Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002
Session 2

1. Topic and Author

Sex and Gender Issues Related to the Heart. Noel Bairey Merz MD

2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Before examining these disease states and pathophysiological mechanisms in women, the terms "sex" and "gender" will be outlined and an approach to understanding how these impact current understanding and future research efforts explored. These will include:

- Difference between "sex", a term relating to biological sexual differentiation, and "gender", a term relating to socioculteral attributes of the biological sex. Research is uncovering important structural and functional differences in heart function related to sex between women and men that have implications for heart disease. We are also finding important gender differences that have implications for symptom reporting, symptom recognition and disease management. Gender differences also impact our understanding of heart disease due to population selection bias.
- "Sex" is furthered categorized. The differences between "sexual genotype", a term relating to the XX genotype, and "sexual phenotype", a term relating to the genotype expression, given the environmental conditions. Over the lifetime, women remain an XX genotype, yet have a variety of phenotypical expressions in the heart and vasculature, depending on estrogen levels, other environmental factors such as dietary phytoestogen intake, and disease states.

Examples of "sex" and "gender" considerations will be presented relative to macro- and microvascular ischemia in women. These include specifically:

- "Sex" neurological considerations, both genotypic and phenotypic. Examples include: 1) sex genotype differences between women and men in perception and cognition (MAKI); 2) sex phenotype (estrogen) differences in chest pain expression (LIT/ WISE); 3) autonomic nervous system differences, both genotypic and phenotypic (CIRC). For example, because of both genotypic and phenotypic differences, women have lower pain thresholds compared to men, impacting symptom reporting, potentially accounting for the reported "delay in hospitalization" among women with MI compared to men. Women have higher resting heart rates but a stronger vagal response to ischemia (Circ), impacting out of hospital sudden cardiac death (lower in women), which influences acute MI 30 day registry data (higher mortality among women compared to men)(Vaccarino).
- "Sex" phenotypic considerations, including estrogen, phytoestrogens, endothelial and microvascular function and blood flow (sex genotype and phenotype)(WISE). For example, women have sex-specific responses of the vascular that are related to genotype (Circ menstrual) but modulated by the current estrogen status (Circ menstrual), such that phytoestrogens act as selective estrogen receptor modulators variably depending on whether a women is premenopausal (high estrogen) or postmenopausal (low estrogen)(WISE).
- "Gender" (cultural symptom reporting) considerations (LIT FP and NERI). For example, women culturally are more open to sharing symptoms and feelings, leading to a higher frequency of physician visits and symptom reporting compared to men. Physicians culturally are more likely to test white male patients for suspected heart disease compared to women or minorities.

3. Current challenges and the most important issues for future research

Current challenges include education of the investigative community with regard to female (as opposed to male) physiology and the impact of "sex" (genotype and phenotype), as well as "gender" on essentially all aspects of health and disease.

Important issues for future research are to continue to define female standards of health and disease, rather than

revising male patterns and models, where relevant, so as to avoid confusing issues later of "sex" and "gender" bias and stereotypes.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

One of the largest challenges in communicating heart disease messages to women are related to "sex" and "gender", where women both feel more sensations that could be attributable to heart disease (related to sex genotype and phenotype), and are more willing to report symptoms to family, friends and physicians (related to gender) compared to men. This makes symptom diagnosis more challenging in women for healthcare workers (symptom models are less accurate for heart disease, particularly in relatively young women). Health education efforts are also difficult relative to instructing patients and the community about symptom reporting (the girl/boy who cried wolf too often and is subsequently ignored when the wolf finally comes).

5. Translating new findings to improved diagnosis and treatment/saving lives.

Ongoing research can address improved heart disease awareness and diagnosis in women given appropriate time and effort directed toward it. Synergy between new diagnosis technology and the information explosion should be utilized toward this effort. If accurate symptom detection cannot be optimized (due to issues of sex and gender), and patterns of ischemia markers prove to be not sufficiently accurate (due to issues of sex-related pathophysiology), future efforts may need to focus on sex-specific constructs using new technology (e.g. CT or MRI which can combine multiple markers each with independent diagnostic information).

6. References.

1. Fillingim R, Maixner W. Gender differences in the response to noxious stimuli. Pain Forum 1995;4:209-21.
2. Shaywitz BA, Shaywitz SE, Pugh KR, et al. Sex differences in the functional organization of the brain for language. Nature 1995;373:607-9.
3. Andersson HI, Ejlertsson G, Leden I, et al. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain 1993;9:174-82.
4. Amodei N, Nelson Gray NO. Reactions of dysmenorrheic and nondysmenorrheic women to experimentally induced pain throughout the menstrual cycle. J Behav Med 1989;12:373-85.
5. Bairey Merz CN, Johnson BD, Bittner V, et al. Reproductive hormones and chest pain in women: the NHLBI-sponsored WISE study (Circ abstract, in press).
6. Hayward CS, Kellyl RP. Gender-related differences in the central arterial pressure waveform. JACC 1997;30:1863-71.
7. Minson CR, Halliwill JR, Young TM. Influence of the menstrual cycle on sympathetic activity, baroreflex sensitivity, and vascular transduction in young women. Circ 2000;101:862-8.
8. Vaccarino V, et al. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. Ann Intern Med 2001;134:173-81.
9. Johnson BD, Holubkov R, Bairey Merz CN, Pepine CJ, Rogers WJ, Reichek N, Sharaf BL, Kelsey SF, Sopko G, Reis SE. HRT modulates brachial artery diameter and flow-mediated dilation: the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study. JACC 2002;39:220A.
10. Stoverinck MJM, Lagro Janssen ALM, Weel CV, et al. Sex differences in health problems, diagnostic testing, and referral in primary care. J Fam Pract 1996;43:567-6.
11. Birdwell BG, Herbers JE, Kroenke K. Evaluating chest pain: the patient's presentation style alters the physician's diagnostic approach. Arch Intern Med 1993;153:1991-5.