



KRONOS LONGEVITY RESEARCH INSTITUTE

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



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## HEART DISEASE – UNDERSTANDING IT’S PERSONAL

### IN THIS ISSUE...

- Hear Disease..... 1
- Director’s Message ..... 2
- Professional/
  - Public Education ..... 5
- The WHI Misunderstood ..... 6
- Improving Health Outcomes
  - for Older Adults ..... 12
- Who We Are! ..... 13
- Board Member Profile.....14
- Board of Directors/
  - Scientific Advisors ..... 15
- Glossary ..... 15
- Participate in a Study ..... 16
- KLRI Staff ..... 16

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The most recent issue of the medical journal, *Circulation* (Volume 109, page 672, Feb, 2004) includes the new American Heart Association (AHA) guidelines for prevention of cardiovascular disease in women. These recommendations were based on a rigorous evaluation of nearly all the available scientific evidence to date by a panel of 27 experts on cardiovascular disease and women’s health. Studies evaluated were limited to those with true clinical endpoints, that is actual cardiovascular events. For example, studies which provided only indirect evidence associating a risk factor, such as obesity, with heart disease were not considered, whereas studies examining the effect of an intervention, such as weight loss, were included.



The importance of heart disease prevention for women can hardly be

overemphasized. Coronary heart disease is the single greatest killer of American women, extinguishing more lives (approximately one death per minute) than the next seven leading causes of female mortality. Interestingly, women’s perception of the leading threats to their lives is not in tune with reality (see Figure 3). According to a recent Gallop poll, women are far more concerned about cancer, and, in particular, breast cancer, than about heart disease.

This fact is a testimony to the effectiveness of the public information and education programs of the American Cancer Society and the National Cancer Institute, and certainly women are well-advised to continue pursuing appropriate measures to prevent cancer including

continued on page 3





## DIRECTOR'S MESSAGE

### C

hoosing Your Mode of Exit

Buckle your seatbelts, friends. This one is going to be a little grim. In conversation with a dear colleague and his wife in Bethesda, MD, in early March, I was somewhat surprised to hear my colleague's wife, a breast cancer survivor, say that she would rather die of a "nice clean heart attack" than go through the agonies associated with death from cancer. She was citing this sentiment as a reason why she would not want to take estrogen replacement treatment, even if, in the long run, estrogen does prove to protect women against heart disease. Heart disease (see our feature article) kills four times as many women as all cancers put together, and I was trying to make the point that one could justify pursuing a strategy that would give the highest probability of long-term survival, even if it means trading a small increase in risk of breast cancer (the highest estimates are about a 30% increase) for a 40% reduction in risk of cardiovascular disease.

I say "somewhat surprised" because I have heard this same idea expressed by other women at various times, but I assumed that my colleague's wife would be better informed regarding heart disease. The fact is that in the majority (over 60%) of people affected, coronary heart disease is a progressive chronic illness, which leads to heart failure, a condition in which their damaged hearts are unable to pump enough blood to sustain normal activities. Patients become progressively disabled and short of breath. Fluid accumulates in their legs and lungs. Modern treatment uses a large pharmacopoeia of highly effective drugs (beta-blockers, statins, ACE inhibitors, diuretics) to draw this process out over many, many years, but, in the end, sufferers succumb to the relentless loss of heart function, drowning in their own body fluids.

It seems that there is little to choose between these two modes of exit. While we are discussing modes of exit, another advantage of estrogen treatment is that it is highly protective against osteoporosis and bone fractures (by some estimates reducing fractures by as much as 60%). Before dismissing this fact with a shrug ("What's a broken bone or two compared to cancer?"), you should be aware that hip fractures are a major cause of death and disability in women older than 65. Approximately half of women who fracture a hip become permanently disabled and a third are dead within three months from complications (usually pneumonia). In the 70+ age group, death from complications of hip fracture is about as common as death from breast cancer. Yet, I have never seen fractures factored in when the overall risk/benefit ratio of estrogen treatment are calculated.

The bottom line is that, until we find the cure for aging (we gerontologists are still working very hard on this), there is no guaranteed, "good way to die." The best strategy then, is to pursue a course designed to optimize health and longevity. This includes regular exercise, healthy nutrition and dietary supplementation as appropriate for the individual, as well as cholesterol-lowering and other preventive medications when indicated. For some (high risk for osteoporosis, low risk for breast cancer), this might include hormone replacement therapy. I still believe that the weight of evidence favors a heart-protective effect of estrogen, when given at the right dose and by the right route, but this remains to be shown (or disproven) by well-designed new research.

*S. Mitchell Harman, MD, PhD  
Director and President*

regular breast examinations, annual mammograms and PAP smears, etc. Nonetheless, women should be aware that far more is known about risk factors for heart disease than for cancer, and, in general, heart disease risk factors are more susceptible to interventions with demonstrable improvements in outcomes. Therefore, it is critically important for women (and their doctors) to understand what risk factors should be determined and what measures can be taken to lower their risk of coronary heart disease.

The coronary arteries supply the heart muscle with blood. Coronary artery disease, which is the most common cause of heart problems in adults, is due to a complex and prolonged process called atherosclerosis. This word translates literally as “artery hardening.” Atherosclerosis is extremely common. It appears to begin as early as childhood or adolescence, and proceeds slowly during the entire lifespan. The process starts with small deposits of cholesterol and fat in the walls of the arteries called “fatty streaks.” Next, white cells from the blood invade these streaks and ingest the fat, so that clusters of “foam cells” form within the streaks, which are now called plaques. Next, some of these cells die leaving areas of fatty debris. Cell death provokes inflammation and scarring, causing a “cap” of fibrous scar tissue to form over the plaque. Crystals of calcium phosphate tend to deposit in the dead material, making the arteries brittle.

As the plaques grow thicker, the inside of the affected areas of the arteries narrow, so that blood flow is

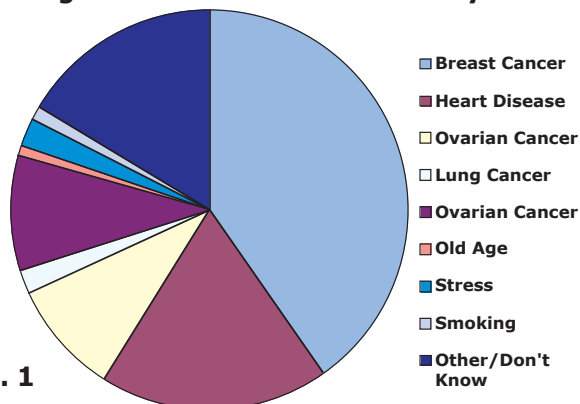


obstructed. When the narrowing reaches 80% or more of an area of coronary artery, symptoms of angina, chest pain during stress or exercise, may occur. Finally, there is a tendency for plaques to break down, losing their fibrous caps. When this happens, the blood comes in contact with fatty and dead material, causing a clot (thrombus) to form. Such clots may block the artery completely causing a heart attack (myocardial infarction) as an area of heart muscle, deprived of blood flow and oxygen, dies. Such episodes are frequently fatal, and, even when survived, leave the heart scarred and prone to rhythm abnormalities and reduced function (heart failure).

Fortunately, over the last 30 years or more, medical science has learned a great deal about the factors that contribute to atherosclerosis and heart attacks and how they can be measured and altered. The new AHA guidelines describe a scale for classifying a woman’s heart attack risk and, based on this classification,

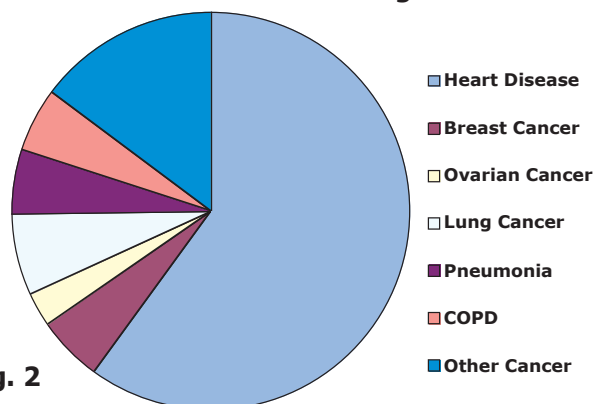
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**Leading Causes of Death Perceived by Women**



**Fig. 1**

**Actual Causes of Death Among U.S. Women**



**Fig. 2**

recommend graded interventions to reduce this risk. Factors that classify women into the “high risk” category (probability of a heart attack greater than 20% in the next five years) are:

- A previous heart attack or angina
- Symptoms from arterial disease in arteries other than the coronaries including
  - o aortic aneurysm
  - o stroke (cerebrovascular disease)
  - o peripheral artery disease
- Diabetes
- Chronic kidney disease

An “intermediate risk” classification (probability of a heart attack 10-20% in the next five years) is made for:

- More than a minimal amount of coronary artery calcium (seen on special x-rays) without symptoms
- The metabolic syndrome (abdominal obesity, high blood sugar and insulin levels, high blood pressure, and low plasma HDL cholesterol and high triglyceride levels)
- Multiple risk factors (such as elevated LDL cholesterol with high blood pressure)
- Markedly elevated levels of a single risk factor
- First degree relative with early onset heart disease (male <55 years, female <65 years)

The “lower risk” (probability of a heart attack less than 10% in the next five years) category may include women with one or more risk factors, depending on the severity with which the factor(s) are affected.

Finally, “optimal risk” is used to describe women with excellent levels of known risk factors and a heart-healthy lifestyle.

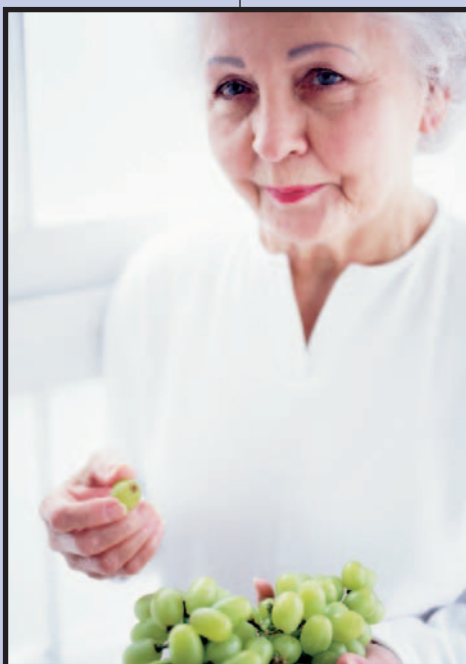
The article in *Circulation* also includes a detailed scoring sheet for determining heart disease risk category by age, range of total

cholesterol, levels of HDL (“good”) cholesterol, smoking history, and blood pressure. A similar, but more detailed scoring sheet is available on the Web at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Not included on this scoring sheet are other known risk factors such as C-reactive protein (also known as “CRP,” a marker of inflammation), coronary calcium determined by X-ray scanning, glucose intolerance (high sugar and insulin levels) best determined by a glucose tolerance test, size classification of blood cholesterol particles, Lp(a) (a modified lipid particle in blood), or homocysteine (a product of amino acid metabolism), all of which are independently associated with increased heart disease risk.

We believe there is enough evidence for the importance of the additional risk factors above that they should be taken into consideration in ultimate determinations of risk. However, currently there is no simple scheme that exists for including these factors in a “risk score.” To reach the most accurate estimate of heart attack risk, we recommend that, between the ages of 40 and 55, women should have this entire set of risk factors measured. Because atherosclerosis appears to accelerate after the menopause, and because lipid profiles (total, LDL and HDL cholesterol and triglycerides) tend to change for the worse at menopause, we further suggest these measures be obtained within a few months after menses cease.

Depending on the severity of risk, determined by risk factor measurements, the AHA panel recommends a graded series of interventions, based on evidence from a large number of carefully reviewed studies. In addition, they provide numerical ratings of the likely effectiveness of potential interventions in women. The strategies evaluated ranged from

*continued on page 5*



regular exercise and a “heart-healthy diet,” both of which have high effectiveness and reliability ratings and are recommended for everyone regardless of risk, to the use of lipid lowering drugs (such as the “statins”) and blood pressure drugs, which are recommended only for women with high risk and/or certain specific conditions. These recommendations are too complex to describe in detail here and should be discussed by women with their physicians after results of risk factor determinations have been obtained and evaluated.

The only evaluation in which we did not agree with the AHA panel’s recommendation is that menopausal hormone replacement therapy (MHT) not be given for prevention of heart disease. We have discussed this question in a previous issue of the Longevity Kronicle. To summarize, we believe that the panel’s conclusion regarding MHT is unduly influenced by the results of the Women’s Health Initiative (WHI) study and other studies of MHT in older women with existing heart disease. From our own review of the literature, we have concluded that the available evidence supports the conclusion that MHT initiated early (at or near the menopausal transition) in women younger than those studied in the WHI hormone trial, is probably effective in preventing coronary heart disease. Unfortunately, no large, randomized, controlled, prospective trial of early MHT treatment has been done to date. The evidence considered by the AHA panel is valid for women in whom MHT is started 5-20 years after the menopause, but should not be generalized to younger women.



Therefore, we would rate the effectiveness of MHT, started at the menopausal transition, as class II (usefulness/efficacy is less well established by evidence/opinion) B (limited evidence from single randomized trial or other nonrandomized studies). This is quite different from the AHA panel’s rating of III (intervention is not useful/effective) A (sufficient evidence from multiple randomized trials).

To summarize, the current recommendations of the AHA panel for cardiovascular disease prevention in women provide important and useful information for women and their physicians. Early intervention to prevent atherosclerosis progression and age-appropriate assessment of risk factors would substantially reduce the rate of coronary heart disease, the number one killer of American women. However, the science supporting these clinical considerations is

## Community Education

**R**LRI faculty members speak at numerous seminars and events and they are willing to speak to your group or organization. Topics focus on strategies for living longer, healthier lives. Sample topics include “Aging and the onset of chronic disease,” “Pros and cons of hormone replacement therapies on aging men and women,” “How exercise and nutrition can impact your life” and “The importance of mental exercise: Ways to stay sharp.”

## Professional Education

**R**LRI sponsors local monthly seminars and an annual symposium featuring world-renowned gerontologists and other experts in aging and other medical fields, which provide continuing education for medical and science professionals. The seminars are designed to inform practicing physicians and other healthcare providers about important age-related topics. Continuing Medical Education credits are available for all of these seminars.

# THE WHI MISUNDERSTOOD AN OLDER POPULATION Intentionally Studied

*Editor's Note: This article is written by Dr. Marcia Stefanick, Professor of Medicine & Professor of Obstetrics/Gynecology, Stanford University, who is also a Women's Health Initiative (WHI) Principal Investigator. The Kronos Early Estrogen Prevention Study (KEEPS) is not related to WHI. It is KLRI's goal to help you better understand the issues of the WHI-related to hormone replacement therapy; therefore, we feel it is necessary to share all views.*

Several physicians and hormone researchers have suggested that the Women's Health Initiative (WHI) was flawed, because it didn't study women of menopausal age. It was not flawed. WHI has simply been misunderstood. The trial was designed to determine whether a therapy approved for treating menopausal symptoms and maintaining bone mineral density, could prevent diseases of aging, such as heart disease, cancer, and osteoporosis, after the menopause.

When WHI was started in the early 90's, the evidence that estrogen prevents coronary heart disease (CHD) was relatively weak, particularly for estrogen combined with a progestin, yet millions of women with no menopausal symptoms, including women well past menopause, were being encouraged to take estrogen, (with a progestin, for those with a uterus). This was because heart disease is the leading cause of death in women and many believed that an effect of estrogen on the heart could justify a small increased risk of breast cancer (suspected from results of some studies).

Many of the effects of estrogens observed in animal research, appeared to support the idea that estrogen replacement might improve cardiovascular health in women after menopause. HDL-cholesterol increases and LDL-cholesterol decreases seen with conjugated equine estrogen [Note: CEE, estrogens extracted from the urine of pregnant mares, are sold as Premarin®, the most popular form of estrogen for menopausal therapy] treatment in the Postmenopausal Estrogen-

Progestin Interventions (PEPI) trial were presented as further evidence of a heart-protective effect of estrogen, despite triglyceride elevations. Hormone replacement therapy was being widely promoted, with little distinction between estrogen only and estrogen combined with a progestin. The PEPI trial showed that the most commonly used progestin, medroxyprogesterone acetate (MPA), significantly reduced the beneficial estrogen effect on HDL-cholesterol.



Surprisingly for those who believed in heart protective effects, the Heart and Estrogen-progestin Replacement Study (HERS) reported no benefit of conjugated equine estrogen combined with MPA in preventing second heart attacks in women with pre-existing heart disease. Also, the Estrogen Replacement and Atherosclerosis (ERA) trial reported no effect of conjugated equine estrogen or conjugated equine estrogen+MPA on progression or regression of atherosclerosis, despite beneficial changes in HDL cholesterol of even greater magnitude than seen in

the PEPI trial. Thus, questions about the role of these hormones in preventing heart disease in women who did not need treatment for menopausal symptoms increased. Similarly, the relative risks and benefits of prescribing estrogen to maintain bone mineral density would be clearer if hip and other osteoporotic fractures, which occur primarily in women over 60 years of age, were shown to be significantly reduced by estrogen.

## The Purpose of the WHI

The Women's Health Initiative addressed a public health question that got lost in the uproar about menopausal symptoms in younger women. The specific aims were to test whether estrogen only – or estrogen combined with progestin:

- reduces the incidence of coronary heart disease (CHD) and hip fractures in postmenopausal women.
- increases breast cancer (the major concern expressed

*continued on page 7*

by women)

- results in an overall health benefit, or harm, when cardiovascular, cancer, and bone health are considered simultaneously, and also with other causes of death.

## Separate Trial of Hormones Chosen for Public Health Reasons

The WHI hormone trial design separated women who had had a hysterectomy (surgical removal of the uterus), who were randomly assigned to either conjugated equine estrogen or placebo treatment; and women with a uterus, who were assigned to either conjugated equine estrogen, combined with MPA, or placebo. Conjugated equine estrogen and MPA were chosen because they were (and still are) the most widely prescribed estrogen and progestin in the U.S. The WHI designers believed that a study of conjugated equine estrogen and MPA would address the broadest public health question regarding hormone benefits and risks to the U.S. population. Therefore, the choice of conjugated equine estrogen and MPA should not be considered a design flaw.

## It was intentional!

It was the National Institutes of Health's intention to study primarily women aged 60 years and older to obtain data of immediate relevance to an increasing proportion of the U.S. population. WHI investigators were restricted from recruiting more than 10% of the study population as women younger than 55 years of age and more than 20% of the women aged 55-59. Although younger women were eager to participate in the study, the chronic diseases of interest, e.g. heart disease and hip fractures, are relatively rare before the age of 60 in women; nonetheless, the number of women aged 50-59 in the conjugated equine estrogen+MPA trial exceeded 5500.

## Monitoring and Making the Decision to Halt the Study

The decision to stop the conjugated equine estrogen+MPA trial was based on a plan approved earlier by the WHI Data and Safety Monitoring Board (DSMB), which was based on eight outcomes: three were cardiovascular, (heart attacks, strokes and

pulmonary emboli (ie. blood clots in the lungs)); three related to cancer, (breast cancer, colorectal cancer, and endometrial cancer (ie. cancer of the Uterus)); the other two were hip fractures; and deaths from other causes. A "Global Index" was constructed from these endpoints, defined as the earliest occurrence of any of the eight outcomes, to provide an overall balance of



benefits and risks.

The stopping rules for benefit emphasized the expected cardio-protective effect of estrogen; it allowed for a significant reduction in heart disease. However, if the cardiovascular benefit were to exceed what was predicted, and the global index provided the overall picture of health benefit, the trial would be stopped to protect women who were not getting active estrogen. The stopping rules for harm emphasized the increased risk of breast cancer, but if the observed risk was higher than expected and the Global Index supported an overall picture of harm, the study would be stopped to protect the women assigned to active hormone pills. Stopping "boundaries" were also established for other outcomes, but these boundaries were less sensitive (less likely to be crossed) than the breast cancer boundary. Several outcomes, in particular, breast cancer, were adjusted, so that events early in the trial, (before it seemed hormones would have time to exert a causal effect, would have less impact than events that occurred later). Crossing a boundary would not stop the trial, however, unless the global index was in the same direction.

In summary, the rules for stopping the trial were based on expectations regarding benefits and risks for the

*continued on page 8*

## THE WHI MISUNDERSTOOD... *Continued from Page 7*

outcomes that were being most closely watched. If we were to start WHI today, different stopping boundaries would likely be set for CHD, stroke, and other outcomes based on new hormone trial results. It is now widely accepted that menopausal estrogens can cause deep vein thrombosis. Similarly, it is now generally accepted that estrogen does not prevent second heart attacks or prevent progression of disease in women with existing heart disease.

As the WHI progressed some surprises occurred:

- First, the DSMB recommended that all 27,347 hormone (both conjugated equine estrogen only and conjugated equine estrogen+MPA) trial participants be informed that there had been more heart attacks, strokes, and blood clots in women on active pills by the time most women had completed their two-year follow-up
- Secondly, the DSMB required that all hormone trial participants receive a second letter in June 2001, to inform them that, after an average of four years of follow-up, there were still more heart attacks, strokes and blood clots in the lungs and legs in women assigned to active pills.
- Thirdly, a recommendation a year later instructed women in the conjugated equine estrogen+MPA trial to stop taking study pills, more than three years before the planned trial ending, because the health risks exceeded the benefits. The DSMB instructed conjugated equine estrogen only participants to continue to take their study pills because the balance of risks and benefits remained uncertain.

In the conjugated equine estrogen+MPA trial, the stopping boundary for breast cancer had been crossed,

and the global index supported overall harm, because of an excess of cases of cardiovascular events (heart attacks, strokes, pulmonary emboli) in addition to the increase in breast cancer. These adverse events were not offset by the reduced rate of hip fractures and colorectal cancer diagnoses observed on the conjugated equine estrogen+MPA group.

### Disease Prevention versus Treatment

It is important to recognize that women in the placebo group had heart attacks and strokes and were diagnosed with breast cancer too, so one cannot assume that hormones caused a heart attack, stroke, or breast cancer in a woman taking active pills; however, hormones increased the rates of these events. The excess risk attributed to conjugated equine estrogen+MPA for heart attacks was reported as seven per 10,000 women per year and for strokes, pulmonary emboli, and breast cancer, it was eight per 10,000 per year respectively; while the benefits of conjugated equine estrogen+MPA were reported as five fewer hip fractures and six fewer colorectal cancer diagnoses. Some of the critics of the trial have downplayed the significance of these risks for an individual woman and have objected to the headlines highlighting the increased relative risks, such as a 29% increase for heart disease. However, the original hypothesis of at least a 30% reduction in heart disease by hormones, could have been proven if WHI had seen seven fewer heart attacks per 10,000 per year, and this would have been presented as strong evidence to start more women on hormones.

The public health significance of these risks is dependent on the number of individual women who use the hormones. Prior to July 2002, it was estimated that 6 million U.S. women were taking conjugated equine estrogen+MPA; therefore, the excess risk of heart attacks attributed to these hormones was 4,200 per year. When combined with

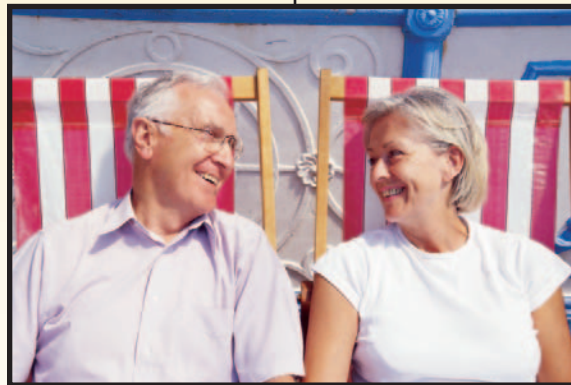


## THE WHI MISUNDERSTOOD... CONTINUED

excess risks of stroke, pulmonary emboli and breast cancer as well as lower than expected benefits, it is clear that conjugated equine estrogen+MPA should not be prescribed for chronic disease prevention. This conclusion has relatively little bearing on the use of conjugated equine estrogen+MPA or other hormones for the treatment of menopausal symptoms beyond the fact that WHI provides clinicians with the best available estimates of risks and benefits of these hormones. [Of some interest, about 3/4 of the women in the conjugated equine estrogen+MPA trial had never used menopausal hormones, but many had been advised by their physicians to initiate hormone therapy long after menopause, not to treat menopausal symptoms which most did not have, but for perceived health benefits.]

The WHI investigators have published sub-group analyses to address specific questions and criticisms that have been raised, such as data for women in their 50's compared to older women, for obese and overweight compared to normal weight women, and a range of other characteristics.

Let's start with CHD. Recent data showed that after 5.6-year average follow up, there was a 24% increase of CHD events. This rate was not statistically significant for CHD harm, as indicated in the July 2002 report; however, the trial clearly rules out CHD benefit for women who are aged 50-79 when they begin taking conjugated equine estrogen+MPA and the hypothesis was therefore clearly tested. Year-by-year analyses, similar to those done for the HERS trial, showed a significant early harm, as evidenced by 81% more heart attacks in the first year with a 95% confidence interval that does not include 1.0. Higher (though not significant) rates were seen in the conjugated equine estrogen+MPA group, versus placebo, in each of the subsequent years, i.e. Year 2, 3, 4, 5, and 6, until year 7, which a relatively smaller proportion of the cohort had completed. The data do not, therefore,



support a hypothesis of later cardiovascular benefit. There were also no significant differences by age decade.

### The Cholesterol Issues

As was reported by PEPI, HERS, ERA, and several other studies, the WHI showed a significant reduction of LDL-cholesterol and increase of HDL-cholesterol in women assigned to conjugated equine estrogen+MPA, compared to placebo, but there was also a significant increase in triglycerides; therefore, based on the effect on heart disease, it seems that conjugated equine estrogen-induced changes in HDL- and LDL-cholesterol are not good indicators of heart disease benefit.

### Body Mass Index

Some have suggested that the WHI was flawed because the study population was overweight, on average, with over a third of participants being obese. Because this closely reflects the weight status of the U.S. population of women aged 50-79, this should not be cited as a study design flaw. It does, however, highlight a different, and important, public health concern than WHI was not designed to address. The WHI updates do attempt to address whether the risks and benefits of conjugated equine estrogen+MPA differ in lean versus overweight or obese women. In general, obese women were more likely to experience adverse outcomes, except for hip fractures, than women of normal weight in the placebo and hormone groups; however, conjugated equine estrogen+MPA produced a similar excess risk within weight status groups.

Although the E+P trial randomized about 2000 women aged 50-54, there were relatively few outcomes in these young women resulting in considerable uncertainty about differences between active and placebo groups; therefore, analyses combined them with the 3500 women aged 55-59, which

*continued on page 10*

included many recently menopausal women, to total 5522 women aged 50-59, which is the largest sample of women in their 50's ever studied in a hormone trial. For heart disease, the rate in the placebo group for women in their 50s was 17 per 10,000 per year, which is about half the rate for women in their 60s and about 1/3 the rate of placebo women in their 70s. However, heart disease was increased by 27% in the women in their 50s who were assigned to conjugated equine estrogen+MPA compared to the placebo women in their 50s, which was similar to the overall finding of 24% increase with conjugated equine estrogen+MPA for the total cohort. For women less than 10 years after the menopause, the relative risk of CHD was 0.89 (slightly less than 1.0), suggestive of a neutral finding, but certainly not evidence of great benefit. Whether benefit would be seen if women initiated hormones before the age of 50 or at the time of menopause was not addressed in the WHI hormone trial.

## Breast Cancer

Breast cancer was diagnosed more often than heart disease in the WHI women in their 50s taking a placebo (26 per 10,000 per year); therefore, even if the trial had shown cardiovascular benefit for younger women, the argument that protection against heart disease may justify an increased risk of breast cancer does not apply to women in their 50s, even if one wishes to focus on long-term benefits. While it is true that the risk for heart disease increases as we age, the risk for breast cancer also increases dramatically with age, as was seen in the placebo women in the WHI. One studies the data for women in their 50s, 60s, and 70s. Although the women in these decade groupings may differ for many reasons, it is of interest that women in their 50s who were assigned to conjugated equine estrogen+MPA had rates of breast cancer similar to women taking placebos in their 60s and the conjugated

equine estrogen+MPA women in their 60s had rates similar to women in their 70s taking placebos, suggesting that the excess breast cancer risk attributed to conjugated equine estrogen+MPA may be equivalent to the risk associated with aging 10 years.

As for the study-wide benefits of fewer hip fractures, this was seen almost exclusively in the 60 and 70-year-old women. There were only six hip fractures in the 5,522 women in their 50's. The Global Index for women in their 50s was one of overall harm, even though the absolute risks (and benefits) were much lower in the younger women compared to older women.

## What about estrogen in symptomatic women 50 to 54?

We cannot answer that question from the WHI. A small percent of WHI women had symptoms. Basically, randomly assigning a woman to take a placebo when she has severe symptoms is not a good study design, because

such women are likely to find a placebo intolerable, which would result in a higher dropout rate for women taking a placebo. This happened in the PEPI trial, which included a large percent of women aged 45-55.

A paper written by Dr. Manson in the Journal of the American Medical Association, August 2003, included analyses of 50 to 59-year old WHI participants with symptoms, including those with hot flashes, which suggested that there might be a difference between the women with and without symptoms, although this difference was not significant, nor did it suggest cardiovascular benefit, but rather less harm. A more confusing picture was seen for women who reported both hot flashes and night sweats, which for many menopausal women, is a bigger problem. In these women, as for the whole cohort, there is a clear suggestion of harm with conjugated equine estrogen+MPA.



continued on page 11

It has been suggested that WHI women had pre-existing CHD because they were much older than menopausal women and therefore, WHI is the same as HERS. With the exception of the 6% of WHI participant who did have pre-established heart disease at baseline, this is clearly not true as evidenced by the rates of heart attacks in HERS women versus the WHI cohort and also in the WHI participants who did not have pre-established CHD versus those that did. There is at least a 4-to 5-fold higher (absolute) rate of heart attacks in women who are known to have disease, but, initiation of conjugated equine estrogen+MPA, increased that (relative) risk similarly in women with established CHD versus those without CHD. (\*\*See Editor Comments at the end of the article)

If a woman did initiate hormones at the time of menopause and has continued on them ever since, do the benefits continue to outweigh the risk? We do not have the answer to that question. But in the absence of good data, a more important question to answer is whether we have other ways to prevent heart disease, which are less likely to increase other health risks.

### **Cognitive (thinking, memory, and problem solving) Function**

Because of the length of the study we were not able to get a clear look at whether conjugated equine estrogen+MPA was beneficial for mild cognitive impairment; however, it was clearly detrimental for dementia, resulting in 23 excess cases per 10,000 women per year.

### **Conclusion**

WHI has done a great service for older women in this country. It has resulted in applying a brake on what had become over- and inappropriate prescribing of a drug that had not been properly tested for purported prevention benefits, conjugated equine estrogen+MPA. Despite an increasing body of literature which supported the hypothesis of a cardioprotective effect of estrogen only, we never had overwhelming data regarding similar benefits for estrogen combined with a progestin – not in the observational literature or case-control studies, or from basic science research, yet we had millions of women taking combination therapy with the expectation that they

would be on these hormones for the long-term. Over the last decade, a series of secondary prevention trials, starting with HERS, have failed to demonstrate benefit of either estrogen only or combination estrogen/progestin therapy on progression of pre-established cardiovascular disease, even though the American College of Cardiologists had developed guidelines to encourage clinicians to initiate estrogen therapy for woman with heart disease the year before the first trial (HERS) was published.

The WHI hormone trials were sorely needed as similar guidelines were being developed to promote widespread hormone use for primary cardiovascular disease prevention. Hopefully, clinicians have learned that trial evidence is required before we can assume a causal relationship based on associations reported from observational studies or before we interpret results from basic science studies as proof that a drug will benefit public health. Therefore, we need new clinical trials to test the hypothesis not addressed by the WHI,-- that younger women who initiate hormones before or at the time their own estrogen levels drop will eventually benefit, i.e. have less heart disease in their 70's and beyond, when 75% of heart disease occurs in women. Meanwhile, because of the excellent study design of WHI, there is now consensus that conjugated equine estrogen+MPA should not be started in older women to prevent heart disease and there is reasonable skepticism regarding its role in chronic disease prevention in women aged 50-79.

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**Stanford, CA**

### **Editor's Comment\*\***

The Editors agree with Dr. Stefanick, except for her suggestion that WHI women did not have pre-existing CHD. Many women develop arterial plaques without symptoms by 5-10 years post-menopause. If 20% of the women in the WHI had undetected CHD, the early event rate, about one-fifth of that observed in the HERS trial, is explained.

# IMPROVING HEALTH OUTCOMES FOR OLDER ADULTS FOCUS ON IMMUNIZATIONS

The following article is the third in a five-part series focusing on strategies older adults can employ to improve their health and quality of life.

Preventing illness by getting immunized against influenza and pneumococcal disease is an important step for older Americans to take to improve their odds of remaining healthy during the flu season.

Immunizations significantly reduce a person's risk for hospitalization and death from the flu. According to the Centers for Disease Control and Prevention (CDCP), more than 50,000 people ages 65 or older die each year of influenza in the United States. Thousands more are hospitalized. In 2000, 34 percent of people ages 65 and older had not received a recent flu shot.

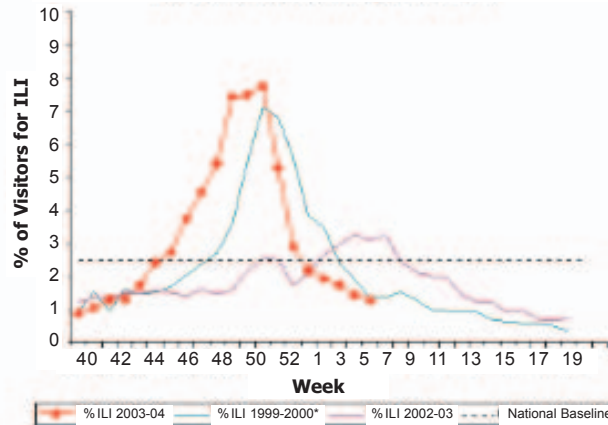
Recent media hype over this season's "flu epidemic" prompted many children, adults and elderly individuals to seek immunization despite a lack of supply. Arizona Department of Health Services Director Catherine Eden said vaccine supplies should be targeted to the elderly, children 6 months through 23 months of age, persons with chronic health conditions, such as asthma and diabetes, and people with weakened immune systems.

Influenza is spread by airborne droplets through coughing and sneezing, or by direct contact with respiratory secretions. Flu symptoms may begin suddenly and include fever (101 F or higher), muscle aches, chills, cough, and/or sore throat.

There are a few simple steps individuals can take to avoid getting sick, these include: washing your hands frequently and thoroughly, and covering your mouth and nose when coughing or sneezing.

Pneumonia, a common bacterial complication of influenza and measles, also affects many older adults. Each year in the United States, there are an estimated 175,000

**Percentage of Visits for Influenza-like Illness Reported by Sentinel Providers  
National Summary, 2003-04**



The 1999-2000 season was selected for comparison because it was the most recent A(H3N2) season of moderate severity.

Nationally, visits to physicians for flu-like illnesses skyrocketed during the 2003-04 flu season (see graph above). In Arizona, about 1,200 people died from flu and pneumonia in 2002. Influenza and pneumonia combined were the sixth leading

hospitalized cases of pneumococcal pneumonia. Yet in 2000, only 53 percent of those 65 years of age and older reported ever receiving the pneumococcal vaccine, according to "Health, United States 2002," a publication of the National Center for Health Statistics.

The CDCP recommends that elderly adults be vaccinated against pneumonia in addition to influenza. The pneumococcal vaccination can occur at any time of the year and those 65 and older only need to be vaccinated once.

Influenza shots should occur annually because flu strands vary year to year. The best time to inquire with your physician about receiving an influenza vaccine is early fall (September or October). For information about where to go for flu shots, contact the Community Information and Referral Hotline in Metro Phoenix at (602) 263-8856 or (800) 352-3792 for the rest of the state.

**Sources:**

- 1) Centers for Disease Control and Prevention.. "Healthy Aging: Preventing Disease and Improving Quality of Life Among Older Americans," January 2003.
- 2) Arizona Department of Health Services. "Health Department Recommends Targeted Use of Flu Vaccine," December 2003.

# Who we are!

**K**ronos 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 market 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 governs 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.*



# BOARD MEMBER PROFILE

## Yvonne R. Hunter, JD

Public Affairs Representative - Pinnacle West Capital Corporation



Ms. Yvonne Hunter joined APS in December 1998 as a Public Affairs Representative, and currently works with Marty Shultz as a Senior Public Affairs Representative. She provides support in the Public Affairs Office working on environmental, growth, construction and other miscellaneous issues on behalf of Pinnacle West

Capital Corporation, the parent company for APS.

Upon graduation from Arizona State University, College of Law in 1984, she joined the Maricopa County Attorney's Office as a Deputy County Attorney. She handled felony prosecutions for theft, sale and possession of illegal drugs, aggravated assaults, etc. After approximately two years, Ms. Hunter accepted a position as a general practice in-house attorney with Salt River Project. After leaving Salt River Project in 1991, she joined the Arizona Attorney's General's Office, where she was assigned to handle a special investigation of CPA firms that had helped Charles Keating build his empire. After successfully settling one of the largest settlements pertaining to a CPA firm's license to practice in Arizona, she joined the Environmental Enforcement Section in representing the

Arizona Department of Environmental Quality.

Ms. Hunter had a very challenging experience representing ADEQ in civil actions and administrative proceedings against violators of the Arizona Environmental statutes and rules. She also defended various APP and air permits issued by ADEQ and challenged by various interest groups. Her duties included tracking legislation for ADEQ and providing technical advice on proposed legislation and issues of concern.

She serves on the Advisory Board for the Salvation Army, Maricopa County Bar Association, the Greater Phoenix Urban League, Greater Phoenix Black Chamber of Commerce, Phoenix Library Foundation, and is a citizen member of the Use of Force Board and Disciplinary Review Board for the City of Phoenix Police Department.

Ms. Hunter completed her Bachelor of Art in English at the University of Nevada - Las Vegas. She completed her Arizona State University, College of Law in 1984. During her career at ASU, Ms. Hunter participated in various activities and externship programs. She worked with the U.S. Attorney's office assisting with one of the largest drug enforcement prosecutions in the state's history. She also interned with Senator Dennis DeConcini assisting the Senate Judiciary Committee address issues such as the Equal Rights Amendment, School Prayer, and revamping the U.S. Bankruptcy code.

## 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 industry's update also will 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.

# GLOSSARY ABC

## **High density lipid cholesterol (HDL) cholesterol -**

This is the “good” cholesterol. High levels appear to pull cholesterol out of plaques in the artery walls

**Low density lipid (LDL) cholesterol -** This is the “bad” cholesterol. High levels appear to promote formation of plaques in the artery walls

**Triglyceride -** This is the kind of fat found in foods and in the fat cells under the skin and elsewhere. It is the body’s main source of stored energy. Triglyceride circulating in the blood is thought to contribute to hardening of the arteries, but how importantly is controversial.

**Medroxyprogesterone acetate –** This chemical compound is a synthetic progestogen. It resembles the natural human compound, progesterone, in that it matures the lining of the uterus, but it also appears to have actions in the body that are different from natural progesterone. It has been widely used to protect the uterus from estrogen during menopausal hormone therapy.

**Pulmonary emboli -** A pulmonary embolus is a blood clot that breaks off from a clot in a vein (usually in the leg during a disease called thrombophlebitis) and travels throughout the heart to an artery in the lung, where it lodges. Such clots can cause serious damage to the lung and even death.

**Deep vein thrombosis –** The formation of clots in the large veins of the leg, also called “thrombophlebitis.” This problem can occur if blood flow in the legs is slowed or in certain other conditions in which tendency of the blood to clot is increased. Estrogens taken by mouth cause an increase in blood clotting factors.

**95% confidence interval -** This is the range of values above and below an estimate of risk, within which the actual risk has a 95% probability of falling by chance alone. Thus, if the 95% confidence interval for a risk does not include 1.0 (1.0 is always the risk for the control group), then there is less than a 5% chance that the risk estimated for treatment is not meaningfully different from that of a control group.

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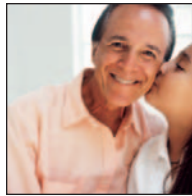
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