clayton agreed and said that in some studies, age is an important variable. The investigator should budget for having to use older animals.

Valerie C. Montgomery-Rice, M.D., asked about the \$32 million that ORWH spends on research. Is ORWH working with other ICs to build research capacity with that money? How will ORWH measure the return on that investment?

Dr. Clayton said that every project is done in collaboration with an IC, so ORWH is leveraging their funding. These are projects that would not get done if no other ICs were involved.

Measuring the impact of the administrative supplements is not a straightforward matter. ORWH is open to different ways to measure impact. The most important outcome is to have scientists use sex as a biological variable. ORWH can track publications as one way to see the return on investment. ORWH did consider whether to provide funding support for something that an investigator should be doing anyway. The new policy requires including sex as a variable, so ORWH will not continue to provide this supplementary funding for much longer.

Dr. Weaver asked whether there is a way to track progress on the implementation of the policy.

Dr. Clayton said that the Office of Extramural Research is developing a way to track that.

Carolyn M. Mazure, Ph.D., said that she would like to return to the issue of statistical power and whether studies might be underpowered as a result of including both male and female animals.

Dr. Clayton said that this is an important discussion that should be deferred to later in the meeting when there is more time to discuss it.

NIH Leadership Presentation

*Kathy L. Hudson, Ph.D., NIH Deputy Director for Science, Outreach, and Policy
Precision Medicine Initiative Cohort Program (PMI-CP)*

The PMI-CP is still being designed, and NIH is seeking advice from scientists. The program was created because many diseases lack effective prevention strategies, diagnostics, or treatments, and the options that are available do not take into account genetic, lifestyle, and environmental differences between

individuals. Participants in research are treated as subjects, not partners, and it takes too long for research findings to become part of clinical practice.

President Obama announced the PMI during the State of the Union address in January. Instant polling during the address found that the PMI was the most positively rated moment of the address.

The core values of the PMI are as follows:

- Participation is open to all.
- Participants will be viewed as partners.
- Information gathered will be made accessible as the project proceeds.
- Data will be shared.

Background on the PMI-CP

NIH has been charged with building the PMI-CP, a longitudinal national research cohort of at least 1 million volunteers. The program will become a model of new progressive research policies for other new research projects to adopt.

Technological advances make this a good time to develop the PMI cohort. The cost of sequencing the human genome is a fraction of what it cost 10 years ago: less than \$5,000, compared with \$22 million. The genome can be sequenced in less than 1 day, compared to the 2 years that it took a decade ago. Other helpful developments are the adoption of electronic health records (EHRs) in more than 90 percent of hospitals.

NIH will spend \$200 million for PMI in FY 2016, including \$130 million for the cohort program, \$70 million to the National Cancer Institute to identify genomic drivers in cancer and develop more effective approaches to cancer treatment, and \$10 million to the Food and Drug Administration (FDA). In March, NIH convened a working group to plan the cohort. Questions include whether the cohort should be built from scratch or incorporate existing cohorts, how to capture the diversity of the U.S. population, and what data types should be included.

Dr. Hudson listed the working group members, who include academics, representatives of large health care systems, advocacy organizations, and technology experts. The working group will hold a series of workshops to gather input on what scientific questions should be asked and to work on issues such as recruitment strategies, participant engagement, and health equity. A request for information is also being prepared.

PMI-CP aims

Scientific opportunities offered by the program include the development of quantitative estimates of risk for disease by integrating environmental exposure, genetic factors, and gene-environment

interactions. The program will help identify the causes of variations in response to therapeutics. The program is expected to provide participants with information they can use to improve their own health.

The cohort will emphasize the inclusion of underrepresented groups. Participants may be contacted to take part in secondary studies. There will be two methods of recruitment: volunteers who sign up on their own and those who come in through health care provider organizations who can share information through the EHRs.

The program intends to align with existing data sets when possible. The plan is to collect self-report measures, get baseline health data through a physical exam, obtain access to the EHR, and collect biospecimens (a blood sample). The program will establish a biobank and consider expanding collection of biosamples in the future to accommodate samples for exposure studies and other research. The study may also include sensor data (e.g., activity, calories expended), geospatial and environmental data (e.g., air quality, environmental pollutants), and health care claims data.

As part of the program's transparency, some of the data will be de-identified and made publicly available. Participants will have the right to know their individual data, get ongoing study updates, and see aggregated results.

PMI-CP governance

The PMI-CP will have a single institutional review board (IRB), will set privacy and security standards for data, and will establish safeguards against unintended data release. The program will set policies for sharing data and results. Special policy considerations are being developed for children, participants who might be unable to make decisions for themselves, and participants who become incarcerated.

There will be a PMI-CP director who will report to the NIH Director. There will be an advisory board, an executive committee, and a steering committee with five subcommittees. Participants will be represented in all aspects of the study, including governance, research design, and the IRB. There is no firm timeline for implementation, but the program will soon launch volunteer enrollment.

Women use health care more than men, are the primary health care decision makers for their families, and have a large health-related online presence. One approach might be to recruit women and have them recruit their mothers and daughters. It is important for women to participate in the program so that results can address women's health across the lifespan and eliminate health disparities between men and women. The cohort program can also train the next generation of women Principal Investigators (PIs), helping to reduce the gender inequality in the workforce.

Discussion

Dr. Nelson said that she is concerned that the EHRs differ across health care organizations and do not integrate well with each other. That has been a problem in patient care. How will that issue be

addressed? Dr. Hudson said that the criticism is legitimate. The different EHRs lack interoperability. The PMI-CP has focused on this issue and expects to help create a solution.

Dr. Mazure asked which researchers will have access to the data. Dr. Hudson said that some data will be freely available. There will be multiple levels of more sensitive or identifiable information available to qualified researchers. Dr. Mazure asked about IRB approvals. Dr. Hudson said that there will be a single IRB, located at NIH, that is being put together now. The cohort participants will provide broad consents so that they do not need to be re-consented for every sub-study. Other sub-studies will require that the participant give specific consent. The program is also drawing up policies and legislation regarding enforcement actions that can be taken when individuals misuse the information from the cohort.

Dr. Montgomery-Rice said that she is interested in engaging diverse populations in the research. Previous studies have had difficulty enrolling participants from underrepresented groups. It will be important to have the study staff reflect the diverse groups that must be enrolled. Dr. Hudson agreed and said that PMI-CP has done a study about concerns that people have about participating in studies. People express concern about an experimental intervention. The cohort program has to make clear that this is an observational study. In terms of diversity, the cohort program will have community leaders who will be asked to help recruit directly through the grassroots. The program has already started conversations with community leaders. Recruitment is going to have to be community focused. The program is reaching out to people who have expertise in recruitment.

Dr. Montgomery-Rice said that the Clinical and Translational Science Awards (CTSA) program had community cores, but they became diluted over time. Dr. Hudson said that partnering with academic organizations is not the best way to involve communities. NIH has drawn some lessons from the National Children's Study, whose PI was at NIH, not out in the community. The study was too rigid, too early. These and other lessons have been learned from that study and from successful large cohort studies, such as the WHI.

Dr. Bird asked what approach the cohort would take to ensure a balanced and diverse group of participants. Will they stop taking volunteers of a certain type when they have reached the target number for that group and then target recruitment to other groups who are not volunteering so readily? Also, many demographics must be accounted for, including income, geographic area, and racial and ethnic groups. Dr. Hudson said that the early days of this program would likely be an experiment in participant engagement. There is some possibility that certain types of people will sign up, raising the issue of whether there should be allocations. There has been some interest from advocacy groups for people with a particular disease; could the cohort have too many people with one type of disease? The cohort program took a survey and found that racial and ethnic groups' interest in the study did not differ. However, older people appeared to be more reluctant. The cohort will be recruited in part from health care organizations, so it will be possible to obtain some diversity through those organizations.

Dr. Green said that LGBTQ (lesbian, gay, bisexual, transgender, and questioning) participants should be included when thinking about achieving diversity. Getting a diverse group of participants will produce

higher-quality science. An effort to achieve diversity has to occur early in the recruitment process. Using a community advisory board could help make recruitment more successful. There has been a history of racial and ethnic minorities not volunteering, and when racial and ethnic minorities have volunteered, they have not received the benefit.

Dr. Hudson said that the working group held a session on community engagement and had a very lively discussion. It is important that members of underrepresented groups be at the table, so people who have expertise in community engagement are overrepresented on the IRB, the community advisory board, and the working group. The working group also considered having a separate group work exclusively on community engagement but decided that it was better to have the entire working group be responsible.

Dr. Green said that the members of the working group and IRB are academics, who may not have the pulse on the everyday community. Dr. Hudson said that these are difficult issues, so NIH has looked at outside models and are seeking input from others. Historically, it has been difficult to recruit participants for research.

Break

NIH Legislative Update

Adrienne Hallett, M.T.S., Associate Director for Legislative Policy and Analysis and Director of the NIH Office of Legislative Policy and Analysis

Leadership in Congress is going through a generational change. Sens. Tom Harkin (D-IA) and Arlen Specter (R-PA) used to shepherd funding for NIH, but they have left Congress. There are new leaders, including some women, who are in positions of power with regard to appropriations.

Because of these generational changes, now is a good time to educate key members of Congress about NIH's work. Also, the average stay of a congressional staffer is 18 months, so NIH is always educating staffers about what NIH does and why.

Ms. Hallett said that the 114th Congress has new leaders on the appropriations and authorizations committees that oversee NIH funding. Sen. Roy Blunt (R-MO) is the chair of the Senate Subcommittee on Labor, Health and Human Services, and Education, while Sen. Lamar Alexander (R-TN) is the chair of the Senate Committee on Health, Education, Labor, and Pensions. Both are new to those roles. Sen. Patty Murray (D-WA) is the new ranking member in both those committees.

The House passed the 21st Century Cures Act, a bill meant to accelerate the discovery, development, and delivery of cures for disease. The bill focuses on NIH and the FDA, establishing a fund of \$1.75 billion over the course of 5 years for NIH. The bill also has other provisions of interest to NIH, including reauthorizing NIH at \$31.8 billion in FY 2016 and \$33.3 billion in FY 2017. The Senate Committee on

Health, Education, Labor and Pensions is expected to act on the bill this fall. The final bill would likely come out next year.

On October 29, the House is expected to elect a new Speaker. On November 3, the nation is expected to reach the debt limit. Government funding expires on December 11; a continuing resolution or a spending bill will be needed to keep the government going. There is general agreement on what to spend money on, but there is not much agreement on where the money should come from.

The House appropriations bill cuts Labor, Health and Human Services (HHS), and Education funding by \$3.7 billion but increases NIH funding by \$1.1 billion. The Senate bill decreases Labor, HHS, and Education funding by \$3.6 billion but increases funding NIH by \$2 billion. In both houses, the increase to NIH funding is financed by cuts to other areas within Labor, HHS, and Education. Some of the cuts may be to the Patient Protection and Affordable Care Act.

Discussion

Dr. Regensteiner asked what will happen to the 21st Century Cures Act in the Senate. Ms. Haslett said that there is strong support in Congress to fund NIH and that Sen. Murray has been a champion for NIH. But the sides will have to agree on offsets, and it is up in the air.

ORWH Interdisciplinary Programs Update

Building Interdisciplinary Research Careers in Women's Health (BIRCWH)

Terri Cornelison, M.D., Ph.D., Associate Director for Clinical Research, ORWH

The BIRCWH program is a career development program. ORWH developed the interdisciplinary program in 1999 to increase the number of researchers in women's health. The program pairs junior faculty members with senior investigators who act as mentors.

One of the program's primary goals is to support scholars by providing them with protected time to do their research. Since its inception, BIRCWH has made 87 awards to 43 academic institutions. Twenty-four programs are currently active. The program has trained 476 scholars, 80 percent of whom are women. More than half of the scholars have been successful at obtaining NIH funding.

The total investment in the program so far has been \$124 million, including \$5.7 million in FY 2015. ORWH manages the programmatic aspects, while the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) manages the grants. During the past 10 years, other ICs and agencies have provided funding support to the program.

Half of the BIRCWH scholars have had a Ph.D., more than one-third have had an M.D., and 11 percent have had an M.D./Ph.D. The scholars represent a range of fields, including the biological and biomedical

sciences, health sciences, and medicine. Nearly half have achieved a rank of associate professor or full professor, and many have achieved leadership positions in academia.

BIRCWH scholars have been successful at competing for NIH grants: 78 percent of BIRCWH scholars have submitted at least one grant application, and 64 percent have obtained at least one grant. About 44 percent of scholars who submitted an R01 application were funded.

Overall, women had greater success at receiving grants. However, when R01 application rates were analyzed separately, there was no difference in success rates between male and female scholars.

Specialized Centers for Research on Sex Differences (SCOR)

Leah Miller, Ph.D., M.B.A., Research Program Officer, ORWH

ORWH established SCOR in 2002 in collaboration with six ICs and the Office of Women's Health at the FDA. The SCOR program is meant to advance interdisciplinary studies on the influences of sex and gender on women's health. The 11 SCOR centers support translational projects that bridge basic and clinical research. Since 2002, \$132 million has been invested in the program.

Research topics have included addiction, smoking, urinary tract infections, and pelvic floor disorders, among others. This is a P50 program, and the awards are for 5 years.

Some of the most highly cited SCOR publications include a study on bacterial community variation in the body (765 citations) and a study comparing anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse (207 citations).

The majority of SCOR publications are published in high-impact journals, which speaks to the importance of the research. The program has advanced sex differences research at the institutions where the centers are located.

ORWH is evaluating the program, which is standard NIH practice for all programs. The results of the evaluation will be used to make decisions internally.

Discussion

Dr. Montgomery-Rice asked whether there were difference in funding success between M.D. versus Ph.D. scientists. She also asked whether racial and ethnic differences of the scholars had been tracked and how many had become PIs. Dr. Cornelison said that there is not much difference in the success rate of M.D.s versus Ph.D.s in BIRCWH, but Ph.D.s apply more often. Juliana M. Blome, Ph.D., M.P.H., of ORWH said that ORWH is evaluating the BIRCWH program and is using surveys and information available at NIH to obtain information on the racial and ethnic breakdown of scholars and PIs. ORWH could share those results at the next ACRWH meeting.

Action Item: Share information regarding the racial and ethnic breakdown of BIRCWH scholars and PIs.

Dr. Montgomery-Rice suggested that ORWH also examine the pilot grants, which are instrumental to getting young scientists into the funding pipeline. Dr. Blome said that ORWH is attempting to collect that information. However, once scholars leave these programs, they can become difficult to track.

Dr. Green asked why these programs target only the junior investigators. Dr. Clayton said that these programs are meant to develop a cadre of female investigators and that the transition point from junior investigator has been identified as a key point where investigators may be lost. The program focuses on helping them through that transition. However, it is also true that there are some troublesome transition points further along the pipeline.

Dr. Green also said that physician/scientists may take longer in their training, so the timing of some of these awards may not work well for them. Dr. Clayton said that the issue of physician/scientists is being considered by the Advisory Committee to the Director. ORWH will give further thought to the issue.

Gerson Weiss, M.D., said that the BIRCWH program's weakness is that there are only a limited number of sites. Scholars interested in the program would have to move to one of those centers, which is not possible for everybody. This decreases the number of women and minorities who take part in research on women's health. Dr. Cornelison suggested that it is better to have the programs than not.

Dr. Weiss also asked about the salary, which must be competitive to attract scholars. Dr. Cornelison said that the scholars earn \$125,000.

Dr. Clayton said that there are other programs through which early career investigators interested in women's health could be funded. BIRCWH is being evaluated right now, and this feedback will be considered during the evaluation.

Dr. Mazure said that her understanding is that ORWH has decided to delay release of the SCOR RFA (Request for Application) because of the evaluation. Will bridge funding for the existing sites be made available? Dr. Miller said that that will be determined on a case-by-case basis. Dr. Mazure said that it is important to let the centers know as soon as possible to ensure the continuity of these programs.

The discussion next turned to the question that Dr. Mazure had raised earlier about including males and females in preclinical studies. What if an investigator does not have sufficient numbers of each sex to do a properly powered statistical analysis?

Dr. Clayton said that they are not encouraging investigators to overstate their results, but if there appears to be a sex difference, it could be stated with the note that there was not sufficient statistical power to draw a conclusion. The value of including both sexes is that it could inform later studies and the data from several studies could be combined so that there is adequate statistical power to do the analysis.

However, whenever an investigator suspects there may be a sex difference, there should be adequate numbers of males and females included in the design.

Dr. Page said that some of the distinctions are subtle. There is a fine distinction between studying both sexes and studying sex differences. This distinction may not be widely understood, especially in the context of studying sex as a biological variable.

Dr. Clayton said that there is widespread misunderstanding about what the terms mean. She clarified that even when an experiment is not powered to detect sex differences, sex could still be considered as a biological variable (e.g., by using a factorial design), so it is still possible to learn something about both sexes. Dr. Page said that he understands the point, but the problem is that it takes a minute to explain this difference to colleagues who have already formed an opinion about what it means.

Dr. Clayton said that this question has come up repeatedly, including in response to the request for information that NIH issued. Many investigators asked for more information. ORWH is producing more materials, including an FAQ section, to help clarify some of this.

Dr. Clayton said that she would appreciate the committee's help in drafting material to explain this concept. A journal article that describes how sex differences can be accounted for in one particular field will soon be published. The problem is that every field is different, requiring different approaches. ORWH needs experts in more fields to help clarify the issue. The details depend on the context of the study, so ORWH cannot give quick guidance, but ORWH has been working hard on the messaging.

Dr. de Vries said that studying sex differences would require greater numbers of animals, which would increase the cost. One cannot draw a conclusion about sex difference without the statistical power. But even if the study finds no sex differences, that is an important result. The problem with reproducibility may trace back to investigators not publishing when no effect is shown.

Dr. Clayton said that NIH has been working with journal editors to standardize requirements for the reporting of sex in preclinical research. In the end, reporting by sex, even when not statistically powered, will help build a knowledge base about male and female biology. It is important to remember that not investigating sex differences degrades the quality of the science.

Dr. de Vries said that it would be important for the ORWH website to give some real-life examples and to note that a study needs to be powered to examine sex differences only when a sex difference is expected. The policy also needs teeth, by having funding at stake if the policy is not followed.

Dr. Bird said that it is important to start finding out where there might be sex differences. Much remains unknown about sex differences, but investigators must begin capturing that information. This has to be reported and made standard. If NIH takes a stand on that, it will help.

Dr. Becker suggested that the first time that a particular experiment is done, it should be powered to see whether there is a sex difference. If there is none, subsequent experiments would not need to be sufficiently powered.

Lunch

ORWH 25th Anniversary Celebration of Science

Introduction to Afternoon Session

Dr. Clayton

Twenty-five years ago, a group of congresswomen held a press conference to express concern that women were not being included in clinical trials. Sen. Mikulski was one of those women and has continued to be a strong supporter of women's health and of ORWH in the intervening 25 years. She had been scheduled to make a presentation but was detained by business on Capitol Hill.

Dr. Clayton also noted the presence at the meeting of Vivian W. Pinn, M.D., ORWH's first director. Dr. Clayton announced that, in honor of Dr. Pinn, NIH has established the Vivian W. Pinn Seminar Series, to be delivered annually during National Women's Health Week.

NIH's 25-year investment in ORWH has been a smart one, leading to advances for men's and women's health. The next portion of the program will include a panel of biomedical researchers who will talk about sex as a biological variable. There will also be a presentation on a new online resource to support clinical researchers in their efforts to engage, recruit, and retain women in clinical trials. The agenda reflects the range of activity that ORWH supports. Dr. Clayton thanked those in attendance for coming to show their support.

Introduction of a Film Clip Featuring Sen. Barbara A. Mikulski

Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

Although Sen. Mikulski was unable to attend the ACRWH meeting as planned, the committee watched a film clip of the talk that she gave at the celebration of the ORWH anniversary sponsored by Women's Policy, Inc. In a short presentation before the film, Dr. Tabak thanked ORWH for their hard work and accomplishments. The office has formed strong working relationships with other government agencies and advocacy groups. NIH's ability to reach its goal of achieving health for all Americans depends on this kind of teamwork.

ORWH continues to address issues critically important to the health of women, ranging from intimate partner violence to heart disease and stroke to cancer. Continual vigilance is needed to ensure that women are included in clinical research, especially women of color.

Dr. Tabak introduced the film clip, saying that Sen. Mikulski is an extraordinary leader and partner who has been dedicated to women's health and to ORWH.

Discussion

Dr. Regensteiner said that ORWH is productive and has broadened its work by addressing basic research, but the office needs more resources: Its dreams are big, and it should receive more funding.

Dr. Pinn said that the scientific community should lobby on behalf of ORWH and NIH through professional societies or by speaking to their representatives in Congress. She also said that one of the ACRWH's functions is to make sure that there is enough funding.

Dr. Green suggested that the committee create a lectureship series in Sen. Mikulski's honor on women in leadership. This item could be discussed in the future. Dr. Palmer and Dr. Montgomery-Rice supported the suggestion.

Dr. Clayton returned to the discussion that had taken place before lunch regarding the study of sex differences and its relationship to scientific rigor. Some studies include women, but the analysis of the data by sex does not appear in the publications. Fewer than one-third of NIH-funded clinical studies have sex-specific data mentioned when they are published, even though some include large numbers of women.

The study of both sexes increases scientific rigor and is the best way to turn science into health. Studies must also establish sex-relevant inclusion criteria, such as in heart failure clinical trials, because men and women present differently in cases of heart failure. Research projects should have recruitment goals for women. Furthermore, when using an animal model, scientists have to use the appropriate model.

Dr. Nelson said that sometimes studies are not published, meaning that a lot of data are never published. Accessing and pooling those data could be useful, even for a trend analysis. Dr. Clayton said that the data should be made available, but how can that be done? NIH cannot do this alone. It will be necessary to continue the conversation with stakeholders.

Dr. Weaver raised the issue of clinical trials in hospitals excluding women of childbearing age because they might become pregnant. Hospital officials see it as a liability. What can be done to stop excluding women of childbearing age from these studies?

Dr. Clayton said that ORWH sponsored a workshop on the inclusion of pregnant women in clinical research. It focused on pregnant women, not women who could become pregnant, because the latter is a very large group of people. One of the calls to action was to use study designs that could incorporate pregnant women. Use of the EHRs would be one such design. This is an area of interest to ORWH and NICHD.

A representative from the FDA said that her agency wants more information on women who take medications during pregnancy. The FDA has encouraged the use of pregnancy registries and encourages women to enroll. She also said that the FDA does not exclude pregnant women from pharmaceutical research.

Dr. Montgomery-Rice said that it is important to educate the hospitals' leadership if women of childbearing age are being excluded. Certain trials are appropriate for pregnant women, and any woman of reproductive age could become pregnant, so this exclusion affects many women.

Dr. McCullough said that women of childbearing age are themselves concerned about their exposure. That has been one reason why women do not want to participate in clinical trials involving pharmaceuticals. But registries could be helpful to follow up in 20 or 30 years on women who do participate in clinical trials.

Dr. Pinn said that there has been recent evidence that pharmaceuticals may also affect sperm. Maybe there will be limitations on clinical trials for men.

Dr. Clayton said that there are concerns about epigenetic modifications. The science and medical community need to learn as much as they can. The committee has made it clear that this is an area of interest, so it will be taken back to ORWH for further consideration.

Action Item: ORWH will consider the issue of the exclusion of women of childbearing age from clinical trials.

Break

Panel Discussion: Sex as a Biological Variable

David C. Page, M.D., Director, Whitehead Institute, Massachusetts Institute of Technology, Moderator

Jennifer Plank, Ph.D., of ORWH introduced Dr. Page.

Dr. Page said that the panel would be an opportunity to talk about sex as a biological variable and the scientific opportunities that this approach presents to understand human health and disease in both males and females. He introduced the panelists and asked them to describe how their careers connect to the question of sex differences.

Heather Cross, D.Phil., Duke University, is the program leader of the Duke University Antibacterial Resistance Leadership Group. Between 42 percent and 55 percent of the participants in their clinical studies have been women. Dr. Cross's previous research was on myocardial infarction (MI) and cell death via calcium accumulation. Her research found a remarkable difference between male and female mice and MI, with females being more highly protected. Her research team would have reached different conclusions if they had not worked with both males and females.

Barbara Stranger, Ph.D., University of Chicago, is in the Genetic Medicine Section. Her field is computational and statistical genetics and genomics. She is part of an NIH-funded analytic group, the Genotype-Tissue Expression project, that is sampling tissues from 1,000 individuals. The project looks at how a gene variant affects different tissues and whether a genetic polymorphism has a different effect in males and females at the transcriptional level. The project is also examining pharmacogenomics questions regarding adverse effects.

Arthur Arnold, Ph.D., University of California, Los Angeles, and Editor-in-Chief of *Biology of Sex Differences*, said that the traditional belief is that cell sex was imposed by influences outside the cell, primarily hormones. When he was studying sex differences in bird brains, he noticed that the differences were not due only to hormones but came from within the cell's nucleus. Using mouse models, he manipulated the sex chromosomes separately from the gonads so that he had XX and XY females with ovaries and XX and XY males with testes. In other words, the chromosomal makeup changed, but the hormonal influences remained the same. Dr. Arnold's team was surprised to find that the cell's sex can make a significant difference in disease outcomes. This is a new idea: that the number of X chromosomes affects disease progression.

Louise McCullough, M.D., University of Texas Medical School, is the chair of the Department of Neurology and a stroke specialist. There is a sexual dimorphism in stroke: Elderly women do worse than elderly men. Dr. McCullough's research has shown that XX and XY cells respond differently to ischemic stress. XX cells do not die as quickly. XY cells are ischemic sensitive. Also, XX and XY cells die by different mechanisms. This demonstrates that men and women can have the same disease by different mechanisms, which helps explain why a drug might work in males but not in females. Investigators should disaggregate the data for males and females, because sometimes a drug will work for one sex but not both. Drugs will be more effective if investigators tailor their preclinical models.

Dr. Page said that the four panelists had already raised many issues and used different approaches, including comparative studies, model systems, and cross-species comparability. He asked whether it is possible to extrapolate between woman and a mouse.

Dr. Arnold said that it is important to approach animal research from both directions: Find the question in women and answer it with the mouse, then test the answer in women. The purpose of comparative biology is to find the principles that apply to humans.

Dr. Cross said that a woman is not a mouse, but a mouse is small and simple, and transgenic versions are available. The comparative approach gives investigators a lot of great ideas. But why do investigators do preclinical trials with only male animals and then use the data as the basis for a Phase I clinical trial that includes men and women? The majority of antibacterial studies are done only in male animals. The Phase I clinical trial is done with male and female patients.

Dr. McCullough gave an example of how failure to include women in an early-phase clinical trial had adverse outcomes for women. The information on carotid endarterectomy surgery was flawed, because the clinical trials had been done predominantly in men. Women's arteries are smaller and more thrombotic, making them harder to bypass or clamp; after about 10 years, it became clear that this surgery should be used only in women with certain symptoms.

The American Heart Association recently came out with sex-specific guidelines for stroke. Another clinical example of the necessity of doing the research on both sexes came from the Women's Health Initiative: Postmenopausal women were given estrogen to reduce stroke risk, because estrogen was thought to be protective, but the hormone increased the risk of having a serious stroke. This was a case of not using the correct animal model in the preclinical phase.

Dr. McCullough used mice that were 20 months old (i.e., senescent) for her stroke research. The animals given estrogen 2 weeks before an induced stroke had a much larger stroke than animals whose estrogens levels had been maintained all along. The study design of older female mice was closer to the real-world model of giving postmenopausal women a course of estrogen.

Dr. McCullough said that she has continued to use animal models because they are simplified systems with parallels to human beings. For example, when animals are socially isolated and a stroke is induced, the stroke will be larger. That shows that there is a biological basis for this effect, but one that cannot be studied in humans.

Dr. Page asked Dr. Stranger how well genome-wide association studies (GWAS) have advanced understanding of sex differences. Dr. Stranger said that there are GWAS for many complex traits, including cardiovascular disease, hypertension, lipids, autoimmune conditions, and neuropsychological conditions. These studies had a balance of males and females, so the data exist and the data sets can be downloaded, but they were not powered to examine sex differences. Many investigators looked informally at sex differences but saw none. Dr. Stranger is now analyzing the gene expression data, much of which is available in databases, for sex differences.

Dr. Arnold said that GWAS data would not show the effect of the Y chromosome in humans, because the effect is always affected by the testes. However, mouse studies do provide information about the genes that are important to follow up on in clinical research.

Dr. Page asked how the panelists became interested in sex differences research.

Dr. McCullough said that she was doing research on stroke and thought that she was doing it wrong, because she kept getting the "wrong" result in her female mice. She tried the same experiment in male mice and got different results. After more than 2 years of using different mouse models and both sexes and still getting the same results, it finally dawned on her that this was a sex difference. She was hooked on the usefulness of the animal model after that.

Dr. Cross said that she was doing postdoctoral research at the National Heart, Lung, and Blood Institute on the effects of sodium–calcium exchange on ischemic injury in the hearts of male and female mice. The male hearts were damaged; those of females showed no effect. Had they not used both male and female mice, they would not have seen this effect.

Dr. Stranger said that she is a population geneticist who became interested in functional genomics and who worked with a Genotype-Tissue Expression project. Looking at sex differences was an obvious line of inquiry.

Dr. Page said that basic science appears to be lagging in sex differences research. Dr. McCullough agreed, saying that there is a tendency to work with a cell line without thinking about the integrated biology. Although Phase III clinical trials have a balance of males and females, the safety and efficacy studies have an overrepresentation of males. There have been recent instances of drugs being taken off the market or restricted because of an unfavorable result in women. For example, women are much more sensitive to Ambien, leading the FDA to issuing a separate set of indications for women.

Dr. Arnold commented that when a sex difference is found, investigators tend to work with the female animals and remove the ovaries. It is much less common to have studies in which testes are removed from the males, even though the sex difference may be due to testosterone. He also asked whether there are studies of the effect of testosterone on stroke.

Dr. McCullough said that there are studies on testosterone and stroke, but this is a complicated area, because testosterone becomes aromatized to estrogen. Overall, testosterone is thought to be deleterious. Premature newborn girls do better than premature newborn boys. The boys who have higher testosterone levels have the poorest outcomes.

Dr. Weaver said that she has found different results between knockout mice and wild-type mice. Given that each strain descends from one female and one male, how should the significance of the result be assessed? Dr. Arnold suggested repeating the experiment with a greater variety of litters. Dr. Cross said that she used different knockout models and then compared those results to their results in wild-type mice. Dr. McCullough suggested that researchers do their own heterogeneous breeding of mice and confirm their findings pharmacologically. That would give greater confidence that this is not an artifact of one mouse line.

Dr. Green asked how this research can take into account a diverse population that includes women of color. Dr. McCullough said that research is needed on racial disparities. For example, African American women do not respond as well to thrombolytic drugs, possibly due to a difference in platelet adhesion. While different strains of mice have different responses in stroke research, there is currently no way to relate that to humans.

Dr. Becker said that there is a need to develop more heterogeneous rodent models with polymorphisms that map back to human conditions. When there are different results for different strains, it would be useful to understand the biology of those differences.

Dr. Page used a painting of pairs of animals boarding Noah's ark to talk about the differences between males and females. Turtles do not have sex chromosomes; a turtle's sex is determined by the temperature of the egg. Male and female turtles are genetically identical; the existence of the sexes is epigenetic. This has led him to hypothesize that males and females have the same genome, but they read their genomes differently. There are male and female readings of the genome across the animal kingdom.

An NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research

Amy C. Mistretta, M.P.H., Epidemiologist, ORWH

The [toolkit](#) (#EngageRecruitRetain), an updated version of the *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* published in 2002, went live on the website on October 19. ORWH updated the content, made it more user-friendly, and added new features, including a section on best practices to ensure that women and minorities are adequately represented in clinical research. The toolkit also contains an extensive literature review, case studies, video interviews, and a printable checklist for investigators to include diverse populations in their research.

Overall, the literature review showed that investigators must employ a range of strategies to recruit a representative group of women to clinical trials. Successful recruitment begins with the investigator learning about the study population and which barriers are likely to be issues for the population. The literature review outlines some of the barriers and facilitators to recruitment.

Each case study provides a summary of a project, its recruitment and retention strategies, and lessons learned. Ms. Mistretta highlighted the Arizona Cervical Cancer Prevention Unit and its PI, Francisco Garcia, M.D., M.P.H. Many participants faced economic barriers, limited formal education, and distrust of researchers. Among other steps, Dr. Garcia employed linguistically and culturally appropriate staff who translated study materials in culturally appropriate ways. Participants also received free contraception, which was an incentive to join.

The toolkit includes a section on human subjects protection, an outreach and recruitment checklist, and video interviews.

Discussion

Dr. Clayton began the final session of the day by asking each board member to name one scientific or clinical question critical to moving forward in research related to the health of women.

Dr. Kashuba said that one question is the disposition of drugs in tissues of males and females, particularly in relation to a cure for HIV. There are clear differences between men and women in disposition in the mucosal tissues. Dr. Kashuba said that she would like to extend that to the disposition of drugs in brains of men and women.

Dr. Bird said that she would like to understand how to lower women's cholesterol and reduce their cardiovascular risk. There is a need to have pharmaceuticals that are effective and well tolerated in women.

Dr. Chen said that he would like to know the best way to educate early-career scientists about appropriate experimental designs and analyses that are appropriate for sex differences research. This would help deal with the reproducibility issues.

Dr. Page said that he wonders whether the genome is read two different ways: male and female. He would like to investigate the question across species.

Dr. Palmer said that she has two questions: first, how to educate the public about partnership in research, and second, how research can help women keep themselves healthier while living longer.

Dr. Montgomery-Rice asked about focusing resources on the people who need it most, such as young women at risk of HIV infection, to help achieve health equity.

Dr. Regensteiner said that she would like to be able to discern which of the disparities between males and females are biological and which are due to other influences. Her second question was how to make the study of sex differences a priority in all disciplines taught at universities.

Dr. Becker asked whether sex differences should be conceptualized as something more than binary. How do scientists build better animal models to reflect the complexity of the human condition?

Dr. Green said that quality of pain care must be explored. Pain has a disproportionate impact on racial and ethnic minorities and women. Another question is why some people still die before their time. A third question is how to translate knowledge already gained from research into clinical practice.

Dr. Weaver said that it is important to find a treatment for menopause symptoms. A second question is to determine the effect on women of contaminants found in birth control pills. Some of those contaminants have been found in the water and are affecting local fish populations.

Dr. Nelson said that she would like more investigation of the social determinants of health, including determinants such as isolation that interact with genetics and the environment. This investigation would include looking at factors behind stress and resiliency and at domestic violence, which kills more women than many diseases.

Dr. Mazure said that depression is more prevalent in women and is one of the greatest causes of disability in women, according to the World Health Organization. The issue of depression must be approached in an interdisciplinary way, because the condition has biological and psychosocial dimensions and because depression co-occurs with cardiovascular disease and autoimmune disease.

Dr. Weiss said that he would like to see sex differences research take a cross-cutting, whole-body perspective.

Motion to Establish Lectureships

Dr. Green said that she would like to put forward a motion. As background, she said that it is important for ORWH to communicate its work and accomplishments. ORWH should develop a series of lectures to be named in honor of Dr. Ruth Kirschstein, Dr. Bernadine Healey, and Sen. Barbara Mikulski and in tandem with the Dr. Vivian W. Pinn lecture. The Sen. Mikulski and Dr. Pinn lectures would take place near the time of the ACRWH meeting, so that members could attend. Other ICs might co-sponsor the lectures. The Sen. Mikulski lecture might focus on patients, the Dr. Kirschstein lecture on emerging leaders in science of women's health, and the Dr. Healey lecture on women in senior science leadership. A second proposal would be to create a summer internship for a young person from Baltimore.

Dr. Montgomery-Rice and Dr. Palmer made comments in support of the proposal. Dr. Clayton asked that Dr. Green make a motion.

Dr. Green made a motion to establish a lecture series and program that focuses on the foremothers who developed ORWH, the science of inclusion, and career development for women scientists.

The motion was seconded and passed unanimously on a voice vote.

Dr. Clayton thanked the committee members, other participants, audience, and staff for their efforts.

Adjournment

Dr. Clayton adjourned the meeting at 4:40 p.m.