



Kronos Longevity Research Institute (KLRI)
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Press Release
Kronos Early Estrogen
Prevention Study

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**Eight Study Centers Announced for Five-Year, \$12 Million Research
on Women, Menopause and Hormone Use**

**Prestigious Institutions Selected to Conduct Study for
the Kronos Longevity Research Institute**

PHOENIX (April 20, 2004) -- Phoenix-based **Kronos Longevity Research Institute (KLRI)** has selected eight national study centers for the **Kronos Early Estrogen Prevention Study (KEEPS)**. Those centers include:

- Albert Einstein College of Medicine of Yeshiva University/Montefiore Medical Center
- Columbia University College of Physicians and Surgeons
- Harvard Medical School/Brigham and Women's Hospital
- Mayo Clinic College of Medicine (Rochester, Minn. campus)
- University of California-San Francisco/Center for Reproductive Health
- University of Utah School of Medicine
- University of Washington School of Medicine
- Yale University College of Medicine

KEEPS is a randomized, controlled, double-blinded trial of 720 women designed to provide prospective data on the risks and benefits of early menopausal hormone therapy (MHT), particularly as it relates to the progression of atherosclerosis. The results of the Women's Health Initiative estrogen plus progestin trial, which was halted by the National Institutes of Health in July 2002, prompted a consortium of health researchers to study the risks and benefits of MHT on a younger subset of women who recently entered menopause. Prior to the WHI, most data suggested that hormone replacement therapy was associated with a high degree of protection (30 to 50 percent reductions) against coronary heart disease, all-cause mortality and osteoporotic fractures, in addition to a small increase in breast cancer risk.

KEEPS was designed to explore issues raised by the WHI, specifically:

Age of Participants - The study will explore whether beginning hormone therapy in women

during the menopausal transition (ages 40 to 55) protects against atherosclerosis, the major cause of heart attacks. WHI participants were postmenopausal, with a mean age of 62.7, yet most women begin hormone treatment much younger, at the onset of menopausal symptoms.

Transdermal Application - KEEPS also will study whether the natural human estrogen, estradiol, delivered through the skin via a patch is equally effective as and potentially safer than oral estrogen. Researchers have speculated this method may be safer since transdermal estrogen does not go to the liver in high concentrations and has been shown to have little or no effect on clotting. On the other hand, transdermal estradiol may be less effective since it does less to increase HDL-cholesterol levels.

Imaging of Key Arteries - KEEPS will image the carotid and coronary arteries in order to measure the effects of hormone replacement on heart disease. Carotid intimal medial thickness (IMT) will be measured by ultrasound and the progression of coronary calcium will be tracked by X-ray tomography. In addition, KEEPS investigators will measure both protective and risk factors for heart disease, which are believed to be affected by hormones. This detailed analysis is particularly important in view of findings from earlier animal and human research indicating that estrogen may be beneficial for preventing early lesions of atherosclerosis, but ineffective, or even harmful, once disease is established.

"There are a lot of data that suggest that estrogen is good early and bad late," said Dr. S. Mitchell Harman, director of KLRI. "The WHI was instrumental in providing a roadmap for the next phase of research to examine whether estrogen protects younger women from cardiovascular disease, as earlier observational studies indicated. KEEPS is designed to provide useful new data to begin answering women's questions and help shape future research."

"When risk ratios are calculated by time since menopause, the WHI suggests that the women who were more recently menopausal had better CHD outcomes with hormone therapy than the older women" said Dr. JoAnn Manson, a noted expert on women and cardiovascular disease and the KEEPS principal investigator located at Harvard University Medical School/Brigham and Women's Hospital. "There is no evidence, in WHI findings or elsewhere, that indicate that recently menopausal women taking estrogen are at increased risk of heart disease. KEEPS is the logical next step in elucidating the effect of estrogen on CHD in younger women, the age group most likely to initiate estrogen therapy."

Study Design

KEEPS will be a randomized, placebo-controlled, double-blinded examination of healthy perimenopausal women aged 40 to 55. Researchers will recruit 720 study participants at eight clinical trial sites. KLRI will serve as the coordinating center.

Participants will be divided equally into three groups. The first group will receive an oral tablet containing conjugated estrogens and a placebo skin patch. The second group will receive an oral placebo tablet and a skin patch delivering estradiol. The third group (control) will receive a placebo tablet and a placebo skin patch. Women receiving active estrogen will also use a progestin to protect the uterine lining from overgrowth (hyperplasia). Comparisons of the recently published WHI estrogen-alone with the WHI estrogen + progestin study results, and data from prior studies, suggest that constant exposure to oral medroxyprogesterone acetate may contribute to risk of breast cancer and heart disease. Thus, the KEEPS protocol requires a

low dose of natural progesterone, by a non-oral route, given cyclically. A vaginal progesterone gel (Prochieve® 4%), applied 10 days each month will be supplied by Columbia Laboratories, Inc.

All participants will be evaluated at 10 formal sessions for data and sample collection procedures and at additional visits for study monitoring, including a compliance check, a review for adverse effects and a brief physical exam.

Subjects will be monitored at three-month intervals by questionnaire for any adverse effects. The subjects also will undergo lab monitoring at various points during the study. All major adverse effects will be reported immediately to the local center's institutional review board and to KLRI, which will relay reports to the data safety monitoring board (DSMB). All adverse effects, major and minor, will be reported quarterly to KLRI for consideration by the DSMB.

About Dr. S. Mitchell Harman, Director of KLRI

Dr. Harman, a graduate of Emory University, received his medical and doctoral degrees from the State University of New York Health Sciences Center at Brooklyn and trained in internal medicine at Yale and in endocrinology at the National Institutes of Health (NIH).

He was an NIH investigator with the Intramural Program of the National Institutes on Aging (NIA) for more than 25 years, where he founded the NIA laboratory for the study of aging of the male and female reproductive hormone systems and served as Chief of the Endocrinology Section in the Laboratory of Clinical Physiology. Dr. Harman also was acting Clinical Director of the NIA for nearly two years. He is a CAPTAIN (retired) in the U.S. Public Health Service and is a former 25-year faculty member at the Johns Hopkins University School of Medicine.

Dr. Harman is certified in internal medicine and endocrinology by the American Board of Internal Medicine. He has authored one book and 19 book chapters, many in major textbooks of medicine, geriatric medicine and endocrinology. He is an internationally recognized expert on hormones and aging, and has authored more than 70 original research papers. [Please see Dr. Harman's biography for additional information.]

About KLRI

KLRI is a not-for-profit 501 (c) (3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. Translational research is the critical link between findings from the basic research laboratory and corresponding improvements in clinical care. In addition to KEEPS, KLRI currently is studying Testosterone Effects on Atherosclerosis in Aging Men (TEAAM Study). For more information, visit KLRI's Web site at www.kronosinstitute.org or www.keepstudy.org or call 1(866) 840-1117 or 1 (866) 878-1221.

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