



KRONOS LONGEVITY RESEARCH INSTITUTE

Research to promote a longer healthier life for you, your children, and your grandchildren.



4th Quarter 2002 Vol. 1, Issue 2

MENOPAUSAL HORMONE THERAPY: THE CONTROVERSY

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Before July 2002, more than 14 million American women were taking Menopausal Hormone Therapy (MHT), previously known as Hormone Replacement Therapy (HRT). Generally, American doctors agreed that the balance of risks/benefits for treating menopausal women long-term with estrogen and progesterin, known as combined MHT, was favorable for most women.

In 1998, the results of the Heart and Estrogen/progestin Replacement Study (HERS) trial were published showing no benefit of MHT for preventing new heart attacks in women who already had heart disease, and in the last two years, the controversy has risen.

Recently, discontinuation of the combined MHT portion of the Womens' Health Initiative (WHI) hormone trial resulted in a report being published in the *Journal of the American Medical Association (JAMA)* in

July 2002 that intensified doubts regarding MHT's value and risks. To understand this controversy and make informed decisions, you must know something about female hormones and what they do.

The female sex hormones, estrogens and progesterone, are steroids which are fat soluble molecules related to cholesterol. Estrogens cause the body to become feminine in appearance at puberty and stimulate the lining of the uterus, which is required for fertility and normal menstrual cycles.

- The main naturally generated estrogen, estradiol, is produced by the ovary.
- A second naturally generated estrogen, estrone, can be produced from other "precursor" steroids by adrenal, fat, liver, and other tissues.

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DIRECTOR'S MESSAGE

Understanding interventions for longer life and better health are as easy as I, II, III. To put health/longevity interventions in perspective, let's take a step back and discuss ways to classify them. First, there are "common sense" measures that create a healthier lifestyle. For example, quit smoking (or don't start), don't drink excessively (two average alcoholic beverages per day, one for women), wear your seatbelts, exercise regularly (both resistance and aerobic training), eat healthy, avoid obesity, keep mentally active, and maintain a social support network of friends and family. I think of these strategies as "Class I interventions." For most of them, there is good evidence for improved health and survival in studies on large populations. Class I measures are not controversial, although the details of how to accomplish them is sometimes a matter of opinion. There is little or no cost to implement them into your life, but they require knowledge, planning, and self-discipline.

Next, there are the Class II interventions which come from mainstream preventive medicine. They include such measures as:

- getting vaccinations against flu and pneumonia
- checking blood pressure
- getting hypertension under control
- measuring blood cholesterol
- receiving treatments to lower LDL (bad cholesterol) and raise HDL (good cholesterol)
- scheduling regular mammograms for women over 50
- scheduling digital rectal examinations and measuring PSA (prostate cancer screening test) for older men
- scheduling annual tests for blood in the stool and colonoscopy after age 50 for both sexes
- checking blood sugar to prevent diabetes, etc.

Most of these measures are proven in large prospective trials to help prevent potentially fatal age-related diseases, such as heart attacks, strokes, or cancer. There is, however, a controversy as to how often these preventative measures should be done and at what age, but all are offered by good primary care physicians. The surprising fact is how few of us actually take advantage of the full range of protection offered by Class II interventions.

Finally, there are the inconclusive Class III interventions. Some of these are strategies or treatments for which there may be some scientific evidence. I classify these interventions as Class IIIa. Class IIIa interventions may be "mainstream," but the risk/benefit ratio has yet to be completely defined, for example, menopausal hormone therapy (MHT). Others are scientifically plausible, in that they have known beneficial effects, but are even more uncertain and require further research. These include testosterone replacement in older men; human growth hormone (hGH) treatment for the normal decrease in GH that occurs with age; antioxidant supplements such as CoQ10, high doses of vitamins E or C, alpha lipoic acid, etc. Finally, there are Class IIIb interventions. These have little or no scientific evidence, but are often justified by anecdote and testimonials. They are generally not mainstream, but vary in how close to the "edge" they coast. Examples might include the use of DHEA and various herbal preparations like ginseng and saw palmetto. Some are heavily advertised products that promise eternal youth, strength, and virility, but have no scientific basis. The latter includes things like "clustered water," magnetic belts, etc. Many of these are harmless, but a few may actually be dangerous.

Unfortunately, there is no universal agreement as to which class a particular strategy belongs. However, using the criteria above, it is usually possible (and helpful) to arrive at a reasonable classification.

S. Mitchell Harman, MD, PhD
Director and President, Kronos Longevity Research Institute

- Progesterone is the hormone which matures the uterine lining. When progesterone-like drugs, progestins, are given as part of MHT, the uterus is protected from overgrowing and bleeding or forming cancers, which may happen when estrogen is given alone. Some progestins may decrease the beneficial effects of estrogens on blood cholesterol.

In addition, estrogens help maintain bone mass by preventing loss of calcium and appear to protect women against coronary heart disease. At menopause, women experience low estradiol levels and may have hot flashes, accelerated loss of bone calcium, and develop coronary disease at an accelerated pace. New studies suggest that estrogen deficiency makes women more vulnerable to Alzheimer's disease and loss of mental capacity.

The conclusion that estrogen has major benefits was supported by many scientific studies comparing large populations of menopausal women who decided to take MHT with women of the same age who did not. Experts concluded that, while long-term MHT was associated with a small increase in breast cancer risk, this risk was more than balanced by 40-60% reductions against coronary heart disease and bone fractures. Women taking estrogen were found to have lower death rates from all causes in several studies. The favorable risk/benefit ratio estimates were favorable because heart disease is approximately five times more likely to kill women over age 60 than breast cancer; and hip fractures contribute almost as much to disability and



death as does breast cancer in women over 70. These conclusions were strengthened by many studies, which showed that estrogens improved risk factors for heart disease, such as lowering "bad" cholesterol (LDL) and raising "good" cholesterol (HDL) by relaxing the muscles in the arteries, which make them more likely to open up. Estrogen also was shown to prevent formation of the bone cells that break down bones (osteoclasts).

The major source of controversy regarding the benefits of estrogen was the lack of controlled trials with enough women to confirm or deny the level of benefits observed in the epidemiologic studies. The skeptics correctly pointed out that MHT lacked the evidence required for FDA approval of a new drug to prevent heart disease. They were concerned because, in the older studies, users and non-users of MHT differed in important ways. There were some educational and economical differences between the users and non-users of MHT, which are associated with a reduced risk of coronary events. Therefore, it is possible that it was not estrogen, but rather differences in the lifestyles of women choosing to take MHT, known as "healthy user bias," that made the difference.

The perception that MHT was not on firm ground scientifically was compelling enough that the National Institutes of Health (NIH) funded a series of randomized trials in postmenopausal women. In these trials, equal numbers of research volunteers were assigned to take

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an active drug or an inactive preparation (placebo). There should be no initial health-risk differences between such groups. These investigations were expected to solidify knowledge regarding the risk/benefit ratio of MHT.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial used a commonly prescribed estrogen tablet, Premarin®. Women were given placebo or Premarin® at different dosages and with different progestins. Results showed increases in the HDL cholesterol and decreases in LDL cholesterol on all active treatments; along with an excellent preservation of bone density with estrogen, but not placebo. However, the PEPI trial

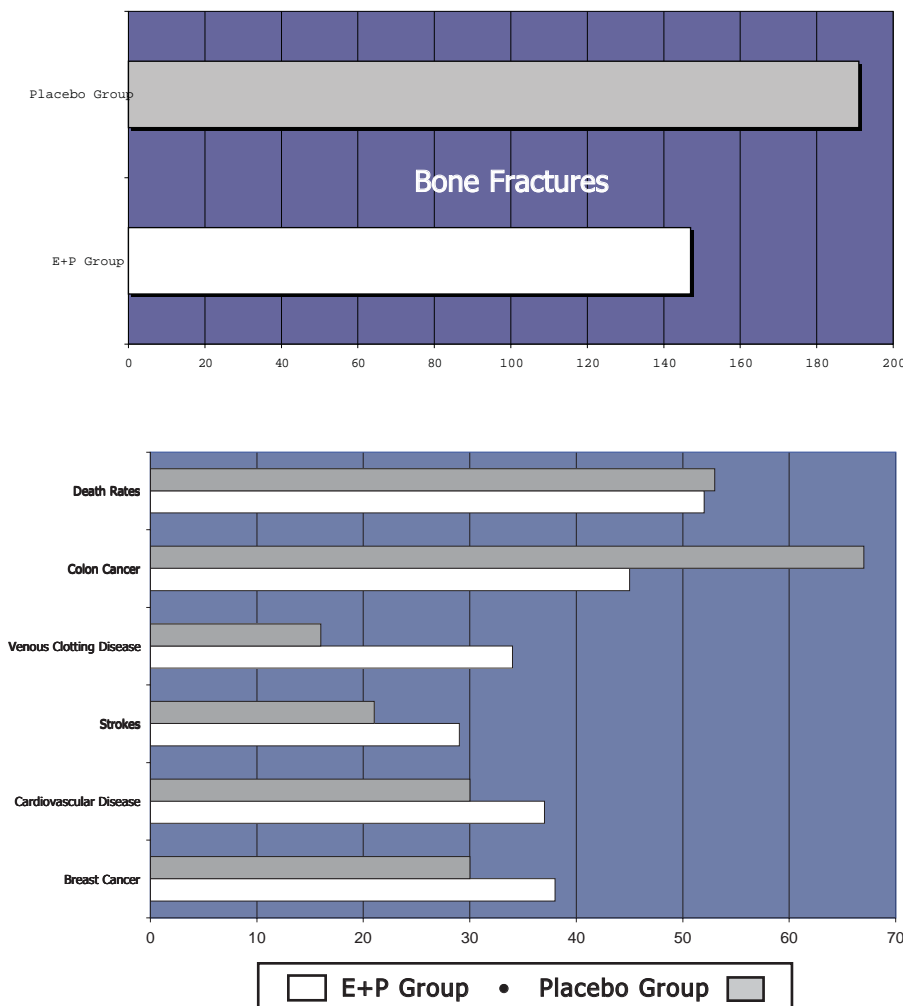
was not long or large enough to demonstrate differences in clinical outcomes, such as heart attacks or hip fractures.

The HERS trial was a study of secondary prevention of heart disease. Women entering this trial had coronary disease and were at high risk for a new cardiac event. This trial was disappointing to MHT advocates because after three years, the results were slightly worse in cardiac outcomes for women taking MHT. However, critics pointed out that most of the risk occurred during the first year and that, by the third year, a weak, but borderline significant, protective effect of MHT had appeared. Moreover, the question of greatest interest is

whether MHT works as primary, not secondary, prevention. The HERS trial was not designed to test this question.

Recently, the safety monitoring committee of the WHI trial decided to stop the estrogen + progestin (E+P) portion of the study. The WHI trial studied approximately 16,000 women in a randomized, controlled design comparing a combination of Premarin® and the progestin medroxyprogesterone acetate (Provera®) with placebo. The investigators reported the E+P group to have increases in new occurrences of breast cancer (38 vs. 30), and, rather than protection, an excess of cardiovascular disease (37 vs. 30), more strokes (29 vs. 21), and more venous clotting disease (34 vs. 16). The total death rates were 52 vs. 53. Beneficial effects were limited to a decrease in bone fractures (147 vs. 191) and an unexpected reduction in

E+P Group vs Placebo Group



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the rates of colon cancer (45 vs. 67). These benefits were considered insufficient to counterbalance the adverse effects observed. Based on the excess of breast cancer and the failure to protect against cardiovascular disease, the investigators concluded that combined MHT was not beneficial in postmenopausal women. Now millions of women are questioning whether they should take or discontinue MHT.

We must ask the question, "Why were these results so different from the observations during more than 30 years of epidemiologic studies?" Is it conceivable that the confounding differences between MHT users and non-users were so pronounced that there was a 40 to 60% lower risk of heart disease in the MHT users? Various attempts have been made to match volunteers or statistically control for educational and economical differences. Such studies have generally shown that there is still protection against heart disease in women taking MHT. Also, there was a study comparing age-matched women with continuing menstrual cycles vs. women who had an early menopause, where there was no choice made to use or not use MHT. It showed a greater incidence of coronary disease in the estrogen-deficient women.

Careful examination of the design and outcomes of the WHI trial reveal some potentially serious issues.

- Most heart disease events in the E+P group occurred in the first year.
- After the first year, the heart disease rates are similar. Thus, neither protection from nor worsening of coronary disease risk is apparent.

One explanation for these results is that oral estrogens cause an increased tendency for blood clotting. Estrogens cause the liver to make clotting factors and decrease its output of certain anti-clotting factors. Estrogens taken by mouth reach the liver in higher concentrations than estrogens produced by the ovaries. This effect may account for the excess of venous clotting disease observed in the MHT group. Most heart attacks are caused by the formation of a blood clot (thrombosis) on pre-existing plaque in the arterial wall. This occurs when such plaques become inflamed and break open. One hypothesis is that if significant numbers of women in the WHI study had pre-existing coronary plaques, then they were more susceptible to clot formation, due to oral estrogens' potential for clotting.

So we ask, is there evidence that the women studied in the WHI might have had pre-existing coronary atherosclerosis? The vast majority had no previous heart symptoms. However, a study of more than 4,000 women with no symptoms of heart disease showed that the "burden" of coronary atherosclerotic plaque becomes substantial in women over 60. This study found that menopausal women, ages 45 to 55, have little or no plaque burden, but that plaque increases rapidly after menopause. Because the WHI study observed women from ages 50-79 with only 33% between the ages of 50 and 59 (the average age being 63 years), many of the women studied had significant amounts of plaque in their coronary arteries. In these women, what the WHI study was really examining was not primary, but rather secondary prevention.

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The clotting hypothesis could account for the increased events observed in the first year whereas in subsequent years, there was no apparent protection by MHT. One explanation is that after the first year, heart-protective effects and clot-forming effects of estrogens were nearly balanced in this population. The bigger question becomes why estrogen had such convincing protective effects in the previous studies. A factor could be the older ages and late start of MHT in the WHI study, which differs from the traditional use of MHT by women in the epidemiologic observational studies. In the prior studies, most women initiated MHT at or near the menopausal transition and were much younger than those in the WHI trial. Thus, WHI women were at greater risk of coronary clotting when exposed to oral estrogens than the MHT “self-starters.”

Although the WHI study has been represented by some as the “definitive last word” on MHT, it leaves much doubt. Women are still asking, “Should we start, continue or discontinue MHT?” There are many questions left to answer:

- Does initiating MHT in women at the menopausal transition provides significant protection against coronary disease.
- Is the alternative way of administering the natural estrogen, estradiol using a patch, gel, or cream, a method known as “transdermal” safer? Transdermal estrogen does not go to the liver in high concentrations and has been shown to have little or no effect on clotting.
- Is estradiol more benign regarding breast cancer than conjugated estrogens, or are lower doses than previously used in the WHI safer, while retaining beneficial effects.
- Would an alternative progestin, such as natural progesterone, produce less risk of breast cancer.



Until these issues are addressed by new trials or further data analysis, it seems prudent to limit conclusions from the WHI to the statement that initiating continuous oral estrogen and medroxyprogesterone acetate in women over age 60, who have not been on MHT before, is probably not advisable. Some physicians suggest that protection of heart and bones can be achieved by using drugs that improve cholesterol, such as the “statins” or niacin, and agents that reduce bone loss, such as the bis-phosphonates (for example, alendronate or risedronate). However, these agents are currently indicated for treatment of severely elevated cholesterol and existing (not prevention of) osteoporosis. They have adverse effects of their own, and do not deal with other aspects of estrogen deficiency, such as hot flashes, thinning of the vaginal lining, etc.

After the recent studies, including the WHI, doctors and scientists find themselves still asking the same question, “Should I advise women at or near menopause to start using MHT?” Relying on the older studies, most women would probably stand to benefit. The same may be true for older women who have taken MHT for many years beginning when they first became menopausal and are now wondering whether to stop. We hope that appropriately focused clinical trials will clarify these issues in the near future.

S. Mitchell Harman, MD, PhD is the director and president of Kronos Longevity Research Institute (KLRI) based in Phoenix. He is an internationally recognized expert on the effects of aging on hormone regulation and the use of hormone therapy in older men and women.

SHOULD POPEYE BE EATING CHOCOLATE INSTEAD OF SPINACH?

PHYTOCHEMICALS AND OPTIMUM NUTRITION - PART 1

**This article is the introduction to a two part series to be published in KLRI Kronicle. To be added to our newsletter mailing list, please call (602) 778-7499 or email info@kronosinstitute.org.*



Eat less and don't eat empty calories. In other words, eat (and drink) only enough to maintain your lean body mass and only foods that contain a nutritional payoff beyond their simple energy content. Optimum nutrition requires the consumption of not only the proper amounts of macronutrients (proteins, carbohydrates, and fats) but, also, the proper amounts of micronutrients (vitamins, minerals, and phytochemicals). Once enough of the proper foods have been consumed to obtain the nutrients (both macro and micro) the fewer additional calories consumed the better.

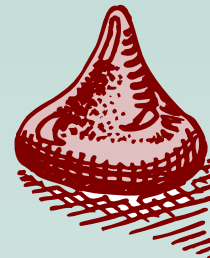
Modern nutrition research has moved past studies of the basic food groups to studies of the specific nutrients in different foods within those groups. Nutrition experts have reported for years that diets low in fat and high in fruits and vegetables are linked to lower risks of heart disease and cancer, but now they are becoming

more specific. The USDA's food pyramid generally tells us to eat five servings of fruits and vegetables a day, but other reports specifically advise us to eat dark green vegetables like spinach and broccoli. Evidence is emerging that certain chemical components (antioxidants) found in colorful foods (such as red wine, blueberries, and even chocolate) may be responsible for a wide variety of health benefits.

Antioxidants - Many studies show a definite relationship between nutrition and health; however we don't really know the details of this relationship. As part of their research into the mechanics of human health, scientists are investigating antioxidants and how they may guard against diseases. The most commonly studied antioxidants are Vitamin C, Vitamin E, and beta-carotene, which are found in a wide range of fruits and vegetables.

More recently, a group of plant derived substances called polyphenols has begun to receive a lot of attention. Polyphenols are a large group of antioxidants composed of several subgroups, including flavonoids and tannins. Generally speaking, scientists investigating the links between nutrition and health are interested in antioxidants because they may help reduce the oxidative stress associated with normal and abnormal chemical reactions within the body.

Oxidation is dangerous because it produces free radicals. Free radicals are substances that have lost an



electron, leaving them incomplete and looking for a way to become whole again. They will snatch an electron from another molecule to balance their own electrical charges, leaving the second molecule unbalanced and setting off an uncontrolled chain reaction called free radical propagation. Oxygen free radicals produced in this way may disrupt normal biochemical reactions, leading in some cases to damage of vital biological molecules such as DNA, RNA, lipids, and proteins. The chemical structures of polyphenols make them natural deterrents to propagation. Thus, polyphenols have excellent antioxidant effects because they are able to absorb oxygen free radicals.

This article overviews the scientific basis for the Kronos Optimal Nutrition Program, which provides the nutritional assessments and dietary prescriptions provided to Kronos patients as part of their custom-tailored Optimal Health Program.

*** A complete list of references for this article series is available upon request. Please call (602) 778-7499 or email info@kronosinstitute.org for a copy.*

In the Next Issue...



Nutrition - The Kronos Approach

In a nutshell, Chris Heward, PhD will discuss how to reduce caloric intake without sacrificing nutrient intake. The Optimal Nutrition Program is a whole new way of thinking that will help you achieve a body weight and composition (% fat) more consistent with optimal health.

STUDY FOCUS

V alidation of Oxidative Stress Assessments:

This multi-stage project characterizes and validates laboratory methods for assessing oxidative stress status in human beings. Over the last few years, research evidence has been accumulating that damage to cell components (proteins, cell membrane lipids, and the DNA of both chromosomes and mitochondria) by oxygen free radicals (also known as “reactive oxygen species” or ROS) is an important mechanism of aging. Oxidative damage also may play a role in various age-related diseases, such as Alzheimer’s, arthritis, diabetes, and atherosclerosis. ROS are generated during the process of energy production in the cell’s miniature “furnaces,” the mitochondria. While most reactive oxygen produced by the mitochondria is used to oxidize fuel and generate high-energy phosphate compounds, which can be used by the cell for energy requiring processes, some ROS “escape” and can react chemically with various cell components. KLRI plans to conduct oxidative stress assays in various human populations in order to validate assays to be used to evaluate promising interventions.



You make a difference!

PARTICIPATE IN A KLRI STUDY

Currently, we are recruiting for the following studies:

- ✓ **Validation of Oxidative Stress Assessments:** The objective is to characterize and validate laboratory methods for assessing oxidative stress. Qualification and time requirements for this study are simple. The qualifying age range is healthy men and women ages 20-89. The time required is a five minute phone interview, and if you qualify, about three hours at the KLRI Clinic.
- ✓ **Omega-3 Fatty Acids and Endocrine/Immune Dysfunction in Humans:** The objective is to examine the effects of a diet high in omega-3 fatty acids on the endocrine dysregulation of normal aging. The qualifying age range is healthy men and women ages 60-75. The time required is a five minute phone interview, as well as, a fish-enriched diet plus nutritional supplements for 18 weeks and time at the KLRI Clinic.

- ✓ **Coenzyme Q10 and Myocardial Function in Patients on Statin Drugs:** The objective is to determine whether the use of hMG-CoA reductase inhibitors (statins) compromises myocardial reserve and if coenzyme Q10 supplementation can reverse this effect. The qualifying age range is healthy men and women ages 45-70 with hyperlipidemia requiring initiation of statin therapy. The time required is a five minute phone interview and the study duration is 30 weeks, with visits to the KLRI Clinic in 10 week increments.

To participate in a study, please call SP Services at (602) 778-7480. Compensation for time and travel varies per study.

We thank you!

We thank the many people who have registered to participate in studies at KLRI. A special thanks to those who have completed a research study.



DIRECTOR'S FORUM

The Director's Forum gives you direct access to the scientific faculty at KLRI. Also, an event will be held to communicate the latest scientific discoveries in longevity research, study status and potential studies being considered. The Forum will also include information

on government issues that may affect the progress of longevity research. The Forum is comprised of our valued friends and supporters. To join our Director's Forum, please call (602) 778-7499.

WHY IS LONGEVITY RESEARCH IMPORTANT?

A FEW OF OUR CONCERNS

- Americans are living longer, but not healthier. Those over age 85 – the oldest of the old – will increase from 4 million today to nearly 19 million by 2050. This group will include more than 1 million centenarians.

- There is a significant lack of qualified health-care providers for the elderly. By 2030, the United States will need up to 36,000 geriatricians and will fall far short of that figure by as many as 25,000 unless effective steps are taken to train new providers.

- Older Americans will soon account for half of all health-care expenditures. Currently, this population accounts for 36 percent of hospital stays, 49 percent of all days of hospital care

and 50 percent of all physician hours.

- Elderly patients are often misdiagnosed and, consequently, mistreated. A study published in the *Journal of the American Medical Association* (December 2001) shows more than one out of every five patients receives prescriptions for inappropriate drugs.

In order for the United States to effectively manage the impending "Senior Boom," we must commit a significant amount of resources to longevity research. Currently, less than one percent of the entire budget of the National Institutes of Health (NIH) is devoted to studying the basic biology of aging. Tens of billions of dollars

are spent annually on the specific study of age-related diseases such as cancer, diabetes, etc., but few dollars are invested in understanding how the processes of aging will impact those illnesses.

By educating Americans about the true health needs of older people, KLRI hopes to propel the issue of longevity research to the forefront of the public agenda. We need more funding in order to continue important studies and prevent the imminent health-care crisis.

Source: Alliance for Aging Research, "Medical Never-Never Land: Ten Reasons Why America is Not Ready for the Coming Age Boom."

DONATE NOW! **BE A PART OF KLRI'S MISSION**

You make a difference; longevity research is vital to all of us. Everyone benefits. All donations will directly benefit research; KLRI's administrative costs are funded. KLRI is a not-for-profit organization, all gifts are tax deductible. KLRI accepts individual and corporate contributions, planned giving and major gifts. Your donation will be recognized at KLRI. Research changes the world; we cannot find cures for chronic diseases or learn to live healthier, longer lives without research. Remember, the inquisitive scientific minds contribute to every aspect of your lifestyle every moment. For questions or to donate, please call (602) 778-7481.



Who we are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization conducting state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

KLRI also performs research to increase our healthy years by improving muscle strength, understanding the role of various nutritional components in our diets, and achieving a better grasp of human aging physiology.

There are many anti-aging remedies and recommendations on the markets today. However, most lack scientific evidence, and have potential side effects. We need reputable scientific organizations to spearhead research to further our understanding of treatments developed to increase our healthy years. Our world-renowned scientific team is comprised of experts in their fields, who are conscience driven to perform at their highest potential to ensure that all research projects are safe, carefully performed and accurately communicated. The KLRI studies performed differ from those of many narrowly focused institutions because we have a wide range of scientific expertise and our focus is on aging itself rather than a single disease.

OUR MISSION

To perform and foster clinical translational research aimed at healthier human longevity and communicate results to the professional and lay communities.

OUR GOVERNANCE

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders govern KLRI. There is also a scientific advisory board of recognized international experts in medical and scientific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer, and heart disease.

WHAT IS AGING?

We see the effects of aging on a grand scale (i.e., graying hair, wrinkling skin, and the development of chronic diseases). We see these effects on a macro level because they are visible to the eye, when actually, they occur on the molecular level. Regardless of the species, a vicious cycle of damage occurs, which results in declining system function and ultimately leads to the deterioration of the organism. The body does implement natural repair mechanisms in an attempt to repair damage at the nuclear and mitochondrial levels. However, the rate of repair cannot keep up with the rate of damage.

So exactly, what is aging? We don't know yet!!! Hence, the Kronos Longevity Research Institute.



RAY CHARLES STILL WOWING CROWDS AT AGE 72

KLRI'S FIRST BENEFIT DINNER AND CONCERT WAS A HIT

International phenomenon and 12-time Grammy Award winner Ray Charles has taken virtually every form of popular music and broken through its boundaries with astounding results. Rhythm and blues (R&B) became universally respectable through his efforts. Jazz found a mainstream audience it had never previously enjoyed. And along the way, Ray Charles was instrumental in the invention of rock 'n' roll.

He is the master of soul, both musically and personally, and the 72-year-old musician made that clear at his Celebrity Theatre performance November 10, 2002. The near-capacity crowd included KLRI supporters who attended the Institute's first benefit concert and dinner, which featured the sensational Ray Charles.

After an entertaining introductory set by his big band, Ray Charles took the stage around 8:30 p.m. and performed many of the hits from his latest disc, "Thanks for Bringing Love Around Again." Highlights of his Phoenix concert included "Georgia on My Mind" and three songs performed by the Raelettes, the heavenly accompanying voices behind his great sound.

"Independence is a hell of a thing, man. And we all appreciate it. I know I do. I feel strongly that, right now, the best way for me to maintain purity and deliver to my fans the music that I believe they want from me is by doing it my way," Ray Charles said. "I can go out and release what I want when I want to. It's the best possible situation for me at this point in my artistic and business career."

For more information on upcoming KLRI benefits, please call (602) 778-7499.



ASK THE DIRECTOR

What is a placebo?

A placebo is an inactive harmless agent used for testing against the active drug. The results of the active compound are compared with the placebo to better understand the actions of the active supplement/drug. One group of participants will receive the experimental drug, while the second group will receive a standard treatment or placebo. Often the participant and the study coordinator is not told which group is getting the actual drug, and which is receiving the placebo. This method is used as a way to prevent bias on the part of the patient and the doctor.

How is clinical research funded?

KLRI sponsors certain clinical studies initiated by the physicians, as part of its ongoing commitment to clinical research. Additional funding may come from the federal government (via the National Institute of Health) or from philanthropic private donations to KLRI that are earmarked for research.

To Ask the Director, please submit your question via email to info@kronosinstitute.org or write to 4455 E. Camelback Rd., Suite B-135, Phoenix, AZ 85018



GLOSSARY

ABC

Antioxidant - One of many types of molecules in our cells which can safely combine with oxygen free radicals, thus rendering them harmless.

Average Life Expectancy - The age at which 50 percent of the members of a population have died, when plotted on a standard survival curve. This statistic is normally calculated from birth, but may be recomputed in terms of expected years remaining at any age.

Baseline - The status of a research subject before any treatment or intervention is begun.

Bis-phosphonates - A class of drugs that help to stabilize calcium in bone (alendronate and risedronate are two bis-phosphonate drugs currently FDA-approved for the treatment of osteoporosis).

Desoxyribonucleic acid (DNA) – DNA is the genetic material. DNA molecules consist of long antiparallel (running in opposite directions) chains of four different nucleotides (abbreviated "A," "T," "G," and "C".) Their order encodes the sequences of all the proteins used by living things. The chains are arranged in a double helix wrapped around each other in a spiral and bound together so that each "A" is paired with a "T" (A:T pair) and each "G" is paired with a "C" (G:C pair). Thus, when the chains unwind and separate, new identical antiparallel sequences can be copied along their lengths, allowing cells to produce daughter cells with the same genetic code.

Flavonoids - Compounds widely distributed in nature as pigments in flowers, fruit, vegetables, and tree barks. Some flavonoids have biological activities and may make a useful contribution to the total antioxidant activity of foods.

Macronutrients - Nutrients that living organisms need in relatively large amounts to sustain growth and health (such as protein and carbohydrates).

Medroxyprogesterone acetate - A popular drug resembling progesterone in action, but which is more soluble in water and hence more easily absorbed when taken by mouth.

Micronutrients - Any essential dietary element that is required only in small quantities in order to sustain growth and health.

Mitochondria - The tiny energy factories in our cells that combine oxygen and sugar to produce a high energy compound that is needed for all cell activities.

Oxidative Stress- Describes the state or rate of ongoing damage to cells and tissues in an organism due to reactive oxygen species (ROS). The most common forms of ROS, such as superoxide and hydroxyl free radicals, are generated from the metabolism of oxygen for energy production and exist in all aerobic organisms. Some toxins from the environment (such as cigarette smoke) also contain or generate ROS. The net damage rate depends on the balance between ROS generation and organismal defense and repair.

Plaques - The hardened, swollen areas on the inner wall of an artery where cholesterol and inflammatory cells have altered and damaged the normal smooth structure.

Phytochemicals - Technically, the term "phytochemical" refers to any chemical produced by a plant. This term usually refers to certain plant chemicals (such as carotenoids) that scientists believe may impart health benefits.

Ribonucleic acid (RNA) - RNA is a sequential chain of the nucleotides Adenosine, Guanosine, Thymidine, and Uridine. In RNA, the sugar molecules are ribose. RNA is typically single stranded. The sequence of most RNA molecules is copied from specific DNA sequences by enzymes in a process called transcription.

Tannins - A group of simple and complex phenol, polyphenol, and flavonoid compounds produced by plants. Tannins are generally protective substances. Their physiological effects vary, however, all tannins act as astringents, shrinking tissues and contracting structural proteins in the skin and mucosa.

Many of the terms above are taken from Kenneth W. Wachter and Caleb E. Finch, Eds., Between Zeus and the Salmon: The Biodemography of Longevity, pp. 269-274 (National Academy Press, Washington, D.C.; 1997).

Calendar of Events 2003

JANUARY 24

PROFESSIONAL EDUCATION SEMINAR*

Speaker: E. Jeffrey Metter, MD
Topic: Aging and Neuromuscular Function

FEBRUARY 5-7

PROFESSIONAL EDUCATION BIOMEDICAL GERONTOLOGY SYMPOSIUM*

Topic: Diet, Health, Aging and Longevity:
Good Fat, Bad Fat
Location: The Wyndham Buttes

FEBRUARY 7: 1:00 – 5:00 P.M.

THE SCIENCE OF GOLF TOURNAMENT

THE PHANTOM HORSE GOLF COURSE AT SOUTH MOUNTAIN
(SEE INFORMATION ON PAGE 15)

FEBRUARY 7: 6:30 P.M.

BREAKING THE RULES OF AGING DINNER & BOOK SIGNING DR. DAVID LIPSCHITZ

(SEE INFORMATION ON PAGE 15)

FEBRUARY 14

PROFESSIONAL EDUCATION SEMINAR*

Speaker: Adrian Dobs, MD
Topic: Testosterone (T) in Older Women

FEBRUARY 28

PROFESSIONAL EDUCATION SEMINAR*

Speaker: Barry Zirkin, PhD
Topic: Male Reproductive Aging, Mechanisms and Consequences

MARCH 14

PROFESSIONAL EDUCATION SEMINAR*

Speaker: James Nelson, MD
Topic: Probing the Role of Hormones in Aging
Processes: Taking Clues from the Calorie-Restricted Longevity Model

MARCH 28

PROFESSIONAL EDUCATION SEMINAR*

Speaker: Paula C. Bickford, PhD
Topic: Motherly Advice Proven Correct: Eating Fruits and Vegetables Improves Functional Life Span

APRIL 11

PROFESSIONAL EDUCATION SEMINAR*

Speaker: Woodie Wright, MD
Topic: Telomeres, Stem Cells and Aging

Professional Education*

Programs designed to educate practicing physicians and other healthcare providers to increase/supplement aging awareness. KLRI sponsors local bi-monthly seminars and a national symposium featuring world-renowned gerontologists, which provide continuing education for medical and science professionals in the field of aging. Continuing Medical Education credits are available for all these seminars. Additional information can be found on our web site (www.kronosinstitute.org) or by calling (602) 778-7499.

Public Education

KLRI faculty speak at numerous events and are willing to speak to you. Topics focus on strategies for living longer, healthier lives. Examples include:

- Aging and the onset of chronic disease (heart disease, diabetes, etc.)
- How exercise can impact your life
- The importance of mental exercise and activities, ways to stay sharp
- Nutrition

Kronos Longevity Research Institute

presents...

The 2003 Biomedical Gerontology Symposium "Diet, Health, Aging and Longevity: Good Fat, Bad Fat"

The Wyndham Buttes Resort
Phoenix Metropolitan Area

February 5-7, 2003

The symposium will assemble a panel of experts to address the role of dietary fats in aging and age-related diseases. The potentially beneficial effects of omega-3 polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) on health and disease will be discussed, as well as the evidence for adverse effects of saturated fats, trans-fatty acids and omega-6 PUFAs. The speakers will review basic research addressing modulation of cellular function by fatty acids, define the current state of knowledge regarding clinical effects of dietary fatty acid content and project future research needed to arrive at realistic nutritional recommendations.

Symposium Speakers:

- ◀ Richard G. Cutler, PhD
KLRI, Phoenix, AZ
- ◀ Jan Eritsland, MD
Ullevål University Hospital, Oslo, Norway
- ◀ Gabriel Fernandes, PhD
The University of Texas Health Sciences Center, San Antonio, TX
- ◀ William Lands, PhD
College Park, MD
- ◀ Alexander Leaf, MD
Harvard Medical School, Charlestown, MA
- ◀ Claudio Galli, MD
University of Milan, Milano, Italy
- ◀ S. Mitchell Harman, MD, PhD
Phoenix, AZ
- ◀ Bruce J. Holub, PhD
University of Guelph, Ontario Canada
- ◀ George Roth, PhD
GeroTech, National Institute of Aging, Baltimore, MD
- ◀ Norman Salem, Jr., PhD
National Institute on Alcohol Abuse & Alcoholism, Bethesda, MD
- ◀ Artemis P. Simopoulos, MD
Center for Genetics, Nutrition & Health, Washington, DC
- ◀ Arthur A. Spector, MD
University of Iowa, Iowa City, IA
- ◀ Leonard Storlien, PhD
AstraZeneca, Mondal, Sweden
- ◀ Panayiotis D. Tsitouras, MD,
Phoenix, AZ

&

Special Golf Tournament, Benefit Dinner, & Book Signing

featuring

Keynote Speaker Dr. David Lipschitz,
Director of the Center on Aging at the
University of Arkansas for Medical Sciences & Author

Friday, February 7, 2003

Dr. Lipschitz has published more than 200 scholarly articles and hosted an award-winning, 26-part PBS series entitled "Aging Successfully with Dr. David." He also has authored a new book, "Breaking the Rules of Aging."

The Science Of Golf Tournament

The Phantom Horse Golf Club at South Mountain

A nine-hole golf tournament, aptly titled, will take place from 1-5 p.m. Players will be divided into teams. You will need to use your scientific knowledge as well as your golfing skills to secure top honors at this tournament.



Do you like golf, but aren't comfortable in a tournament setting? Then KLRI's tee-off program, "Golf Tournaments Demystified," is just for you! This program, which will be held from 1-3 p.m., is an opportunity to learn about tournaments, golf etiquette, strategy and gender-related issues. There also will be a skills clinic and a mock scramble tournament complete with prizes.

Registration

Symposium	\$135/person
The Science of Golf	\$125/person
Tee-off Program	\$100/person
Benefit Reception, Book Signing & Dinner	\$100/person

Please contact KLRI at (602) 778-7499 for more information on purchasing a golf and/or dinner package.

KLRI Staff

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