

FUNCTIONAL MEDICINE UPDATE
JANUARY 2008
ISSN 1092-1761
Vol. 28, No. 1

**The Women's Health Initiative (WHI) and HRT
Five Years Later, the Debate Continues**

In July 2002, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) announced the premature termination of the estrogen and progestin (EPT) arm of the Women's Health Initiative (WHI) study. What followed this announcement and an article published in the *Journal of the American Medical Association* by WHI investigators that stated, "Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2 year follow-up among healthy postmenopausal US women," can be characterized as a firestorm in women's health. REF #1

In 2002, Dr. Wulf Utian, Editor-in-Chief of *Menopause Management* and a recognized expert in women's health, published an editorial that predicted that the decision to terminate the EPT arm of the WHI would be debated for years. Now, five years later, Dr. Utian has published a follow-up editorial that is critical of WHI investigators and raises questions about the potential human toll of the decision to terminate the study early (i.e. younger peri- and early postmenopausal women who may have benefited from continued therapy). Dr. Utian states, "...had the WHI kept to its original study objectives and reported the results impartially and by decade of chronological age and time from menopause there would not be the international disapproval that the study is now receiving...it is well time for the NIH to bring all their WHI investigators together to develop a transparent and comprehensive summary of their results...there are important and relevant data in the WHI study that need to be clearly and honestly placed in perspective..." The WHI controversy was further spotlighted in a September 2007 piece that appeared in *The New York Times* about the "here-today-gone-tomorrow nature of medical wisdom." REF #2-3

Heart Disease Risk: From Dietary Intervention to Shotgun Proteomics

In review of the state of research on a diet-heart connection published in *The New England Journal of Medicine* in 1977, Dr. George Mann took issue with scientists, the media, and the food industry over confusion about the role of diet in the causation and management of coronary heart disease. Dr. Mann observed that despite an era of promotion of low-fat, low-cholesterol, polyunsaturated diets, the epidemic of cholesterolemia within the US population continued unabated. REF #4

Jump ahead to 2007. Mortality from cardiovascular disease has decreased significantly in the United States over the past 30 years due to a combination of factors: identification of cardiovascular risk factors, development of interventions that reduce risk factors, and new treatments for acute coronary syndromes. And yet, despite these advances, cardiovascular disease remains the leading cause of mortality in the United States.

A group of researchers from the University of Washington, Wake Forest University, and Harvard Medical School recently collaborated on an investigation into the antiatherosclerotic properties of HDL. Using an analytical strategy called shotgun proteomics, the composition of HDL isolated from healthy subjects and subjects with coronary heart disease (CAD) was examined. Multiple complement-regulatory proteins and a diverse array of distinct serpins with serine-type endopeptidase inhibitor activity were identified. Many acute-phase response proteins were also detected, supporting the proposal that HDL is of central importance in inflammation. Collectively, the observations of this group of collaborators suggest that HDL plays previously unsuspected roles in regulating the complement system and protecting tissue from proteolysis and that the protein cargo of HDL contributes to its anti-inflammatory and antiatherogenic properties. REF #5

Oxidative Stress and Bone Loss in Estrogen-Deficient Mice: Results of a Recent Experiment

Researchers from Emory University and the University of Udine (Italy) recently published the results of an animal experiment in the *Proceedings of the National Academy of Sciences*. In summary, reactive oxygen species accumulation in the bone marrow is an upstream consequence of ovariectomy that leads to bone loss by activating T cells through enhanced activity of bone marrow dendritic cells. These researchers demonstrated that bone loss is prevented by treatment of ovariectomized mice with either antioxidants or CTLA4-Ig, an inhibitor of the CD80/CD28 pathway. These findings suggest that the CD80/CD28 pathway may represent a therapeutic target for postmenopausal bone loss. REF #6

Thyroid Function Considerations in Postmenopausal Women

Based on the use of estrogen therapy/hormone therapy (ET/HT) in postmenopausal women and the prevalence of hypothyroidism in this population, it is estimated that approximately 5% of all postmenopausal women receive treatment with both ET/HT and thyroid hormone replacement. Because of its hepatic first-pass effect, oral estrogen therapy, the most commonly used modality of ET/HT, raises the circulating levels of thyroxine-binding globulin (TBG), thereby increasing the bound fraction and decreasing the free (bioactive) fraction of circulating thyroxine (T_4). As a consequence, oral ET/HT may increase the T_4 dosage requirements of women being treated for primary hypothyroidism as well as alter the pituitary-thyroid axis in euthyroid women. REF #7

Despite the safety review conducted by the US Food and Drug Administration (FDA) in the process of awarding a health claim for cholesterol-lowering properties of soy protein, concerns about the possible goitrogenic effects of soybean isoflavones persist. Concerns are based primarily on *in vitro* research, animal studies, and older reports of goiter in infants fed soy formula not fortified with iodine. In 2006, a collaborative of researchers from notable institutions conducted a randomized, double-blind, placebo-controlled study to investigate the effects of a daily supplement containing 90 mg of isoflavones on thyroid function in postmenopausal women. These results, published in the *Journal of Medicinal Food*, indicated that in this group of healthy iodine-replete subjects, soy isoflavones did not adversely affect thyroid function. These findings are consistent with

the results of a literature review of 14 trials that was published in *Thyroid*, as well as a clinical study published in the American Journal of Clinical Nutrition involving 73 subjects. Collectively, there is little evidence that in euthyroid, iodine-replete individuals, soy foods or soy isoflavones adversely affect thyroid function in postmenopausal women. REF #8-10

Clinician/Researcher of the Month

Eleanor Rogan, PhD
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For more than 30 years, Dr. Eleanor Rogan has conducted research at the Eppley Institute for Research in Cancer at the University of Nebraska. She has twice been a previous guest on *Functional Medicine Update*, and was the recipient of the 2006 Functional Medicine Linus Pauling Functional Award.

The goal of Dr. Rogan and her collaborators is to reduce the incidence of cancer. They believe they have identified the initiating step in the induction of breast and other human cancers and know how to prevent its occurrence. The hypothesis driving this research is that endogenous estrogen metabolites, catechol estrogen-3,4-quinones, react with DNA to form predominantly depurinating estrogen-DNA adducts, which generate the mutations leading to the initiation of a variety of human cancers. Preventing formation of estrogen-DNA adducts could be accomplished by limiting formation of catechol estrogen-3,4-quinones and/or preventing their reaction with DNA.

Dr. Rogan's research group have already demonstrated that women at high risk of breast cancer excrete relatively high levels of depurinating estrogen-DNA adducts in urine. They anticipate that the daily ingestion of selected antioxidants will significantly reduce the DNA damage caused by catechol estrogen quinones. If these antioxidants reduce the level of estrogen-DNA adducts in urine, the compounds could be potential agents to prevent development of breast, prostate, and other human cancers.

Dr. Bland and Dr. Rogan have a detailed discussion about this research, both the biochemistry and the clinical implications. REF #11-15

In Closing: Neurohormetic Phytochemicals

In follow-up to his December 2007 discussion of nutritional hormesis and xenohormesis, Dr. Bland discusses an article published in *Trends in Neuroscience* on the topic of neurohormesis. In this article, authors Mark Mattson and Aiwu Cheng state that many dietary and lifestyle factors that promote health of the nervous system might act by imposing a mild stress on neural cells, which respond to the stress by enhancing their ability to cope with more severe stress and resist disease. Physical exercise, dietary energy restriction, and cognitive stimulation all induce adaptive cellular stress responses

in neurons resulting in enhanced neurogenesis and synaptic plasticity, and resistance to injury and disease. Hormetic phytochemicals might tap into the same adaptive stress-response pathways, but how beneficial phytochemicals might activate such neuroprotective pathways is largely unknown. REF #16

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