The Future

~ The WHI Legacy to Future Generations of Women ~

Opening, WHI Extension, BAA

- Opening Remarks (Putting It All Together)
  Moderator: Richard Hodes, MD, NIA
- WHI Extension Study
  Data and Specimen Resources
  Broad Agency Announcement (BAA)
  Jacques Rossouw, MD, NHLBI

Opening Remarks (Putting It All Together)

Richard Hodes, MD
Office of the Director

National Institute on Aging
National Institutes of Health
Bethesda, Maryland

WHI Extension Study
Data and Specimen Resources
Broad Agency Announcement (BAA)

Jacques Rossouw, MD

WHI Project Officer

National Heart, Lung, and Blood Institute

National Institutes of Health

Bethesda, Maryland

WHI Extension Study 2005-2010

- All participants in clinical trials and observational study invited
- Estimate that more than 116,000 will participate (80% of eligible)
- Participants asked to provide data on health outcomes, hormone use
- Rationale:
  - Study possible delayed effects of study treatments (e.g., breast and colorectal cancer in trial of low fat dietary pattern)
  - Collect greater numbers of outcomes for future studies
    - To study subgroups e.g., by race/ethnicity
    - To study less frequent outcomes e.g., ovarian cancer

Access to WHI Data for Publications

- Collaboration with WHI investigators
  - Writing group proposal
  - Review by study committees
  - www.whiscience.org
- Datasets available for research use
  - Observational study baseline data
  - E+P trial data (soon)
  - www.nhlbi.nih.gov/resources/deca/directry.htm

WHI Resource

- Bloods from
  - Baseline and Year 1 in Clinical Trials (N=68,135)
  - Baseline and Year 3 in Observational Study (N=93,676)
  - Serum, plasma, DNA, red blood cells
  - Urine in subsample (N=12,615)
- Data on wide range of clinical outcomes
- Data on wide range of demographic and exposure variables

Potential of the WHI Resource

- Large, well-documented data including women of diverse background
- Find predictors of health and disease in the blood samples (several studies already completed)
- Find genetic markers of disease (some studies completed)
- Interplay between genes and environment
- Better understanding of effects of specific treatments, e.g., effect of combination hormones on heart attack, stroke, and breast cancer (currently ongoing)
- Fits within broader NHLBI goal of encouraging studies of the entire gene in relation to disease (whole genome association studies)

Access to the WHI Resource

- Ancillary study in collaboration with WHI investigators (requires separate, non-WHI funding)
- Core study defined by WHI investigators (funded from WHI funds as subcontract with WHI Clinical Coordinating Center)
- Broad Agency Announcement (NHLBI contract funding for laboratory investigations)

Broad Agency Announcement NHLBI-WH-06-09

Posted January 6, 2006
Receipt of Proposals April 7, 2006

- BAAs are used for scientific study that advance the state of the art or increase knowledge or understanding rather than focusing on a specific outcome
- Translation: the investigators propose the studies to be done
- Contract mechanism

Title: "Towards Maximizing the Scientific Value of the Biologic Specimens from the Women's Health Initiative"

- Solicits the best ideas for research studies
- Open to WHI and non-WHI investigators
- WHI program intended to improve knowledge about some of the common diseases of older women
- Many studies have been completed, are still being done, or are being planning by WHI investigators and their colleagues
- The BAA makes available $17.5 million over 2 years for additional studies by experts from the entire scientific community
- A second BAA will be issued in late 2007

WHI BAA

- The current BAA will focus on laboratory studies of biologic markers for cardiovascular diseases, cancers of the breast, colon and rectum, and fractures
- Studies involving other outcomes of interest will also be considered
- Anticipate proposals will include application of genomics, proteomics, and other "high-dimensional" laboratory techniques to resource
- Focused studies of candidate markers or genes will also be considered
- Details of WHI resource can be found at www.whiscience.org

National Guidelines, Recommendations & Potential Impact of WHI

- Heart and Brain (Stroke)
  Marian Limacher, MD
- Brain (Cognitive Function)
  Sally Shumaker, PhD
- Breast, Colon and Other Cancers
  Dorothy Lane, MD, MPH
- Gynecological Health and Hormones
  Susan Hendrix, DO
- Overall Recommendations for Older Women
  Robert Wallace, MD
- Closing Remarks for Guidelines Session
  Richard Hodes, MD

Heart and Brain (Stroke)

Marian Limacher, MD
Principal Investigator
Gainesville Clinical Center

Professor of Medicine
Division of Cardiovascular Medicine
University of Florida
Gainesville, Florida

How WHI has modified Guidelines for CVD Prevention

- Hormone Trials
  - Substantial impact
- Dietary Trials
  - The discussions have begun….However,
    - Primary goal was cancer reduction
    - Intentionally targeted total fat reduction, not saturated fat or trans fat
    - this (lower fat, higher complex carb) is the most studied eating pattern of any we have--and it is safe and healthy.
    - There are evidence-based approaches to preventing morbidity and mortality from cancer and heart disease through screening and risk factor modifications that can and should be followed.
    - Stay tuned--longer f/u is underway and more studies are in the works.

    (Evelyn Whitlock, email 2/9/06)

FDA Labeling Change, 2003

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.

FDA Labeling Change, 2003

…Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, ***estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration*** consistent with treatment goals and risks for the individual woman.

WOMEN'S HEALTH INITIATIVE

US Preventive Services Task Force Grading

- A : strongly recommends (good evidence)
- B : recommends (fair evidence)
- C : no recommendation (balance of evidence is too close)
- D : recommends against (at least fair evidence of ineffectiveness or harm outweighs benefits)
- I : insufficient evidence

USPSTF: Hormone Therapy

- Recommends against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women
  - Rating: D
- Recommends against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.
  - Rating: D

USPSTF, release date 2005. www.ahrq.gov

WOMEN'S HEALTH INITIATIVE

2004 AHA Guidelines for CVD Prevention in Women

Class III interventions (Intervention is not useful/effective and may be harmful)

Hormone therapy: **Combined estrogen plus progestin hormone therapy *should not be initiated* to prevent CVD in postmenopausal women. (Class III, Level A)**

Combined estrogen plus progestin hormone therapy *should not be continued* to prevent CVD in postmenopausal women. (Class III, Level C)

Other forms of menopausal hormone therapy (eg, unopposed estrogen) should not be initiated or continued to prevent CVD in postmenopausal women pending the results of ongoing trials. (Class III, Level C)

***Circulation* 2004 109:672– 693**

Current Recommendations for CVD Prevention

Strategies we *should* be using!

2004 AHA Guidelines for CVD Prevention in Women

- **Lifestyle:**
  - Discourage cigarette smoking
  - Minimum 30 min. moderate physical activity on most, if not all, days of the week
  - BMI < 25 [between 18.5 and 24.9 kg/m2]
    - Waist circumference < 35 in
  - Heart Healthy Eating Pattern
    - Variety of fruits, vegetables, legumes, lean meats
    - < 10% cal sat fat
    - chol < 300 mg/day
    - Limited trans-fats

Mosca et al, AHA Guidelines: evidence-based guidelines for Cardiovascular disease prevention in women. *Circulation* 2004:109;672-92.

Individual Risk Factor Interventions

- Blood Pressure
  - Rx for BP >140/90
  - Goal BP <120/80
- Treating Lipids
  - LDL > 130 (Optimal < 100); *with CAD or DM, goal LDL < 100 or < 70 if high risk*
  - HDL > 45 (Optimal >50)
  - TG > 150 (Optimal < 150)
  - Statins = 1st line; niacin, fibrates for HDL, TG goals
- Diabetes
  - Goal: HgA1C < 7

Mosca et al, AHA Guidelines: *Circulation* 2004

WOMEN'S HEALTH INITIATIVE

Brain (Cognitive Function)

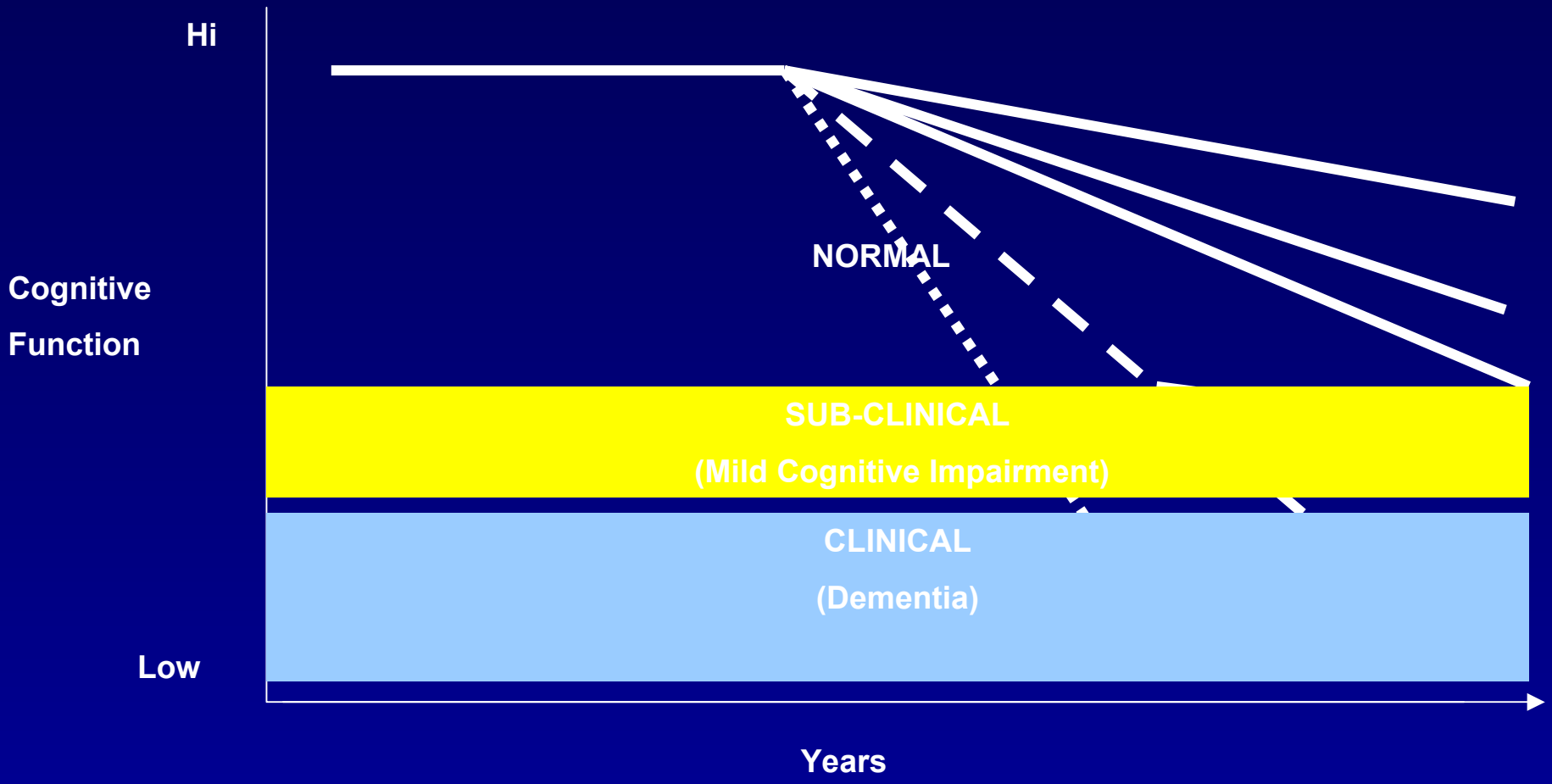
Sally Shumaker, PhD
Principal Investigator
WHI Memory Study (WHIMS)

Professor and Associate Dean of Research
Wake Forest University School of Medicine
Department of Public Health Sciences
Winston-Salem, North Carolina

Critical Issues Regarding Women and Aging:

- Brain-related disorders are on the rise
  - Women (and men) are living longer
  - Early detection of brain-related disorders is improving
- A major worry among older adults is dementia and cognitive decline
- There is an urgent desire for treatments or preventatives – giving rise to claims of efficacy for medications, herbal and nutraceutical agents that may not have been tested adequately
- WHIMS represents a well-designed response to this challenge

Trajectories of Cognitive Function over Life Span

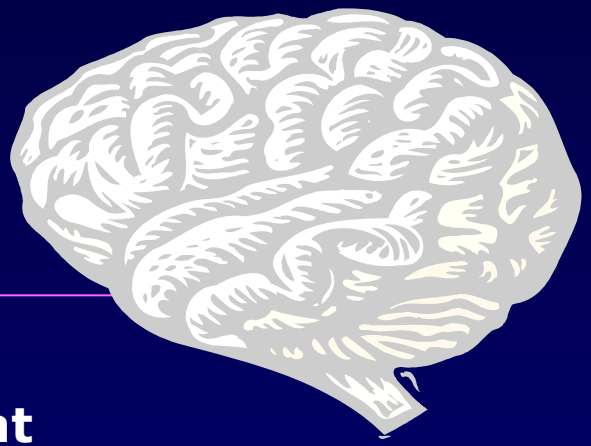


WHIMS

- Hormone therapy was presumed to prevent dementia before it was tested in a clinical trial
- WHI and WHIMS provided the first, long-term, randomized trial to investigate the effect of hormone therapy on thinking and memory
- 7,500 women, 65 years and older, joined WHIMS
- We learned that hormone therapy does not protect against cognitive decline or dementia in post-menopausal women aged 65 and older – in fact, hormone therapy may accelerate cognitive decline

WOMEN'S HEALTH INITIATIVE

WHIMS: Implications/Future



- WHIMS focused attention on related questions that need answers
  - If not beneficial, what effects do hormones have on the brain?
  - Is there a "window of opportunity" in which younger women (less than 65) might benefit from hormones?
  - Do the negative effects of hormones in women 65 and older persist once women stop taking the medication?
- WHIMS demonstrated that important and complex questions about cognition & dementia can be addressed in large (multi-site) studies
- WHIMS underscores the need to carefully assess the effects of other agents on the brain to determine if there are unintended risks or benefits (for example, SERMS, Aromatase Inhibitors, Statins, etc.)
- WHIMS keeps the spotlight on women's cognitive health!

WOMEN'S HEALTH INITIATIVE

Breast, Colon and Other Cancers

Dorothy Lane, MD, MPH
Principal Investigator
Stony Brook Clinical Center

Distinguished Service Professor
and Vice Chair Department of Preventive Medicine
Stony Brook University School of Medicine
Stony Brook, New York

Changes in National Guidelines
U.S. Preventive Services Task Force

USPSTF evidence-based review of HT:

- Good evidence that use of E + P results in increased risk for breast cancer and fair evidence of a reduced risk of colorectal cancer
- Insufficient evidence to assess the effects of E + P on the incidence of ovarian cancer and mortality from breast cancer

Changes in National Guidelines
U.S. Preventive Services Task Force

For the prevention of chronic conditions in postmenopausal women, the USPSTF recommends:

- Against the routine use of E + P
- Against the routine use of E-alone in women who had a hysterectomy

WHI Messages for Cancer Prevention

- Reinforced adage "do no harm" when prescribing for healthy women without symptoms
- Highlighted importance of randomized, double-blinded, clinical trials to establish cancer risk/benefit ratios for preventive interventions
- CTs with cancer outcomes should be sufficiently large and long to yield definitive answers

WHI Lessons for Cancer Prevention

Preventive interventions can impact on cancer screening, e.g.:

- E + P increases abnormal mammograms
- E + P increases endometrial biopsies (to rule out cancer as a cause of bleeding)
- E-alone increases recommendations for a shortened interval between mammograms

WHI Lessons for Cancer Prevention

- Many U.S. women have adopted healthy lifestyles making it more challenging to measure intervention effects
- Calcium/Vitamin D supplementation should not be recommended for prevention of CRC, at this time
- Lifestyle dietary changes that reduce fat intake and increase fruits and vegetables can be accomplished and maintained over 8 years
- Longer (extension) follow-up among low-fat diet group may reveal further reduction of breast and CRC risk
- WHI-OS suggests increased physical activity is related to reduced breast cancer risk (requires CT testing)

Gynecological Health and Hormones

Susan Hendrix, OD

Principal Investigator

Detroit Clinical Center

Professor
Wayne State University
Department of Obstetrics and Gynecology
Detroit, Michigan

Impact of WHI on Gynecological Issues

- Systemic estrogens still approved and prescribed for vaginal dryness
- No change in recommendations for use other than with respect to urinary incontinence

Postmenopausal Hormone Therapy (PHT) and Urinary Incontinence

Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA.* Dec 2005:293:935-948

PHT and Urinary Incontinence Background

- PHT staple in the management of menopause, credited with many benefits well beyond the indications for symptomatic relief of hot flashes, night sweats, and vaginal dryness
- Purported benefits of PHT was to improve the symptoms of urinary incontinence (UI)

JAMA 2005;293:935-948

PHT and Urinary Incontinence
WHI Findings

- Significant increase in risk for new onset urinary incontinence among continent women
- Worsening of the characteristics of incontinence among incontinent women using CEE+MPA or CEE after one year
- Considerations regarding the use of hormone therapy by postmenopausal women for any duration should incorporate the current findings into the established risks and benefits of these agents.

JAMA 2005;293:935-948

WOMEN'S HEALTH INITIATIVE

PHT and Urinary Incontinence

- American College of Obstetricians and Gynecologists
  - Practice Bulletin on UI, June 2005
  - "Oral estrogen regimens cannot be recommended as treatment or prevention for any type of urinary incontinence"
  - No mention of evaluation or management of women who develop incontinence or have worsening on hormone therapy

American Urogynecologic Society

- Current patient information page on UI
- "Estrogen therapy-can help increase urine control by increasing blood flow to the genital tissues. Hormones work more quickly if they are applied directly to the vagina so vaginal estrogen creams or pills are often prescribed. Oral estrogen can also be successful."
- No mention of WHI findings

Gaps in Translation

- Informed consent does not include risk of new or increasing incontinence as a risk of therapy
- Lack of recommendations to temporarily discontinue hormones to see if incontinence improves, especially prior to surgery to correct incontinence

Gaps in Translation

- WHI has brought into question longstanding clinical practice
- It will take time to bring practice in line with the evidence
- The WHI investigators are committed to assisting in any way possible

Overall Recommendations for Older Women

Robert Wallace, MD
Principal Investigator
Iowa Clinical Center

Professor of Epidemiology & Internal Medicine
University of Iowa
College of Public Health
Iowa City, Iowa

Closing Remarks for Guidelines Session

Richard Hodes, MD
Office of the Director

National Institute on Aging
National Institutes of Health
Bethesda, Maryland

Synthesizing, Celebrating, and Closing

- Women's Health Questions of the Future?
  Vivian W. Pinn, MD
- Celebrating WHI Participants
- Audience Questions
  Richard Hodes, MD
- Closing Remarks for the Conference
  Elizabeth Nabel, MD

Women's Health Questions of the Future?

Vivian W. Pinn, MD

Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health
Bethesda, Maryland

The WHI legacy to future generations of women

The Future: The WHI Legacy Continues In Women's Health Research

NIH

February/March 2006

Vivian W. Pinn, M.D.

Associate Director for Research on Women's Health

Director, Office of Research on Women's Health

National Institutes of Health

Department of Health and Human Services

To Effectively Address Questions That Women & Their Physicians Have About Their Health & Health Care

<<<>>>

Needs & Strategies

Must Be Based Upon

Scientifically Determined Knowledge

&, Ultimately, Results of

Randomized Controlled Trials

Women's Health Research

MYTHS ??? *REALITIES*

Research is providing new knowledge through science, while posing new questions to explore…

Women's Health Research Priorities

'The broad concept of what constitutes women's health has led to the recognition that research priorities… must be comprehensive and interdisciplinary and should include not only clinical studies but also the full spectrum of research, from molecular and genetic studies to those of prevention, behavior, outcomes of interventions, and clinical translation of newly proven hypotheses.'

Pinn, JAMA, 2005

Agenda for Research on Women's Health for the 21st Century

Women's Health & Sex/Gender Factors in Biomedical Studies: Implications for Health and Clinical Practice

Research:

Needed to provide answers

That can guide clinical practice…

And, shape future scientific endeavors to expand knowledge about women's health

Will the results of, and future examination of, WHI study data affect the national research agenda for women's health??? YES!!!

MENOPAUSE: Why More Research?

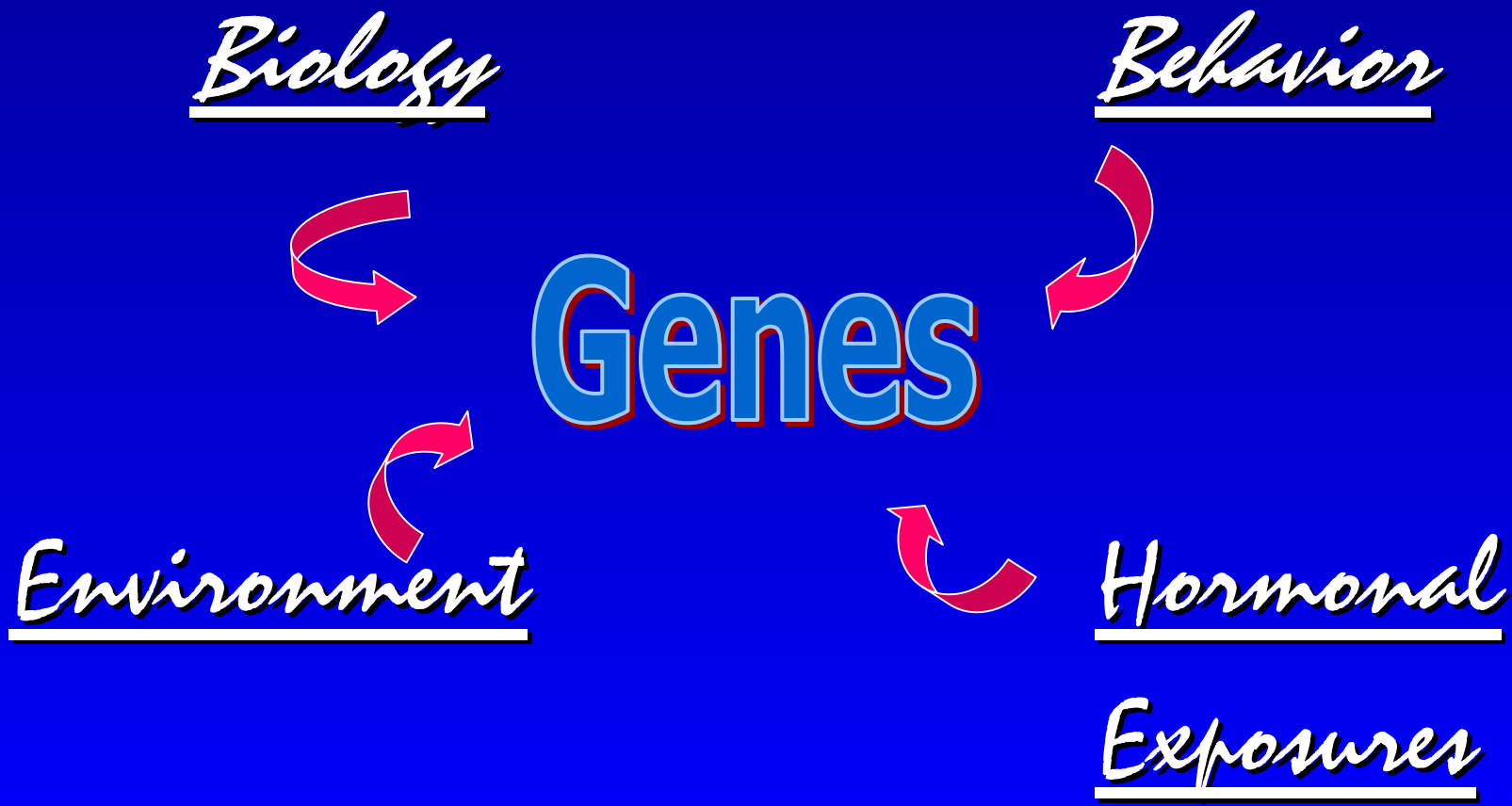
<<<<◇>>>>

To better understand the biology, symptomology, and socio-cultural implications of the menopausal transition and postmenopausal years is essential to address the health concerns of the aging female population…

WOMEN'S HEALTH RESEARCH in the 21st CENTURY

What directions for the future???

Some Influences Contributing to Differences in Genetic Risk Manifestations



The Future... Research needed to address:

- Basic molecular, genetic, biological and physiologic properties of hormones and hormone receptors
- Identification of estrogen-sensitive genetic phenotypes
- Efficacy and risks & benefits of different formulations (for short or long term use), modes of administration, dosages, when to start or stop
- Mechanisms & markers for adverse events/risks
- Alternatives to hormone therapy and expanded concepts of prevention

The Future…

- Continue quality research to understand the menopause transition and aging in women, including proven prevention strategies
- Expand basic nutritional science and validate markers of intake and susceptibility
- Explore more concepts of disease and health in aging, considering biomedical, behavioral and societal issues in women's health and disease
- Give attention to basic genetic markers and pathobiology for diseases and conditions that affect the QOL or longevity of women that can help to explain risk factors and risks and the role of behaviors in prevention

Women's Health Research & Health Care for the 21st Century

A strengthened commitment to research that seeks to better understand health disparities and sex/gender factors in health & disease across the lifespan…

… and to educational initiatives for health care providers and consumers about effective, culturally and sex/gender appropriate, diagnostic, prevention and treatment strategies,

… & for evaluation and implementation into public health policies and performance in standards of care....

The NIH Policy: Inclusion of Women & Minorities in Clinical Research

NIH Inclusion Guidelines for Clinical Research

Effective Strategies for the recruitment and retention of women in clinical research studies:

* Older Women
* Communicating Results
* Establishing Trust

Research & Communication

Importance of translating results of research,

…often conflicting or confusing or different from common impressions or existing health care practices…

Into standards of health care delivery

&

Into usable knowledge for women (and men) and their health care providers to make informed decisions….

To the WHI Participants

Thank You!

For your participation in the WHI,

For showing that women can and will participate in research,

And, for enriching the experiences of all who attended this conference…

To the WHI Investigators & Staff

Thank You, also!

http://orwh.od.nih.gov/whiconference.htm

Celebrating WHI Participants

Final Words of Appreciation and Acknowledgement

Audience Questions

Richard Hodes, MD - Moderator

Office of the Director

National Institute on Aging
National Institutes of Health
Bethesda, Maryland

Closing Remarks for the Conference

Elizabeth Nabel, MD
Director

National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

WHI Investigators - A Short List

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Barbara Alving, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (Medical Research Labs, Highland Heights, KY) Evan Stein; (University of California at San Francisco, San Francisco, CA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX) Jennifer Hays; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn Manson; (Brown University, Providence, RI) Annlouise R. Assaf; (Emory University, Atlanta, GA) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Judith Hsia; (Harbor-UCLA Research and Education Institute, Torrance, CA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR) Evelyn Whitlock; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn; (Rush Medical Center, Chicago, IL) Henry Black; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ) Tamsen Bassford; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA) Howard Judd; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Hawaii, Honolulu, HI) David Curb; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV) Robert Brunner; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (University of Tennessee, Memphis, TN) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski; (University of Wisconsin, Madison, WI) Gloria E. Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC) Denise Bonds; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI) Susan Hendrix.

Thank you!
To the 161,808 WHI participants

The Women's Health Initiative
Sponsored by the
National Heart, Lung, and Blood Institute,
National Institutes of Health,
Department of Health and Human Services

The NIH, ORWH, and WHI investigators and staff thank the 161,808 participants of the WHI for their extraordinary commitment and legacy to future generations.

WHI Web Sites

www.whi.org

http://orwh.od.nih.gov/WHIConference.htm

www.nhlbi.nih.gov/whi

www.whiscience.org